Economic Analysis for the Renovation, Repair, and Painting Program Proposed Rule

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Notice

This is not an official guidance document and should not be relied upon to determine applicable regulatory requirements. This document was prepared to provide economic information for the rulemaking process, and to meet various administrative and legislative requirements. Due to the nature of the information available to EPA, the document contains various assumptions that may not reflect the regulatory determinations that an individual firm would make were it to apply the rule's requirements to its specific circumstances. Persons seeking information on regulatory requirements as they apply to specific facilities should consult 40 CFR Part 745, the preamble for the regulatory action, EPA guidance documents, and EPA's National Lead Information Center.

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Executive Summary

This report presents an economic analysis of alternative regulatory options to establish work practice standards, plus training and certification requirements, for persons engaged in renovation activities for compensation in housing units containing lead-based paint. These requirements apply to contractors who renovate, remodel and/or paint housing units where there is lead-based paint, as well as to residential building owners and managers who may perform these activities themselves or have their staff do so. The regulation is being proposed under authority of §402(c) of the Toxic Substances Control Act (TSCA). Title IV of TSCA was established by the Residential Lead-Based Paint Hazard Reduction Act of 1992, also known as Title X of the Housing and Community Development Act of 1992 (Public Law 102-550).

Past use of lead-based paint has resulted in contamination that continues to pose human health hazards. Disturbing the lead-based paint, such as happens during renovation activities, is likely to create lead hazards. Since many residences built before 1978 have lead-based paint, it is likely that renovation activities occurring in these units will contribute to lead hazards unless appropriate containment and clean-up practices are employed. The Renovation, Repair and Painting (RRP) Rule is designed to prevent lead hazards from renovation activities.

The training and work practice standards required and fostered by the proposed RRP rule will yield health benefits to individuals living in renovated units and to their neighbors. The proposed rule will reduce lead exposure by containing the lead contamination generated by renovation activities and reducing the amount of such contamination remaining after completion of the activities. EPA anticipates that the rule will further develop a market for lead-safe renovation services that has been established by past lead awareness rules, such as the §406(b) rule which requires compensated renovators to distribute lead awareness pamphlets to owners and occupants of most pre-1978 residential housing before beginning renovations.

The proposed rule requires certification of firms (including self-employed contractors and property manager/lessors) that perform renovation, remodeling and/or painting in housing units subject to the regulations. A certified firm must assign to each renovation performed by the firm at least one renovator who has received formal training in EPA-approved work practices from an EPA-accredited course. In addition, certified firms must provide on-the-job training in these approved work practices for the rest of their staff who will be performing RRP activities in regulated housing. The proposed rule also requires containment of the work area to prevent the spread of dust and debris, specialized cleaning practices, and cleaning verification procedures to ensure that proper cleanup has occurred.

EPA considered two regulatory approaches: prescriptive and flexible regulations for the proposed work practice standards. Under the prescriptive approach, EPA would require the use of specific work practices for all RRP jobs covered under the rule and that are at risk of causing lead contamination. The flexible approach relies on the required training, and the renovator's own experience, to determine the extent of containment needed in any particular situation. The flexible approach increases the cost effectiveness of the regulation by reducing work practice costs.

This economic analysis considers four regulatory options with two phases. In Phase 1, Option A addresses pre-1978 housing, Option B and D both address pre-1960 housing, and Option C addresses pre-1950 housing. In Phase 2, all the options address pre-1978 housing. In both phases coverage of the rule is limited to rental housing and owner-occupied housing where a child under the age of six resides. Table ES-1 describes the housing stock subject to the regulations under each of the four options. Options A, B

and C are flexible in terms of the application of specific work practices while Option D is prescriptive. EPA is proposing Option B.

Table ES-1: Definitions of the Regulatory Options

	First Year – Phase 1	Second Year – Phase 2
Option A	All renter-occupied target housing units built before 1978, and owner-occupied target housing units built before 1978 where a child under the age of six resides. Flexible application of work practices	All renter-occupied target housing built before 1978, and owner-occupied target housing units built before 1978 where a child under the age of six resides. Flexible application of work practices
Option B	All renter-occupied target housing units built before 1960, and owner-occupied target housing units built before 1960 where a child under the age of six resides, plus all target housing units built before 1978 where a child with an increased blood-lead level resides.[a] Flexible application of work practices	Same as Option A.
Option C	All renter-occupied target housing units built before 1950, and owner-occupied target housing units built before 1950 where a child under the age of six resides, plus all target housing units built before 1978 where a child with an increased blood-lead level resides.[a] Flexible application of work practices	Same as Option A.
Option D	The prescriptive option. Covers the same housing units as Option B – but requires specific work practices.	The prescriptive option. Covers the same housing units as Option B – but requires specific work practices.

[a] Where increased is defined as greater than or equal to 10 µg/dL or a State or local government level of concern, if lower.
The proposed rule is Option B.

Cost of the Various Options

For purposes of this analysis, the costs associated with the regulatory impact of the Renovation, Repair, and Painting (RRP) Rule are divided into three categories: (1) training costs, (2) work practice costs, and (3) certification costs (which include the firm's paperwork burden and government administrative and enforcement costs). The general approach of the analysis is to first estimate the number of affected activities or entities, then estimate the incremental regulatory cost per-activity or entity affected. Finally, the incremental costs and the number of affected activities and entities are combined to estimate the total costs.

The number of RRP events covered by the rule varies across regulatory options in Phase 1 because the coverage of the regulation in Phase 1 varies across options, but under any of the options the number of events covered is substantial, as are the number of events that are performed in compliance with the rule. As shown in Table ES-2, approximately 10.7 million events per year would be conducted in compliance with the rule under Option A. Slightly more than one-half this amount, about 5.8 million events, would be conducted in compliance with the rule in the first year under Options B and D. In the first year, about 4.3 million events would be conducted in compliance with the rule under Option C. (Based on existing

literature about regulatory compliance rates in the construction industry, the analysis assumes that 75 percent of events in regulated housing are conducted in compliance with the rule.) In Phase 2 of the rule, the number of RRP events conducted in compliance with the rule is the same for all four options, about 4.4 million events per year.

Because not all housing units built before 1978 have lead-based paint, the number of RRP events that need to use lead safe work practices (LSWP) is a subset of the total number of units covered by the rule. In Phase 1, between 8.1 million (Option A) and 3.7 million (Option C) events will use LSWP. In Phase 2, an estimated 4.4 million RRP events will be using LSWP. Despite the increased coverage of the rule in Phase 2, the number of events with LSWP in Phase 2 is smaller than in Phase 1 because the accuracy of lead paint test kits in terms of detecting the presence or absence of lead is expected to have improved by then. The current tests have a high false positive rate (estimated to average 63 percent), resulting in the frequent use of LSWP when they are not necessary, i.e., when lead is not present. The improved tests are expected to have a false positive rate of 10 percent.

Table ES-2: Number of RRP Events

Description of Options				Number of Events per Year (millions)			
	Phase 1 Scope	Phase 2 Scope	Work Practices Flexible?	Phase 1 Events	Phase 1 Events with LSWP	Phase 2 Events	Phase 2 Events with LSWP
Option A[a]	Pre-78 R/C	Pre-78 R/C	Yes	10.7	8.1	10.7	4.4
Option B[a]	Pre-60 R/C	Pre-78 R/C	Yes	5.8	4.8	10.7	4.4
Option C[a]	Pre-50 R/C	Pre-78 R/C	Yes	4.3	3.7	10.7	4.4
Option D[a]	Pre-60 R/C	Pre-78 R/C	No	5.8	4.8	10.7	4.4

Notes:
R/C = All rental units plus owner-occupied units with children under the age of 6 years
LSWP = Lead Safe Work Practices
Number of events assumes 75% post-rule compliance
In Phase I, paint spot tests assumed to have a false positive rate of 63%, in Phase 2 they are assumed to have a 10% false positive rate.

[a] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied or child-occupied housing. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing.

Work practice costs are estimated for each of several types of RRP events and for different sizes of housing units. These unit costs are multiplied by the number of events of each RRP type and housing type to estimate the total work practice-related costs for each regulatory option. The RRP events and the range of unit costs associated with each type are shown in Table ES-3.

Table ES-3: Summary of Housing Unit Containment, Cleaning, and Verification Compliance Costs (2005$)		
Event Type	**Range of Costs per Event**	
	Low	**High**
Kitchen Remodel	$28	$132
Bathroom Remodel	$23	$63
Additions	$26	$117
Non-Room-Specific Interior Wall[a]	$57	$528
Non-Room-Specific Window/Door[b]	$58	$528
Interior Paint	$42	$285
Whole Exterior Remodel	$161	$281
Exterior Remodel in Contained Area[c]	$77	$77
Exterior Paint	$161	$281

[a] Events that involve changes to a wall or walls, where the location is not specified. For example: re-wiring or repair/replace heating or cooling systems.
[b] Repair/replacement of windows and/or doors, where the room is not specified.
[c] Outside repair/remodeling work that involves a specified part of the home, e.g. installation of a deck.
Source: See Section 4.5.8.

In addition to the number of covered RRP events in compliance with the rule and their unit costs, the other major factors in determining the costs of the rule are the number of firms certified, the number of personnel trained, and the costs of training and certification. All of the regulatory options require that each certified firm (including property managers and lessors who perform their own RRP work in regulated housing, as well as construction firms conducting RRP in regulated housing) employ at least one renovator who has taken an EPA-accredited training course and provide on-the-job training for all other staff who will be performing RRP activities in regulated housing. As shown in Table ES-4, the number of firms certified and the number of persons trained expands as the coverage of the rule expands. Thus Options B/D and C have larger numbers in the first year of Phase 2 than does Option A. By the second year of Phase 2, the number of firms certified and persons trained each year has leveled out to approximately 54 thousand firms certified or recertified, approximately 62 thousand renovators taking training or refresher courses, and nearly 277 thousand other workers getting on-the-job training each year.

Table ES-4: Estimated Number of Establishments Seeking Certification and Workers and Renovators Seeking Training			
	Option A[a]	**Options B & D[a]**	**Option C[a]**
Year 1			
Total Number of Establishments (with Employees and without) Seeking Certification [c]	163,979	86,539	59,571
Total Number of Renovators Trained [b,c]	186,811	98,588	67,866
Total Number of Workers Trained [b,c]	279,221	147,357	101,437
Year 2			
Total Number of Establishments (with Employees and without) Seeking Certification [c]	54,436	105,851	123,756
Total Number of Renovators Trained [b,c]	62,015	120,589	140,987
Total Number of Workers Trained [b,c]	278,076	278,076	278,076
Year 3			
Total Number of Establishments (with Employees and without) Seeking Certification [c]	54,212	54,212	54,212
Total Number of Renovators Trained [b,c]	61,761	61,761	61,761
Total Number of Workers Trained [b,c]	276,935	276,935	276,935

[a] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing. Of the regulated housing, 75 percent are assumed to comply with the regulations.

[b] Components may not add up to totals due to rounding.

[c] The number of firms and individuals certified and trained, respectively, is reduced by 0.04 percent per year to account for housing that is removed from the regulated housing stock due to demolition or conversion to non-housing uses. Thus the demand for lead-safe renovation services is reduced over time.

See Table ES-1 for option descriptions.

Source: EPA calculations – see Section 4.3.

The costs of the various regulatory options follow the number of events, with Option A having the largest costs under Phase 1 (see Table ES-5). Option D costs exceed the costs of Option B, even though they cover the same units, because Option D provides less flexibility in defining the extent of the area to be contained and cleaned. Option A costs decline substantially in Phase 2 for two reasons. First, most of the initial training and certification costs for Option A have been borne in Phase 1, while under Options B, C and D, a substantial amount of initial training and certification is occurring in Phase 2. Second, with the improved lead paint test kits available in Phase 2, the number of RRP events that use LSWP declines for all the options. The 50-year annualized costs provide a measure of the steady-state costs for each option. As shown, once the initial start-up costs have been absorbed, Options A through C have relatively similar annual costs of between $488 million and $505 million, using a 3 percent discount rate, or between $518 million and $551 million using a 7 percent discount rate. Option D continues to have substantially higher costs due to its prescriptive nature.

The cost estimates account for the RRP events in the baseline that already use some of the work practices to be required under this rule. In situations where contractors are already using these practices they will experience a smaller increase in operating costs, which is accounted for in the cost estimates. All

contractors that perform RRP in regulated housing, however, will incur the training and certification costs due to the rule.

Table ES-5: Estimated Total Costs

Description of Options				Costs (millions 2005$)			
	Phase 1 Scope	Phase 2 Scope	Work Practices Flexible?	Phase 1	Phase 2	50-Year Annualized	
						3% Discount Rate	7% Discount Rate
Option A	Pre-78 R/C	Pre-78 R/C	Yes	$ 924	$ 495	$ 505	$ 551
Option B	Pre-60 R/C	Pre-78 R/C	Yes	$ 531	$ 552	$ 492	$ 526
Option C	Pre-50 R/C	Pre-78 R/C	Yes	$ 393	$ 572	$ 488	$ 518
Option D	Pre-60 R/C	Pre-78 R/C	No	$ 645	$ 649	$ 588	$ 629

Notes:
R/C = All rental units plus owner-occupied units with children under the age of 6 years
Assumes 75% post-rule compliance
In Phase I, lead paint test kits are assumed to have a false positive rate of 63%, in Phase 2 they are assumed to have a 10% false positive rate

Benefits of the Rule

The number of people protected by this rule varies with the variation in the universe of housing units covered by the rule. In Phase 1, Option A covers the largest number of individuals, including the largest number of children under the age of six years (see Table ES-6). By Phase 2, all options cover nearly 5.3 million individuals per year, including over 780 thousand children under the age of six years old. Similar to the cost estimates, the number of individuals and children protected assumes that 75 percent of RRP work will be in compliance after the rule takes effect, and that there is some baseline use of LSWP. Based on the limited amount of information currently available about the baseline use of LSWP, the analysis assumes that approximately 20 percent of individuals and children living in regulated units with RRP already receive the benefits that the rule would provide.

As discussed earlier, based on other compliance studies, this analysis assumes a compliance rate of 75 percent. However, the Agency's goal continues to be 100 percent compliance. If that goal were achieved, then over 1 million children under the age of six years old would be protected by the rule. At that rate, however, both the costs and the benefits would be higher than shown in the other tables.

Table ES-6: Number of Individuals Protected by the Regulatory Options

Description of Options				Number of Individuals Occupying Units with LBP, where LSWP are Used Due to the Rule[a] (thousands per year)				
				Children under 6 Years of Age			All Individuals	
	Phase 1 Scope	Phase 2 Scope	Work Practices Flexible?	75% Compliance Rate		100% Compliance Rate[b]	75% Compliance Rate	
				Phase 1	Phase 2	Phase 2	Phase 1	Phase 2
Option A	Pre-78 R/C	Pre-78 R/C	Yes	787	783	1,138	5,309	5,287
Option B	Pre-60 R/C	Pre-78 R/C	Yes	668	783	1,138	4,529	5,287
Option C	Pre-50 R/C	Pre-78 R/C	Yes	520	783	1,138	3,659	5,287
Option D	Pre-60 R/C	Pre-78 R/C	No	668	783	1,138	4,529	5,287

Notes:
R/C = All rental units plus owner-occupied units with children under the age of 6 years
LSWP = Lead Safe Work Practices
In Phase 1, lead paint test kits are assumed to have false positive rate of 63%, in Phase 2 they are assumed to have a 10% false positive rate
[a]Number of individuals is incremental above those occupying units where LSWP are currently practiced in the baseline.
[b] If 100 percent compliance were achieved, both the costs and the benefits would be higher than shown in the tables based on 75 percent compliance.

Lead causes a number of adverse health effects in people of all ages. Of particular concern are children under the age of six years, but older children and adults also suffer effects from lead exposure In this analysis, only a few of these health effects have been quantified. One of the factors restricting the scope of the benefits estimation is the limited amount of available data, including well-specified dose response relationships, on which to quantify and monetize many of the health and developmental effects. Therefore this benefits assessment focuses on two major categories of health effects: effects on cognitive function in young children (under the age of six) and cardiovascular disease (hypertension, coronary heart disease and stroke) and premature mortality in adults. There are additional uncertainties in the quantification of adult effects, which are addressed in Section 5.5.5.

Even where the dose-response relationships are known, many cases are not included in the estimates because exposure levels cannot be estimated for all potentially affected individuals. For example, the benefit estimates presented in this report are based on reductions in lead ingestion; they do not include reductions in lead inhalation, although that is also likely to occur. Likewise, benefits are estimated only for people living in the housing units; they do not include potential benefits to visitors or neighbors. In addition, ecological benefits, as well as benefits to family pets, are not included in the estimates.

It is important to note that the monetary values assigned to the avoided adverse health effects are based on medical costs avoided, not willingness-to-pay to avoid these ailments and/or premature death. Likewise, the value of the IQ points that will be gained due to this rule are valued in terms of increased earnings, not willingness-to-pay.[1]

[1] Note that dose-response functions only allow for estimating IQ impacts among children less than six years of age, and the health effects only for adults over the age of 40. Other groups who are among the total individuals occupying units with lead-based paint in Table ES-6 are not included in the benefit estimates.

This analysis estimates the benefits of the proposed regulation in terms of IQ deficits in children and increased blood pressure and related health effects in adults. Quantitative estimates of benefits are provided in two scenarios. Scenario 1 quantifies benefits for both children and adults. Scenario 2 assumes additional cleaning in the baseline compared to Scenario 1, and only quantifies benefits for children. This approach is in recognition of the relatively larger uncertainties associated with adult health effects (pending completion of other EPA documents), as well as the particular concern about children expressed in Title X of the Residential Lead-Based Paint Hazard Reduction Act of 1992. The Agency is more confident in the estimates for children's IQ effects then it is for the estimates of adult benefits. While recognizing that adults may also benefit from the training and practices required under the rule, Scenario 2 does not try to quantify these benefits due to the uncertainties that currently exist.

Net Benefits

Based on the subset of benefits that have been monetized in this analysis, Table ES-7 and Table ES-8 display the annualized net benefits estimated for the four regulatory options under Scenarios 1 and 2, respectively. Each table presents annualized net benefits calculated at both a 3 percent and a 7 percent discount rate. Net benefits under Scenario 1 are substantially greater than those under Scenario 2. Scenario 1 assumes less baseline cleaning than Scenario 2 and it quantifies adult health benefits as well as children's IQ benefits. Under either Scenario, annualized net benefits calculated using a 7 percent discount rate are slightly larger than those calculated using a 3 percent discount rate. Under both scenarios and all options net benefits are positive, i.e., the benefits are larger than the costs.

When comparing options on the basis of annualized net benefits, there is relatively little difference among the three flexible options (Options A, B and C). This is not surprising, since the primary differences in these options occur in the first year the rule takes effect. After that year, all options address the same universe of pre-1978 housing. And after the second year, the population of firms and renovators being trained and re-trained levels off to approximately the same number each year. The only substantial difference is between the flexible options and the prescriptive Option D. The lack of flexibility appears as a roughly $100 - $150 million reduction in annualized net benefits as compared to the other options.

Table ES-7: Comparison of Options – Scenario 1 -- Annualized Costs and Net Benefits					
	Annualized Cost (millions 2005$)[a]	**Children's IQ Benefits – Annualized (millions 2005$)[b]**	**Adult Health Benefits – Annualized (millions 2005$) [b]**	**Sum of Children's IQ and Adult Benefits -- Annualized (millions 2005$)**	**Net Benefits – Children's IQ and Adult Health -- Annualized [c] (millions 2005$)**
	Annualized using 3 Percent Discount Rate				
Option A	$ 505	$947 - $5,336	$2,262	$3,209 - $7,599	$2,704 - $7,093
Option B	$ 492	$941 - $5,311	$2,250	$3,191 - $7,562	$2,699 - $7,069
Option C	$ 488	$934 - $5,267	$2,235	$3,170 - $7,503	$2,682 - $7,015
Option D	$ 588	$941 - $5,311	$2,250	$3,191 - $7,562	$2,603 - $6,973
	Annualized using 7 Percent Discount Rate				
Option A	$551	$1,008 - $5,680	$2,408	$3,415 - $8,087	$2,865 - $7,537
Option B	$526	$997 - $5,633	$2,385	$3,383 - $8,019	$2,857 - $7,493
Option C	$518	$984 - $5,551	$2,358	$3,342 - $7,909	$2,824 - $7,391
Option D	$629	$997 - $5,633	$2,385	$3,383 - $8,019	$2,754 - $7,390

[a] Developed in Chapter 4

[b] Developed in Chapter 5 – range for children's IQ benefits reflects alternative models for blood lead, exposure estimates and population of children

[c] Difference between sum of benefits and costs

Table ES-8: Comparison of Options – Scenario 2[a] – Annualized Costs and Net Benefits			
	Annualized Cost[b] (millions 2005$)	**Children's IQ Benefits – Annualized[c] (millions 2005$)**	**Net Benefits[d] – Children's IQ Only (millions 2005$)**
Annualized using 3 Percent Discount Rate			
Option A	$ 505	$774 - $4,354	$269 - $3,849
Option B	$ 492	$770 - $4,329	$277 - $3,837
Option C	$ 488	$764 - $4,298	$276 - $3,810
Option D	$ 588	$770 - $4,329	$181 - $3,741
Annualized using 7 Percent Discount Rate			
Option A	$551	$824 - $4,635	$273 - $4,084
Option B	$526	$816 - $4,587	$290 - $4,061
Option C	$518	$805 - $4,530	$287 - $4,012
Option D	$629	$816 - $4,587	$187 - $3,958

[a] While recognizing that adults will benefit from the rule, Scenario 2 does not try to quantify adult benefits. There are additional uncertainties in the quantification of adult effects, which are addressed in Section 5.5.5.

[b] Developed in Chapter 4

[c] Developed in Chapter 5 – range reflects alternative models for blood lead, exposure estimates and population of children

[d] Difference between sum of benefits and costs

Impact on Small Entities and Other Analyses

The vast majority of firms in the industries affected by this rule are small firms: approximately 145,000 small contractors and real estate establishments will be affected per year under the proposed Option B. Using studies from the economic literature, the analysis estimates that nearly 90 percent of the cost of the rule will be passed on to the purchasers of RRP services in the form of higher prices. The rest of the costs will be borne directly by the firms involved. This annual direct cost to small firms is estimated to range from about $1,600 to $6,100 per year per firm, depending on the number of RRP events typically undertaken by a small firm in the industry sector involved (see Table ES-9). These costs range from six-tenths of one percent for small Lessors of Residential Real Estate up to about 2.0 percent of revenues for small Painting and Wall Covering Contractors. They represent less than 1 percent of revenues for all types of small firms. The number of small governments and small non-profits affected was not calculated, but the cost per event is expected to be similar to that for businesses.

Table ES-9: Impact on Small Businesses

NAICS	Industry Description	Direct Cost of Rule Incurred by Contractor	Cost-Impact Ratio
236118	Residential remodelers	$1,659	0.9%
238170	Siding contractors	$2,212	1.1%
238350	Finish carpentry contractors	$1,558	1.5%
238290	Other building equipment contractors	$4,825	0.8%
238390	Other building finishing contractors	$2,463	1.1%
238340	Tile and terrazzo contractors	$1,810	1.4%
238220	Plumbing and HVAC contractors	$3,619	0.8%
238150	Glass and glazing contractors	$2,614	0.8%
238320	Painting and wall covering contractors	$1,759	2.0%
238210	Electrical contractors	$3,619	1.0%
238310	Drywall and insulation contractors	$2,563	1.1%
Average, Small Construction Establishments		**$2,111**	**1.0%**
531311	Residential Property Managers	$6,082	1.8%
531110	Lessors of Residential Real Estate	$4,725	0.6%
Average, All Industries		**$2,563**	**0.9%**

In terms of potential unfunded mandates, the rule is not expected to result in the expenditure by State, local, and Tribal governments, in the aggregate, of $100 million or more. The impacts on Children's Health and Environmental Justice are both likely to be positive. By focusing on owner-occupied housing with children under six years of age and all rental housing the regulatory options are structured to maximize protection of children and low income/minority households. The rule is not anticipated to have any negative impacts in terms of technology transfer, energy availability or federalism.

1. Introduction

This report presents an economic analysis of alternative regulatory options to establish work practice standards, plus training and certification requirements for renovators, remodelers and painters who work in housing units containing lead-based paint. These regulations will ensure that persons engaged in renovation activities for compensation, in housing units with lead-based paint, are trained and certified by EPA approved programs. The regulation is being proposed under authority of §402(c) of the Toxic Substances Control Act (TSCA). Section IV of TSCA was established by the Residential Lead-Based Paint Hazard Reduction Act of 1992, also known as Title X of the Housing and Community Development Act of 1992, Public Law 102-550. While some of the regulatory options considered in this analysis would allow for a phasing in of the requirements, eventually these rules will apply to all renovation activities performed in renter-occupied target housing units constructed before 1978 and owner-occupied target housing units constructed before 1978 where children under the age of six reside.

Past use of lead-based paint has resulted in contamination that continues to pose human health hazards. While intact lead-based paint is not likely to contribute to such hazards, the deterioration of a structure over time or acute environmental stresses, such as are commonly present during renovation activities, have been found to create lead hazards. Since many residences built before 1978 have lead-based paint, it is likely that renovation activities occurring in these units will contribute to lead hazards unless appropriate containment and clean-up practices are employed.

1.1 Purpose of the Proposed Rule

The training and work practice standards required and fostered by the proposed RRP rule will yield health benefits to renovation households and their neighboring communities (not including the RRP workers). The proposed rule will reduce lead exposure by reducing the amount of lead contamination generated by renovation activities, and thus reduce the health and ecological risks in their vicinity. EPA anticipates that the rule will further develop a market[1] for lead safe renovation services that has been established by past lead awareness rules, such as the §406(b) rule, which requires compensated renovators to distribute lead awareness pamphlets to owners and occupants of most pre-1978 residential housing before beginning renovations.

The proposed rule requires certification of firms (including sole practitioners) that perform renovation, remodeling and/or painting in housing units subject to the regulations. To be certified, the firm must employ at least one renovator who has received formal training in EPA-approved work practices from an EPA-accredited course. In addition, certified firms must provide on-the-job training in these approved work practices for workers who will be performing RRP activities in regulated housing. In addition, the proposed rule requires cleaning verification procedures to ensure that proper cleanup has occurred. Supporting these work practices, training and certification requirements, EPA will be undertaking an enhanced outreach program to educate the general public about the dangers of lead exposure and ways to limit exposure resulting from RRP activities.

EPA has considered two regulatory approaches: prescriptive and flexible regulations for the proposed work practice standards. Under the prescriptive approach, EPA prescribes the size of the work area that must be contained, cleaned, and verified. The flexible approach relies on the required training, and the

[1] These markets are expected to consist of suppliers who offer lead safe renovation services (LSRS) and consumers who are willing to pay the incremental costs associated with using LSRS over non-LSRS.

renovator's own experience, to determine the size of the work area in any particular situation. The flexible approach increases the cost effectiveness of the regulation by reducing work practice costs.

1.2 Goal of the Economic Analysis

The purpose of this report is to present policy options that are under consideration and to analyze their respective costs and benefits. The report also meets the requirements for economic analysis of Executive Order 12866 – *Regulatory Planning and Review*; the Regulatory Flexibility Act (RFA) and Small Business Regulatory Enforcement Fairness Act (SBRFA); Executive Order 12898 – *Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations*; Executive Order 13045 – *Protection of Children from Environmental Health Risks and Safety Risks*; the Unfunded Mandates Act and Executive Order 12875 – *Enhancing the Intergovermental Partnership*; and the Paperwork Reduction Act (PRA).

This economic analysis considers four regulatory options. Options A, B, and C allow certified renovators who are performing the RRP activity to decide the work practices necessary, while under Option D, the required work practices are specified by the rule. The options also differ in terms of the age of housing subject to the regulation in the first year – by the second year they all cover the same housing stock. Options A, B, C and D cover the following housing units (Note that Options B and D are the same in terms of the housing subject to the regulations). The proposed rule is Option B.

	First Year	Second Year
Option A	All renter-occupied target housing units built before 1978, and owner-occupied target housing units built before 1978 where a child under the age of six resides.	All renter-occupied target housing built before 1978, and owner-occupied target housing units built before 1978 where a child under the age of six resides.
Option B	All renter-occupied target housing units built before 1960, and owner-occupied target housing units built before 1960 where a child under the age of six resides, plus all target housing units built before 1978 where a child with an increased blood-lead level resides.[a]	Same as Option A.
Option C	All renter-occupied target housing units built before 1950, and owner-occupied target housing units built before 1950 where a child under the age of six resides, plus all target housing units built before 1978 where a child with an increased blood-lead level resides.[a]	Same as Option A.
Option D	The prescriptive option. Covers the same housing units as Option B – but requires specific work practices.	The prescriptive option. Covers the same housing units as Option B – but requires specific work practices.

[a] Where increased is defined as greater than or equal to 10 µg/dL or a State or local government level of concern, if lower.
The proposed rule is Option B.

1.3 Organization of this Report

Chapter 2 examines the supply of and demand for renovation, remodeling and painting services. Using data from the U.S. Economic Census, the chapter discusses the size of the RRP industry and characteristics of its firms, as well as the organizational structure and competitiveness of the industry. Using a variety of secondary source material the demand for RRP services is characterized and the factors that affect demand are discussed. Other affected industries (e.g. training providers, property owners and managers) are also profiled in this chapter.

Chapter 3 characterizes the lead contamination problem to be addressed under the proposed rule. It discusses how incomplete information and external costs have resulted in inefficient levels of lead contamination resulting from renovation activity, and introduces regulation as a reasonable solution for these market failures. The chapter also reviews state and local regulations that affect RRP activities and demonstrates that these are not sufficient to address the problem.

Chapter 4 describes in detail the methods used to calculate costs of the various regulatory options considered. It describes the data sources used and is organized around the four general categories of costs for complying with the proposed rule: training costs, work practice compliance costs, cleaning verification costs, and administrative costs. The last section of the chapter estimates the costs of each option over a 50-year period.

Chapter 5 describes in detail the benefit estimation, covering IQ benefits in children and a variety of health effects in adults. Four appendixes are presented that include a technical discussion of how the benefits were estimated and provide a brief discussion of the lead-related adverse health effects, both included and not included in the benefit analysis, as well as ecological effects.

Chapter 6 provides a summary of the costs and benefits, and the corresponding net benefits. This chapter also provides a summary of the number of individuals living in these units who would otherwise be at risk.

Chapter 7 presents the results of several sensitivity analyses conducted to measure the effect of particular components of the model. These analyses address uncertainties in both the cost and the benefit analyses.

Finally, Chapter 8 presents findings of distributional analyses relevant to specific rule-making requirements, including small business impacts, environmental justice, protection of children and unfunded mandates.

2. Renovation, Repair and Painting Industry Profile

Under the Renovation, Repair and Painting (RRP) Rule, firms that renovate, repair or paint housing subject to the regulations will need to obtain EPA certification, train their employees as either renovators or workers and ensure that lead-safe work practices are used whenever a project disturbs more than the exempt amount of lead-based paint. Eleven construction industry sectors and two residential real estate sectors include, in all likelihood, the vast majority of firms affected by the RRP Rule. These industries are the primary focus of this profile. Because the proposed rule will also affect the training provider market by requiring training for certified renovators, this profile examines the technical trade school industry as well.

The industry profile is organized into six sections. Section 2.1 examines the supply-side of renovation by defining the relevant industry sectors and identifying the number of potentially affected firms. Section 2.1 also contains financial profiles of the renovation industry sectors, highlighting each sector's firm size and value of construction work. Section 2.2 focuses on the demand-side of renovation by identifying the quantity of renovation activities performed. This section also discusses trends in the demand for renovation services. Section 2.3 focuses on the overall market organization for the renovation industry and assesses the competitiveness of the industry. Section 2.4 discusses property owners and managers likely to be affected by the rule. Section 2.5 discusses training providers.

2.1 The Supply of Renovation Services

Renovation encompasses a wide variety of construction activities. Renovation is defined as

> the modification of any existing structure, or portion thereof, that results in the disturbance of painted surfaces, unless that activity is performed as part of an abatement as defined by this part (40 CFR 745.223). The term renovation includes (but is not limited to): the removal or modification of painted surfaces or painted components (e.g., modification of painted doors, surface preparation activity (such as sanding, scraping, or other such activities that may generate paint dust)); the removal of large structures (e.g., walls, ceiling, large surface replastering, major replumbing); and window replacement (40 CFR 745.83).

Thus, renovation includes repair and painting work. Renovation activities are conducted without the intent of removing lead, but may disturb it in the process. Lead abatement activities, on the other hand, are conducted with the intent to remove lead-based paint or otherwise permanently eliminate a lead-based paint hazard. Depending on the reason they are undertaken, many activities, such as replacing windows, can be either renovation or abatement. Because the proposed RRP regulations will address renovation, rather than abatement activity, this profile focuses on the residential renovation industry as opposed to the abatement services industry. Providers of abatement services (i.e. abatement supervisors and workers) will not require additional training to perform renovation work and will be grandfathered in under the RRP regulations.

2.1.1 Industry Definition and Characteristics

Data from the U.S. Economic Census were used to identify North American Industry Classification System (NAICS) industry groups that may be involved in renovation, repair and painting work (U.S. Census Bureau 2001). An establishment is assigned to a NAICS group based on the activities from which it derives the greatest share of its revenues. These activities may or may not make up the majority of work (i.e. labor hours) performed by the establishment, which may also be involved in a variety of other related (or unrelated) lines of work. EPA identified eleven NAICS codes that are likely to include the vast majority of establishments that will be affected by the RRP regulations. Affected industry groups include one building construction sector (NAICS 236118 – Residential Remodelers) and ten specialty trade contractor sectors. These sectors, as well as examples of the work they perform, are presented in Table 2-1.

Table 2-1: Sectors likely to be affected by the RRP regulation	
2002 NAICS	**Examples of Work Performed**
236118 - Residential Remodelers	• Addition, alteration and renovation of single-family homes • Addition, alteration and renovation of multifamily building • Home improvement (e.g., adding on, remodeling, renovating)
238220 - Plumbing, Heating & Air Conditioning Contractors	• Heating equipment installation • Plumbing fixture installation • Plumbing and heating contractors
238320 - Painting and Wall Covering Contractors	• House painting • Paint and Wallpaper Stripping • Paperhanging and removal contractors
238210 - Electrical contractors	• Electrical wiring contractors • Lighting system installation • Electric power control panel and outlet installation
238350 – Finish Carpentry contractors	• Door and window, prefabricated, installation • Millwork installation • Paneling installation
238310 - Drywall and Insulation Contractors	• Panel or rigid board insulation installation • Mineral wool insulation installation • Plastering (i.e., ornamental, plain) contractors
238170 - Siding Contractors	• Vinyl Siding, soffit and fascia, installation • Wood Siding, installation
238340 - Tile and Terrazzo Contractors	• Ceramic tile installation • Mantel, marble or stone, installation • Mosaic work
238150 - Glass and Glazing Contractors	• Mirror installation • Window pane or sheet installation
238390 - Other Building Finishing Contractors	• Window shade and blind installation • Building fixture and fitting (except mechanical equipment) installation • Drapery fixture (e.g., hardware, rods, tracks) installation
238290 - Other Building Equipment Contractors	• Pipe, duct and boiler insulation • Water pipe insulating • Deodorization (i.e., air filtration) system installation
Source: U.S. Census Bureau 2001	

2.1.2 Renovation Establishment Characteristics

Establishments that provide renovation services fall into two general categories: those with employees (employer establishments) and self-employed contractors, also referred to as non-employer establishments.

Number of Establishments with Employees

Although some establishments[1] in the identified NAICS industries may specialize in residential renovation, the majority (with the exception of Residential Remodelers), in all likelihood, do not. Establishments in these sectors work on commercial, educational and industrial structures in addition to residential buildings. An establishment that does specialize in residential structures may perform work on new construction as well as on existing structures; the former is, of course, not considered a renovation. The U.S. Economic Census does not provide data on the number of establishments that specialize in residential renovation, but does present the number of establishments that specialize in single-family and apartment building construction, a category that includes both new construction and renovation work. Because the RRP rule applies only to residential renovations, however, these numbers provide an idea of the extent to which the regulations will affect each of the industry sectors.

The U.S. Economic Census tracks businesses with paid employees (employer establishments) and non-employer establishments (self-employed contractors) separately. This discussion deals with employer establishments only; non-employers are addressed later in this section.

Table 2-2 presents the total number of establishments as well as the number of establishments specializing in residential construction in each of the identified NAICS industries. The number of establishments "includes all establishments that were in business at any time during the year. It covers all full-year and part-year operations" (U.S. Census Bureau 2005j). According to the U.S. Census Bureau, an establishment is considered to specialize in a certain type of construction if it derives at least 51 percent of its revenues from this construction type. Note that for NAICS 236118 and NAICS 238320, the number of establishments specializing in residential construction includes establishments that specialize in single-family and apartment building work. For the remaining NAICS codes, the number of establishments specializing in apartment building work is not provided (number specializing in single-family construction is available) and the number specializing in Other Building Construction was used as a proxy. Because the Other Building Construction category includes both apartment buildings and various types of non-residential structures, this approach is likely to lead to an overestimate of the number of establishments specializing in residential construction.

As demonstrated in Table 2-2, about 54 percent of Residential Remodeler (NAICS 236118) establishments specialize in residential work. The portion of specialty contractor establishments that specialize in residential work varies from 86 percent of Finish and Carpentry contractors to only 31 percent of Other Building Equipment contractors. Notably, none of the Other Building Equipment contractor establishments specialize in single-family residential construction; all potentially affected establishments specialize in Other Building construction, which may include apartment buildings. Based on the data presented in Table 2-2, up to 215,513 of the 357,154 establishments in the identified NAICS sectors (60 percent) may specialize in residential construction (including both new construction and renovation).

[1] The U.S. Census Bureau defines an "establishment" as "a single physical location at which business is conducted. It is not necessarily identical with a company or enterprise, which may consist of more than one establishment" (U.S. Census Bureau 2005j). Most economic census data represent a summary of reports for individual establishments rather than companies. For cases where a census report was received, separate information was obtained for each location where business was conducted." (U.S. Census Bureau 2005j)

Table 2-2: Number of Employer Establishments in Construction Sectors Affected by the RRP Rule				
NAICS code	**Industry**	**Total Number of Establishments**	**Number of Establishments Specializing in Residential Work**	**Residential Establishments as Percent of Total**
238350	Finish carpentry contractors	35,087	30,232[b]	86
238340	Tile and terrazzo contractors	8,950	7,583[b]	85
238170	Siding contractors	6,632	5,596[b]	84
238320	Painting and wall covering contractors	38,943	27,021[a]	69
238310	Drywall and insulation contractors	19,598	13,271[b]	68
238220	Plumbing and HVAC contractors	87,501	52,443[b]	60
236118	Residential remodelers	82,747	44,492[a]	54
238390	Other building finishing contractors	3,729	1,947[b]	52
238210	Electrical contractors	62,586	28,758[b]	46
238150	Glass and glazing contractors	5,294	2,281[b]	43
238290	Other building equipment contractors	6,087	1,889[b]	31
Total		**357,154**	**215,513**	**60**

a. Sum of establishments specializing 51 percent or more in single family attached and detached units construction and establishments specializing 51 percent or more in apartment building construction.

b. Sum of establishments specializing 51 percent or more in single family attached and detached units construction and establishments specializing 51 percent or more in other building construction. Data on establishments specializing in apartment building construction not available.

Sources: U.S. Census Bureau 2005e,f

Number of Employees

Table 2-3 presents the number of employees in each NAICS group of interest, as well as the total for establishments specializing in residential construction for each industry. The 215,513 establishments that specialize in residential construction employ about 1.4 million people.

Table 2-3 also presents the average per-establishment employment numbers by NAICS code, for all establishments and for establishments specializing in residential construction. Average employment numbers are also presented in the form of a bar graph in Figure 2.1. The average employment numbers are small for all affected sectors. Overall, Other Building Equipment contractors have the largest number of employees per establishment (20.8 people), while Residential Remodelers have the smallest (3.9 people). While establishments that specialize in residential construction make up 60 percent of all establishments in the identified sectors, they employ only 47 percent of the people who work in these industries.

Table 2-3: Number of Employer Establishments and Employees by NAICS Code				
NAICS code	**Industry**	**Number of Establishments**	**Number of Employees**	**Average Size**
236118	Residential Remodelers	82,747	320,201	3.9
	Establishments specializing in residential work	***44,492***	***208,867***	***4.7***
238170	Siding contractors	6,632	43,042	6.5
	Establishments specializing in residential work	***5,596***	***33,493 [b]***	***6.0***
238210	Electrical contractors	62,586	771,184	12.3
	Establishments specializing in residential work	***28,758***	***236,815 [b]***	***8.2***
238220	Plumbing and HVAC contractors	87,501	974,368	11.1
	Establishments specializing in residential work	***52,443***	***393,599 [b]***	***7.5***
238310	Drywall and Insulation contractors	19,598	311,077	15.9
	Establishments specializing in residential work	***13,271***	***165,202 [b]***	***12.4***
238320	Painting and Wall Covering contractors	38,943	234,562	6.0
	Establishments specializing in residential work	***27,021***	***115,645 [a]***	***4.3***
238350	Finish Carpentry contractors	35,087	179,476	5.1
	Establishments specializing in residential work	***30,232***	***148,171 [b]***	***4.9***
238340	Tile and Terrazzo contractors	8,950	60,001	6.7
	Establishments specializing in residential work	***7,583***	***42,658 [b]***	***5.6***
238150	Glass and Glazing contractors	5,294	50,800	9.6
	Establishments specializing in residential work	***2,281***	***14,725 [b]***	***6.5***
238290	Other Building Equipment contractors	6,087	126,559	20.8
	Establishments specializing in residential work	***1,889***	***31,923 [b]***	***16.9***
238390	Other Building Finishing contractors	3,729	50,617	13.6
	Establishments specializing in residential work	***1,947***	***22,237 [b]***	***11.4***
Total, All sectors		**357,154**	**3,121,887**	**8.7**
Total, All establishments specializing in residential work		***215,513***	***1,413,335***	***6.6***

a. Sum of establishments specializing 51percent or more in single family attached and detached units construction and establishments specializing 51percent or more in apartment building construction.

b. Sum of establishments specializing 51percent or more in single family attached and detached units construction and establishments specializing 51percent or more in other building construction. Data on establishments specializing in apartment building construction not available.

Sources: U.S. Census Bureau 2005e,f

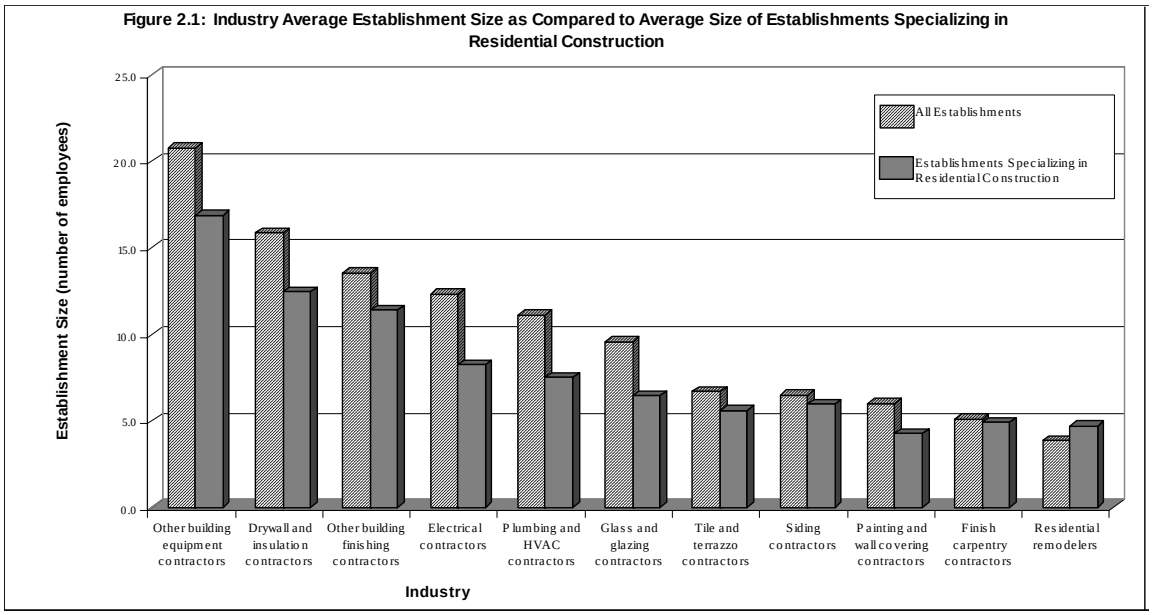


Table 2-4 presents the total number of employees and the number of construction workers in each identified industry. These data are only available at the industry level and can not be obtained for establishments that specialize in residential construction. The number of employees "includes all full-time and part-time individuals on the payrolls of construction establishments during any part of the pay period which included the 12th of March, May, August and November" (U.S. Census Bureau 2005f). The number of construction workers "includes all payroll workers (up through working supervisory level) directly engaged in construction operations" including, but not limited to "painters, carpenters, plumbers and electricians… journeymen, mechanics… truck drivers and helpers." Non-construction employees include "executives, purchasing, accounting, personnel… and routine office functions" (U.S. Census Bureau 2005f). Because construction workers form the vast majority of the people who require training under the RRP rule, their role in the composition of each sector's labor force provides an indication of the extent to which each sector will be affected by the regulations.

In total, over 3 million people work for the 357,154 establishments in the potentially affected industries. About 75 percent of these employees are construction workers. The affected sectors differ in terms of the composition of their labor force. For example, construction workers make up 84 percent of employees in the Drywall and Insulation contractor sector. In the Finish Carpentry contractor and the Residential Remodeler sectors, however, construction workers make up only 72 percent and 65 percent of the labor force, respectively (U.S. Census Bureau 2005b,f).

Table 2-4: Number of Employer Establishments, Total Employees and Employees involved in Construction				
NAICS Code	**Industry**	**Total Number of Employees**	**Number of Construction Workers**	**Construction Workers as Percent of Total Employees**
238310	Drywall and Insulation contractors	311,077	261,239	84
238210	Electrical contractors	771,184	606,403	79
238320	Painting and Wall Covering contractors	234,562	184,328	79
238340	Tile and Terrazzo contractors	60,001	44,729	75
238390	Other Building Finishing contractors	50,617	37,353	74
238220	Plumbing and HVAC contractors	974,368	712,452	73
238350	Finish Carpentry contractors	179,476	129,888	72
238290	Other Building Equipment contractors	126,559	90,504	72
238170	Siding contractors	43,042	30,284	70
238150	Glass and Glazing contractors	50,800	34,086	67
236118	Residential Remodelers	320,201	207,633	65
Total		**3,121,887**	**2,338,899**	**75**
Sources: U.S. Census Bureau 2005b,e,f				

Number of Non-Employer Establishments

As mentioned at the beginning of this section, the U.S. Economic Census tracks non-employer establishments separately from establishments with employees. Data on the number of non-employer establishments was available from the U.S. Small Business Administration. A non-employer firm "is defined as one that has no paid employees, has annual business receipts of $1,000 or more ($1 or more in the construction industries), and is subject to federal income taxes" (U.S. Small Business Administration 2005). Essentially, non-employers are self-employed contractors. Because little financial and operational data is available for non-employers, the vast majority of this profile focuses on establishments with employees. This subsection discusses the number of non-employers in the affected industry sectors and the receipts of these establishments. Non-employers are addressed further in Chapter 4 of this Economic Analysis.

The U.S. Small Business Administration does not currently provide data on the number or revenues of non-employer establishments in each of the 6-digit level NAICS industries addressed in this profile. Data on the number of such establishments is available for Plumbing and HVAC contractors (NAICS 238220) and Electrical contractors (NAICS 238210) only; for the remaining industries, data is provided at the more general 4-digit NAICS level.

To estimate the number of non-employer establishments in each of the 6-digit sectors, EPA assumed that the distribution of non-employer establishments in each 4-digit NAICS code is the same as the distribution of establishments with payroll in the same 4-digit group. Similarly, to estimate the revenues of these establishments, EPA assumed that the distribution of receipts in each 4-digit NAICS code is the same as the distribution of revenues of payroll establishments in the same 4-digit industry. In other words, EPA assumed that if Residential Remodeler establishments with employees (NAICS 236118) make up 48 percent of the Residential Construction sector (NAICS 2361) and earn 30 percent of the revenues in that sector, then 48 percent of non-employers in the Residential Construction sector would be involved in the Residential Remodeling industry, and would earn 30 percent of the NAICS 2361 non-employer receipts.

Table 2-5 presents the estimated number and revenues of non-employer establishments in each of the eleven sectors affected by the RRP regulations.

Table 2-5: Number and Annual Revenues of Non-Employer Establishments in Affected Sectors

NAICS	Description	Number of Non-Employer Establishments	Revenues of Non-Employer Establishments (000)
236118	Residential Remodelers	194,182	$6,187,917
238170	Siding contractors	15,939	$485,112
238350	Finish Carpentry contractors	185,118	$5,254,955
238290	Other Building Equipment contractors	9,710	$356,461
238390	Other Building Finishing contractors	19,674	$1,396,611
238340	Tile and Terrazzo contractors	47,220	$1,684,174
238220	Plumbing and HVAC contractors	110,183	$5,920,986
238150	Glass and Glazing contractors	12,723	$720,934
238320	Painting and Wall Covering contractors	205,462	$4,823,217
238210	Electrical contractors	102,219	$3,834,347
238310	Drywall and Insulation contractors	103,398	$8,798,899
	Total Non-Employer Establishments	**1,005,829**	**39,463,613**

Source: U.S. Small Business Administration 2005, U.S. Census Bureau 2005i

Contribution of Residential Renovation Work to Total Value of Construction

Another way to assess the relative importance of renovation work to each of the NAICS industries is to compare each sector's value of renovation work to that sector's total value of construction work. The Value of Construction is defined as "receipts, billings and sales for construction work… [including] new construction, additions, alterations or reconstruction, and maintenance and repair construction work." The Value of Construction includes the value of the installation and receipts covering the price of the items installed," but excludes "the cost of industrial and other special machinery and equipment that are not an integral part of a structure" (U.S. Census Bureau 2005f). Although the 2002 Economic Census does not provide data on the number of establishments involved in residential renovation, it does provide the total value of construction work derived from these activities. These data are only available for each industry sector as a whole and are not available for establishments that specialize in residential construction.

Table 2-6 presents the total value of construction, as well as the value of construction from residential renovation activities, for each of the eleven identified industries in order (highest to lowest) of the percentage of revenues contributed by residential renovation to total value of construction. Residential renovation activity includes additions, alterations, reconstruction, maintenance and repair work performed in single-family buildings (attached or detached) and apartment buildings. When data on the value of construction work performed in apartment buildings was not available, the value of construction work performed in Other Buildings was used instead.[2]

As demonstrated in Table 2-6, residential RRP plays a different role for establishments in each construction sector. Residential Remodelers rely more on residential RRP than the other industries, deriving about 56 percent of their construction revenues from these activities. Specialty contractors, on

[2] This may lead to an overestimate of the percent contribution of residential RRP activity to total value of construction as Other Buildings include non-residential structures as well as apartment buildings.

the other hand, derive between 21 and 50 percent of their construction revenues from residential renovation (U.S. Census Bureau 2005d,f). Note that the percentage of total value of construction derived from residential RRP is a better indicator of the importance of RRP to that industry sector than the value of RRP construction. For example, although Plumbing and HVAC contractors have the highest residential RRP revenues of the eleven sectors, these contribute just over a quarter of the total value of construction for that industry. The interpretation of data is further complicated by the inclusion of materials used and installed, which is likely to be greater for sectors such as Plumbing/HVAC than for sectors such as Painting/Wall Covering.

Table 2-6: Annual Value of Construction Work: Renovation Activities Compared to Totals

NAICS Code	Industry	Total Value of Construction Work (000)	Value of Residential RRP[a] (000)	Value of Residential RRP as percent of Total Value of Construction
236118	Residential Remodelers	$45,031,231	$25,439,187	56
238170	Siding contractors	$4,253,327	$2,145,705 [c]	50
238350	Finish Carpentry contractors	$18,153,924	$9,107,821 [c]	50
238290	Other Building Equipment contractors	$14,503,280	$4,788,697 [c]	33
238390	Other Building Finishing contractors	$4,861,928	$1,467,134 [c]	30
238340	Tile and Terrazzo contractors	$5,858,390	$1,643,848 [c]	28
238220	Plumbing and HVAC contractors	$117,785,785	$31,416,931 [c]	27
238150	Glass and Glazing contractors	$6,284,748	$1,643,915 [c]	26
238320	Painting and Wall Covering contractors	$16,852,809	$4,208,354 [b]	25
238210	Electrical contractors	$82,141,261	$19,118,532 [c]	23
238310	Drywall and Insulation contractors	$30,821,528	$6,386,249 [c]	21
Total		**$346,548,211**	**$107,366,373**	**31**

a. Value of includes additions, alterations, reconstruction, maintenance and repair.
b. Sum of value of RRP work in single-family homes (attached and detached) and in apartment buildings.
c. Sum of value of RRP work in single-family homes (attached and detached) and in Other Buildings.

Source: U.S. Census Bureau 2005d,f

2.1.3 Financial Profile

In this section, Census data is used to examine key financial indicators for the renovation industry. The indicators include net value of construction (value of construction less value of construction subcontracted out to others) and labor costs. Net value of construction work is used instead of the total value of construction work because it is a measure of the work actually performed by the establishment. Table 2-7 presents the average per establishment net value of construction work (NVCW) for each industry sector and for establishments that specialize in residential construction. The table also presents labor costs as a percent of the net value of construction for each of the affected NAICS codes and for those establishments in each industry that specialize in residential construction.[3]

Data on the value of construction and payroll was not available for Residential Remodeler establishments that specialize in apartment building construction. As such, the NVCW reported in Table 2-7, which includes single-family buildings only, understates the total value of residential work performed by these establishments.

[3] Residential construction includes both new construction and renovation work. Data on the number or financial characteristics of establishments that specialize in residential renovation work is not available from the 2002 U.S. Economic Census.

Table 2-7: Financial Summary for Industry Sectors Affected by the RRP Rule				
NAICS code	**Industry**	**Annual Net Value of Construction Work (000)**	**Net Value of Construction Work per Establishment (000)**	**Payroll as % of Net Value of Construction Work**
236118	Residential Remodelers	$30,626,002	$370	28
	Estab. specializing in residential work	***$18,054,608***	***$406[a]***	***31[a]***
238150	Glass and Glazing contractors	$6,016,766	$1,137	29
	Estab. specializing in residential work	***$1,702,264***	***$746***	***27***
238170	Siding contractors	$3,810,070	$574	31
	Estab. specializing in residential work	***$2,954,747***	***$528***	***30***
238210	Electrical contractors	$77,671,846	$1,241	38
	Estab. specializing in residential work	***$20,553,832***	***$715***	***37***
238220	Plumbing and HVAC contractors	$105,323,163	$1,204	34
	Estab. specializing in residential work	***$39,115,100***	***$746***	***31***
238290	Other Building Equipment contractors	$13,680,062	$2,247	36
	Estab. specializing in residential work	***$3,134,176***	***$1,659***	***36***
238310	Drywall and Insulation contractors	$27,046,301	$1,380	36
	Estab. specializing in residential work	***$14,217,161***	***$1,071***	***32***
238320	Painting and Wall Covering contractors	$15,316,726	$393	39
	Estab. specializing in residential work	***$6,759,709***	***$250***	***36***
238340	Tile and Terrazzo contractors	$5,639,641	$630	33
	Estab. specializing in residential work	***$3,916,447***	***$516***	***31***
238350	Finish Carpentry contractors	$15,640,544	$446	30
	Estab. specializing in residential work	***$12,525,747***	***$414***	***30***
238390	Other Building Finishing contractors	$4,560,138	$1,223	38
	Estab. specializing in residential work	***$1,992,734***	***$1,023***	***34***
Total, All Establishments in All Industries		**$305,331,259**	**$855**	**32**
Total, Estab. Specializing in residential work only		***$124,926,525***	***$580***	***32***

a. Includes establishments specializing in single-family building construction only. Note that the revenue figures presented in this table include both new construction and renovation revenues.

Source: US Census Bureau 2002a,e,f

The data in Table 2-7 indicate that the average net value of construction work of Residential Remodeler establishments that specialize in residential construction is significantly higher than the industry sector average. The opposite is true for all 10 specialty contractor sectors. The difference is most pronounced in the electric industry sector, where the NVCW of specialized establishments is 42 percent lower than the industry sector average. The difference is smallest (7 percent) for Finishing Carpentry contractors (U.S. Census Bureau 2005e,f).

As demonstrated in Table 2-7, while labor constitutes about 32 percent of net value of construction for all the industry sectors and for those establishments that specialize in residential work, the within-industry differences vary across industry sectors. Glass and Glazing, Plumbing, Drywall/Insulation, Painting/Wall Covering and Other Building Finishing contractors that specialize in residential construction spend a slightly smaller portion of their net value of construction work on payroll expenditures than their industry

average. For example, labor costs of Drywall and Insulation contractors specializing in residential work amount to 32 percent of net value of construction, as compared to 36 percent for all establishments in that industry sector. On the other hand, Residential Remodeler establishments that specialize in residential work spend a slightly larger portion of the net value of construction work on labor than that industry's average (U.S. Census Bureau 2005a,e,f).

The Painting and Wall Covering contractor (NAICS 238320) industry is most dependent on labor, with an overall labor cost to net value of construction ratio of 39 percent. Glass and Glazing contractors, with an overall labor cost to net value of construction work ratio of 29 percent, are least labor dependent of the eleven sectors (U.S. Census Bureau 2005a,e,f).

2.1.4 Establishment Size by Revenue Bracket

The Small Business Administration (SBA) defines a small business in the Residential Remodeler industry as one that has revenues of $28.5 million a year or less. The small business definition for the ten affected specialty contractor industries is $12 million per year (U.S. Small Business Administration 2004). The SBA size standards apply to firms rather than establishments; revenue data in the 2002 Economic Census, however, is only available at the establishment level. By using establishment rather than firm data, this analysis overestimates the number of small businesses in the affected industries.

The remainder of this section examines the number of establishments, number of employees, net value of construction work and value of business done[4] distributed by establishment revenue bracket. These data were available from the 2002 Economic Census at the NAICS code level only. Establishments were classified into two revenue categories based on the total value of business done – those with revenues less than $10 million and those with revenues greater than $10 million. Because the Census groups all establishments with revenues of $10 million or more into one revenue bracket, it is not possible to determine what percentage of Residential Remodeler establishments have revenues of $28.5 million or less. Note, however, that nearly 100 percent of Residential Remodeler establishments have revenues of less than $10 million per year. The percent of establishments, employees and net value of construction contributed by establishments in each revenue bracket is presented in Table 2-8.

[4] Total value of business done is defined by the U.S. Census Bureau as "the sum of value of construction work and other business receipts. Value of business done is the sum of receipts, billings, or sales from establishments of construction business activities plus receipts from other business activities" (U.S. Census Bureau 2005f). As such, total value of business done represents the total revenues of a typical construction establishment.

Table 2-8: Small and Large Establishments as Percent of Industry

NAICS	Industry Description	Percent of Establishments	Percent of Employees	Percent of Net Value of Construction	Percent of Value of Business Done
238220	**Plumbing and HVAC contractors**				
	Revenues < $10 million	98	70	63	61
	Revenues $10 million or more	2	30	37	39
236118	**Residential remodelers**				
	Revenues < $10 million	100[a]	95	92	91
	Revenues $10 million or more	0	5	8	9
238210	**Electrical contractors**				
	Revenues < $10 million	98	68	61	60
	Revenues $10 million or more	2	32	39	40
238350	**Finish carpentry contractors**				
	Revenues < $10 million	100 [a]	86	84	83
	Revenues $10 million or more	0	14	16	17
238310	**Drywall and insulation contractors**				
	Revenues < $10 million	97	64	60	60
	Revenues $10 million or more	3	36	40	40
238290	**Other building equipment contractors**				
	Revenues < $10 million	95	60	55	55
	Revenues $10 million or more	5	40	45	45
238320	**Painting and wall covering contractors**				
	Revenues < $10 million	100 [a]	92	88	88
	Revenues $10 million or more	0	8	12	12
238170	**Siding contractors**				
	Revenues < $10 million	100 [a]	90	88	87
	Revenues $10 million or more	0	10	12	13
238340	**Tile and terrazzo contractors**				
	Revenues < $10 million	100 [a]	91	86	86
	Revenues $10 million or more	0	9	14	14
238390	**Other building finishing contractors**				
	Revenues < $10 million	98	81	74	74
	Revenues $10 million or more	2	19	26	26
238150	**Glass and glazing contractors**				
	Revenues < $10 million	98	82	77	77
	Revenues $10 million or more	2	18	23	23
	Total				
	Revenues < $10 million	99	75	68	68
	Revenues $10 million or more	1	25	32	32

a. 100 percent = establishments in this revenue category make up over 99.5, but less than 100 percent of establishments in the industry.

Source: U.S. Census Bureau 2005c,f

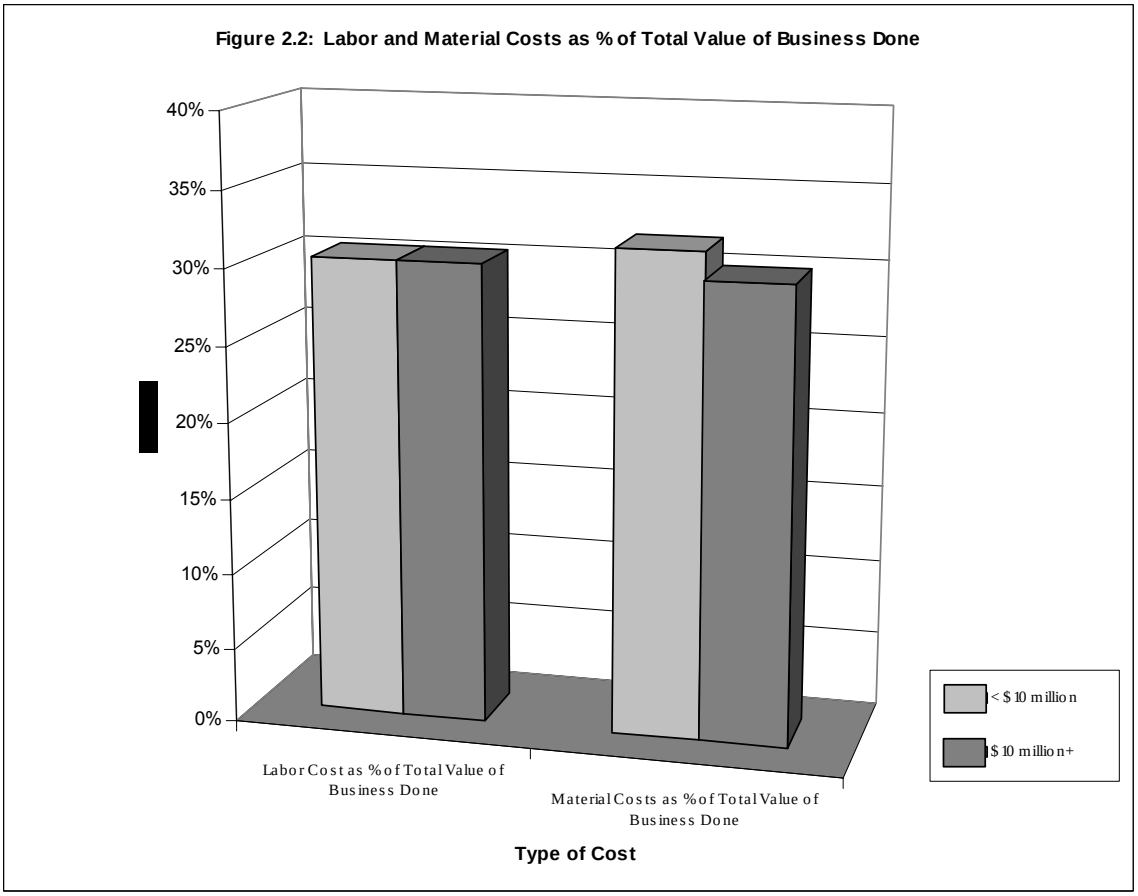
The distribution of the number of establishments for all eleven NAICS codes is greatly skewed toward smaller establishments. In five out of eleven industry sectors, over 99.5 percent of establishments have revenues below $10 million. Establishments with revenues greater than $10 million make up less than five percent of establishments in any sectors and about 1 percent of the total establishments in the affected industries (U.S. Census Bureau 2005c,f). As such, over 95 percent of establishments in each of the sectors have revenues below $12 million, which is the SBA small business definition for ten of the eleven industry sectors.

Establishments with revenues of less than $10 million account for between 60 and 95 percent of total employment for each sector, and about 75 percent of employment overall. The distribution of the net value of construction work and the total value of business done for all six-digit NAICS codes is skewed toward smaller establishments in a manner similar to the distribution of employees. Establishments with revenues of less than $10 million account for between 55 and 92 percent of the net value of construction work and between 55 and 91 percent of the total value of business done for each sector. Overall (across all industry sectors) they contribute about 68 percent of both the net value of construction work and the total value of business (U.S. Census Bureau 2005c,f).

Labor and Material Costs as a Percentage of Total Value of Business Done

In order to better understand the potential impacts of the RRP rule on the affected industries, and particularly on small businesses, it is important to observe whether establishment costs as a percentage of the establishments' total revenues differ for small and large establishments. Figure 2.2 examines labor and material costs as a percentage of the total value of business done for the eleven affected sectors. Each of the sectors was broken down into two size categories by revenue bracket: less than $10 million and $10 million and more. Labor and material costs as a percentage of the total value of business were calculated for each individual sector. An overall ratio of labor and material costs to the total value of business were also calculated for all sectors (the sum of labor (materials) costs for the eleven industries divided by the sum of the total value of business done for these sectors).

As demonstrated in Figure 2.2, based on data for all eleven affected sectors, the ratio of labor costs to the total value of business done is approximately 30 percent for both small and large establishments (U.S. Census Bureau 2005c,f). While material costs make up a slightly higher percent of revenues for small establishments (32 percent vs. 30 percent for large establishments), the ratios are not significantly different. As such, based on Census data for the eleven affected industries, it appears that the costs structure for small establishments is similar to the cost structure for larger establishments.



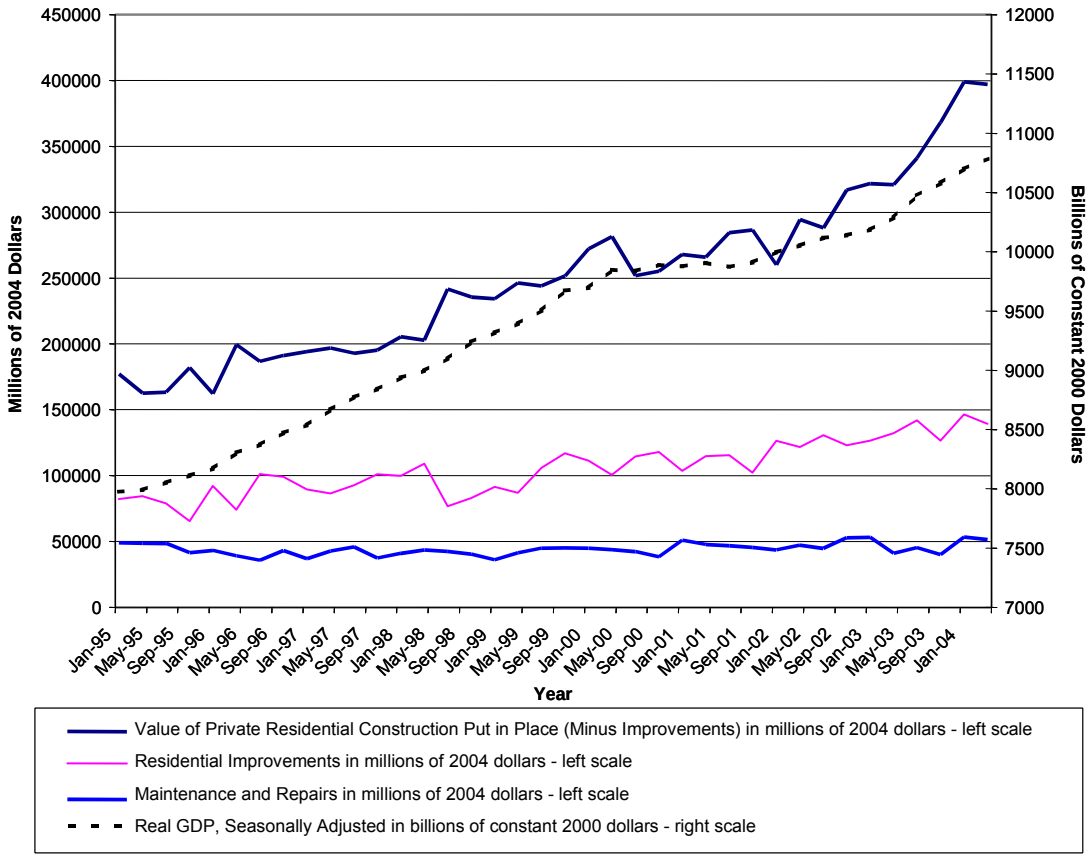
Source: U.S. Census Bureau *2005c,f*

2.2 The Demand for Renovation Services

The demand for renovation is responsive to changes in the overall economic conditions. The same factors that stimulate economic growth, such as low unemployment, high consumer confidence and low interest rates, also stimulate the demand for renovation services. Using U.S. Department of Commerce data, Figure 2.3 illustrates the relationships between the value of new construction, residential improvements and maintenance spending and real GDP.[5] Both new construction and real GDP experienced a substantial increase over the past 10 years. In the 1995 – 2002 period, GDP increased at a faster rate than new construction. In the 2002 – 2004 period, new construction has greatly outpaced GDP. Expenditures on residential improvements have also increased during this ten-year period, but at a slower rate than new construction. Like new construction, improvement expenditures are highly volatile. Spending on maintenance and repairs has remained fairly constant over this period and is not nearly as volatile as either new construction or improvements. This is expected because much of the maintenance (e.g., replacing heating systems or roofs) is not voluntary and the choices usually involve the amount to be spent, not whether the spending should be done.

[5] U.S. Department of Commerce 2004a,b; U.S. Department of Commerce 2005.

Figure 2.3: New Construction Compared to Improvement and GDP



Source: U.S. Department of Commerce 2004a,b; U.S. Department of Commerce 2005

2.2.1 Number of Renovation Activities Performed

The American Housing Survey (AHS) collects data on the number of owner-occupied households performing a renovation activity.[6] The AHS is a bi-annual survey of approximately 55,000 households in the United States conducted by the U.S. Census Bureau for the U.S. Department of Housing and Urban Development (HUD). The AHS includes data on single-family and multi-family units as well as data on publicly-owned and privately-owned housing units. The survey is stratified and weighted to represent the nation's housing stock and can be used to determine the state of the housing stock in a given year or to document changes in the housing stock over time.[7] The AHS traces the same set of households, adding observations each year to represent new construction.

Renovation tasks can be classified as "professional" projects and "do-it-yourself" projects. A project was classified as a "do-it-yourself" job if the AHS respondent reported that they or someone in their household completed the work. Professional jobs encompass all other work performed, and classification of a project as professional does not necessarily indicate that the contractor was licensed, certified or trained. The distinction between professional and do-it-yourself work is important because the regulatory requirements apply only to professional contractors.

[6] The AHS collects renovation data only from owner-occupied units; the number of events in rented units was calculated from another data source.

[7] As described in more detail in Chapter 4, the weights used throughout this analysis were developed by the Harvard

Renovation activities are not done with the intent to remove lead from the housing unit, although lead-based paint may be disturbed. Abatement activities, on the other hand, are performed with the sole intent to remove the lead-based paint from the housing unit. The AHS does not provide the data necessary to determine the intent of an activity. Hence, it is not possible to differentiate between the demand for renovation services or abatement activities.

Since the AHS is a bi-annual survey, the weights have been adjusted to calculate annual counts. As shown in Table 2-9, over 13.5 million pre-1980 owner-occupied housing units performed at least one renovation event in 2003.[8] Of these, over 70 percent had at least one professionally conducted RRP event and over 52 percent undertook at least one do-it-yourself RRP event. Note that a household's renovation activities can include a combination of both professionally done and do-it-yourself events. Thus the sum of households in these two categories exceeds the total number of households performing any renovation project. "In-scope" activities refers to households that had professionals undertake one or more renovation events that are likely to disturb more than two-square-feet of paint and thus might be subject to these regulations.[9] Approximately 5.9 million households undertook in-scope renovation projects in 2003. They comprise about 43 percent of all households undertaking RRP that year. In other words, about 12 percent of all households in owner-occupied target housing undertook at least one RRP event in 2003 that would fall under this regulation.

University's Joint Center for Housing.

[8] The housing unit age groupings in the AHS require that homes built in the 1975 to 1979 period be treated as a group. Thus the number of target housing units (defined as pre-1978 units except housing for the elderly or persons with disabilities where no children under age 6 reside or are expected to reside, or any 0-bedroom dwelling) undertaking RRP is slightly overestimated.

[9] This estimate does not adjust for the likelihood of lead in the paint. Unless an inspection or risk assessment has been conducted and no lead found (or an abatement performed) the regulatory requirements would apply.

Table 2- 9: Owner-Occupied Households Performing Renovations in 2003 (Pre-1980 Housing Only)				
Type of Renovation Activity	**Number of Households (thousands)** [a]	**Percent of All Housing Units**	**Total Annual RRP Spending (billions, 2005$)**	**Median RRP Spending** [b] **(per-household, 2005$)**
All Activities	14,000	28%	$88	$2,100
Professional Activities	10,000	20%	$63	$2,140
Do-It-Yourself Activities	7,000	15%	$25	$790
In-Scope-Activities [c,d]	6,000	12%	$53	$2,500

a. Rounded to the nearest million households.
b. Median spending per-household reporting some positive amount. Rounded to nearest $10.
c. In-scope activities are renovation projects that may disturb over 2 sq. ft. of paint. Out-of-scope activities are projects that are not likely to disturb more than 2 sq. ft. of paint.
d. Total and Median household RRP spending includes out-of scope RRP spending.

Note: It is assumed that all RRP reported by a household occurred in the same year. That is, the number of households estimated to have RRP performed annually is half the number of households that reported RRP in the bi-annual 2003 AHS.

Source: EPA Calculations Using the American Housing Survey (2003) and revised weights provided by the Joint Center for Housing Studies

The AHS also provides data on the amount that households typically spend for renovation. Because some households spend very large amounts on renovation, the median expenditure is a better indicator of typical behavior than is average expenditures. As shown in Table 2-10, in 2003 the median amount spent by households that undertook renovation was $2,100. The median amount spent on professional renovation work (at $2,140) was only slightly higher, while the median amount spent on do-it-yourself renovation was substantially less (at $790). The do-it-yourself expenditure does not include the value of the respondents' labor, just materials and other direct costs.

2.2.2 Determinants of Demand

Renovation spending tends to be volatile and is affected by a complex set of factors including, but not limited to, the income and age of the homeowner, the length of time that the homeowner has resided on the property and the location of the home. Although it is often hard to predict future spending on renovation in any particular year, impacts of these and other factors on the renovation and remodeling market have been studied extensively by Harvard University's Joint Center for Housing Studies. The work of the Joint Center serves as the basis for this discussion. [10]

As discussed earlier in this chapter, there are two main types of renovation projects – discretionary renovations and maintenance/repair projects. Unlike discretionary renovations, maintenance and repair projects are usually performed out of necessity and, as demonstrated in Figure 2.2, are less volatile than discretionary renovation and improvement projects. Note that a significant portion of the projects affected by the RRP Rule are likely to be repair/maintenance projects, rather than home improvement activities and thus may be less affected by the factors discussed in this section.

Income of the Homeowner

Traditionally, higher income households have spent more on improvement projects than other income groups, but recently the high-end market has grown expansively. Households with annual incomes over

[10] See reference list at the end of this chapter for the Joint Center studies used.

$120,000 have more than doubled their improvement spending from 1995-2001. In particular, spending on projects that cost over $35,000 has increased substantially in the past decade. The projects in this high-end market are more likely to be discretionary projects (e.g., room additions) as opposed to required system replacement (e.g., heating and roofing). It is important to note that despite the rapid growth in the high-end market, the vast majority of renovation projects are still comparably low-budget, with the median spending per household equal to about $2,100 per year.

Contrary to some impressions, improvement work in the high-end market is not done entirely by professionals. High-income households have greatly increased their share of do-it-yourself spending. From 1995-2001; owners with annual incomes over $120,000 were responsible for 54 percent of the growth in do-it-yourself expenditures. Once again, note that despite the fact that these households are spending a lot on do-it-yourself projects, the spending does not necessarily mean that the high-income households are taking on the greatest number of do-it-yourself projects. According to Harvard University's Joint Center for Housing (JCFH), most do-it-yourself projects cost less than $2,500 and are done by those with $40-80,000 annual incomes. While do-it-yourself projects have long played an important role in renovation, their share of RRP expenditures has decreased over time. The do-it-yourself share declined for all but 2 of the 15 years before 1999.

Age of the Homeowner

In addition to income, certain age ranges undertake more home improvement work. Households with heads between the ages of 35 and 44 take on many more home improvement projects than other age ranges. This age range includes families who are more likely to have children living at home and are more likely to be active in the housing market. On the other hand, the oldest segments of the population spend significantly less on improvements, especially discretionary improvements. Between 1994 and 2001, 35-44 year olds spent an annual average of $2,270 compared to $1,050 for those 65 and older.

When considering older homeowners it is important to remember that the baby boomer generation is reaching retirement age. This has important implications for the home improvement industry. As the population ages, and especially among those over 65, there is a noticeable decline in improvement spending. Those over 65 do, however, spend a larger share (over 80 percent) of their improvement budget on professional contractors as opposed to do-it-yourself projects. This may cause a future shift in the type of service demanded by homeowners.

Amount of Time Owner Has Resided in the Home

The amount of time that a family has resided in a home is another strong determinant of demand for home improvement. Households spend the most immediately after they move into a home, usually in the first two years. In all income brackets, trade-up buyers (those who sold a previous home and bought a new one) spent substantially more than first time buyers. First time buyers in turn spent substantially more than families that stayed in their homes without moving. Regardless of whether a home is the owner's first or not, improvement spending tends to taper off steadily as the time spent in a home increases. The improvement spending cycle for rental properties is slightly different. Rental properties are frequently improved during the turnover period after previous renters move out.

Changes in Family Composition
When a change occurs in family composition, such as the birth of a child, households are significantly more likely to do home improvement work. Although the demographics of households that have children already match those that are doing the majority of home improvement projects, the addition of a family member, with all other factors held constant, is a significant determinant of demand for home improvement. Households often want to optimize the space within their home and changes frequently include the renovation or the addition of bedrooms and bathrooms. Households adding a family member are also more likely to take on do-it-yourself projects rather than hiring a professional, typically because they are younger and have lower incomes than other households.

Location of Home
Geographically, the demand for home improvement has been strong in urban areas. For example, almost half of all home improvement spending occurs in the 35 largest metropolitan areas. Recently, as metropolitan housing prices have increased quickly, home improvement has become an attractive alternative to buying a new home. On the other hand, improvement spending is also shifting to high growth suburban areas in the South and West. A sizeable share of the housing stock in these areas is nearing the 25-30 year old range when improvement spending is common.

Minority Spending
Another factor in the changes in demand for home improvement is the recent growth in minority spending. From 1995-2001, minorities accounted for around 60 percent of the total increase in households. The largest growth was in the Hispanic community, in which home improvement spending increased almost 80 percent in inflation-adjusted terms over the same 1995-2001 period. This was more than 3 times the growth of spending for white households. In the future, minority spending is expected to continue as one of the largest areas of home improvement growth.

Interest Rates and Other Financial Factors
Recent low interest rates and escalating housing prices have sparked a large increase in home equity borrowing. The current pace of new construction is slow when compared to the demand for new housing and sellers have benefited from resulting price escalation. Thus the housing market has become one of the main supporters of consumer spending and the overall economy. The relative rate of construction and the increase in borrowing have provided a strong boost to the demand for home improvement.

The costs and ease of investment in home improvement are sometimes preferred over restructuring of debt. In a recent analysis, the Federal Reserve of New York found that households buffer fluctuations in year-to-year income with spending on home improvements (Fed of NY 2003). Discretionary projects like additions and remodeling are used more frequently than system replacements to buffer against income fluctuations. Thus fluctuations in economic growth, as well as the long-term trend, influence the decisions of homeowners to spend on discretionary improvements.

2.3 Market Organization

The previous sections focused on the supply and demand for renovation services. This section discusses the overall market structure of the renovation industry.

Firms and consumers interact in markets for goods and services. The results of these interactions differ depending on the competitive characteristics of the market. Competitive markets are characterized as markets with a large number of buyers (e.g., consumers) and sellers (e.g., firms) and relatively

homogenous goods. In competitive markets, neither firms nor consumers can influence the price of the good by altering their supply or demand decisions. Oligopolistic, monopolistic and monopsonistic markets are markets where either firms or consumers have market power and exhibit strategic behavior designed to change the price of the good sold. The competitive nature of an industry can be estimated by examining the following market characteristics:

- Number of establishments;
- Specialization of establishments;
- Number of consumers;
- Barriers to entry;
- Availability of substitutes; and
- Homogeneity of the good/service.

The data in Section 2.1 indicate that there is a large number of firms in the renovation industry. Using data for the eleven NAICS codes, there are approximately 357,154 establishments with employees in construction sectors affected by the RRP rule. Of these establishments, approximately 68 percent have annual revenues under $500,000, and only 1.4 percent have revenues of $10 million or more. In addition, there are about 1.1 million self-employed contractors in these industries, all of which are, in all likelihood, considered small by SBA standards. Given the large number of small establishments, it is unlikely that any one firm exhibits substantial market share in the overall market for residential renovation services. It is possible in some geographic areas for a small number of firms or a single firm to establish a market niche, but overall the market for renovation services appears to be quite competitive on the supply side.

Competition within the renovation industry is enhanced by the relatively low barriers to entry in this industry. Much of the work covered by this rule does not require particularly unusual or high levels of skills. Renovation work has traditionally attracted recent immigrants because lack of English is not important (Farzad 2005). While any training required as part of this rule will increase the skill level, the cost of the training is expected to be relatively low.

There are also a large number of consumers in the industry. As such, no single consumer of renovation services is expected to exhibit influence over the price of these services.

There are three sources of substitutes for renovation services. First, consumers can substitute from one contractor to another. Second, consumers can substitute away from professional renovation and into do-it-yourself work. Third, consumers can reduce the extent of the project or forgo renovation all together. This may occur if they decide to purchase new housing rather than renovate old housing, or if they choose to defer maintenance or renovation on their home. Together these sources of substitutes usually result in consumers being price sensitive (i.e. a relatively elastic demand with respect to prices).

Offsetting this are other characteristics of the RRP market. First, some differentiation in RRP services does exist. Contractors can provide services at a higher price if they can convince consumers that their services are better or distinctly different from their competitors. This is an important factor in anticipating the impact of the RRP requirements on contractors. The costs of safely renovating or repairing a home are expected to be higher than traditional methods. If the consumer is indifferent between safe- or unsafe-lead work practices, then those companies that choose not to safely renovate and repair homes may have a competitive advantage in the market due to lower costs. However, if the consumer recognizes that higher quality renovation jobs are those jobs completed with lead-safe work

practices, then firms may be able to comply with the regulation and charge a higher price. Under such a scenario, the consumer's marginal benefit for an additional unit of safe renovation may be higher than for an additional unit of unsafe renovation. The consumer who has a preference for lead-safe work practices would choose to do lead-safe renovation as long as the incremental cost of the lead-safe renovation is less than the incremental benefit of such a renovation. Because the lead-safe practices, training and certification will be required of all firms, it will be easier for firms to increase their prices than it is under the current voluntary situation. In addition, the market for RRP services is fragmented and there are substantial costs involved in getting prices. Getting bids from various contractors takes time and consumers need to compare prices across services that differ along many dimensions. These difficulties make it easier for firms to increase their prices to cover the costs for the new requirements.

The combination of a large number of firms, a large number of consumers, low barriers to entry, and available substitutes indicates that the renovation industry is likely to have a relatively high price elasticity of supply. The price elasticity of demand, however, maybe small in absolute value.

2.4 Property Owners & Managers

Property owners and managers also will be affected by the RRP rule if they choose to perform their own RRP projects rather than hire an outside contractor or if their renovation and maintenance costs rise as a result of the regulations.

Property owners and managers may have in-house crews that perform RRP activities. If this is the case, then the property owners and managers will directly bear the costs of training and certifying their workers as well as the cost of safe work practices. Furthermore, because all firms that perform regulated RRP projects will experience an increase in costs due to training of supervisors and workers and the use of safe work practices, it is assumed that costs to property owners and managers who hire outside contractors will increase.

2.4.1 Industry Definitions and Characteristics

Establishments involved in the leasing of apartments and other residential units are classified under NAICS 531110 - Lessors of Residential Buildings and Dwellings. This industry, in turn, is divided into two sub-sectors, NAICS 5311101—Lessors of Apartment Buildings and NAICS 5311109—Lessors of Dwellings Other than Apartment Buildings. According to the 2002 U.S. Economic Census data, together these industries include a total of 61,787 establishments that employ 292,405 people (U.S. Census Bureau 2004b).

Establishments involved in the management of residential properties are classified under NAICS 531311—Residential Property Managers. In 2002, this industry included 26,233 establishments that employed 289,870 people (U.S. Census Bureau 2004b). Table 2-10 presents summary statistics for the businesses in NAICS 531311 as well as NAICS 531110 and its sub-sectors.

Table 2-10: Summary Statistics for NAICS 531110, NAICS 5311101 and NAICS 5311109				
NAICS Code and Description	**Establishments**	**Annual Revenues (000)**	**Annual Payroll (000)**	**Paid Employees**
5311101 - Lessors of Apartment Buildings	51,502	$51,708,553	$5,831,398	257,624
5311109 - Lessors of Dwellings other than Apartment Buildings	10,285	$5,263,795	$748,821	34,781
531311 - Residential property managers	26,223	$19,988,344	$8,193,831	289,870
Total	**88,010**	**$76,960,692**	**$14,774,050**	**582,275**
Source: U.S. Census Bureau 2004b				

2.4.2 Establishment Size and Industry Environment

The U.S. Small Business Administration indicates that to qualify for small business status, a firm in NAICS 531110 must have annual revenues of less than $6 million, while establishments in NAICS 531311 must have revenues of less than $1.5 million (U.S. Small Business Administration, 2004). Although data on the number of firms by revenue bracket is not yet available from the 2002 U.S. Economic Census, average revenues of establishments in these NAICS codes are significantly below the small business designation threshold (Table 2-11).

Table 2-11: Summary Statistics for NAICS 531110, NAICS 5311101 and NAICS 5311109 (Per Establishment)			
NAICS Code and Description	**Average Annual Revenues ($)**	**Average Annual Payroll ($)**	**Paid Employees per Establishment**
5311101 - Lessors of Apartment Buildings	$1,004,011	$113,227	5.0
5311109 - Lessors of dwellings other than apartment buildings	$511,793	$72,807	3.4
531311 - Residential property managers	$762,245	$312,467	11.1
Source: U.S. Census Bureau 2004b			

In 1997, 98.7 percent of the then 51,572 establishments in the Lessors of Residential Buildings and Dwellings sector had annual revenues below $5 million and about 85 percent of the 19,000 establishments in NAICS 531311 had revenues less than $1 million (U.S. Census Bureau 2000a)[11]. Because 2002 data on the number of establishments by revenue bracket is not yet available, 1997 data was used to estimate the percent of establishments in each industry that qualify for small business status. Table 2-12 presents the percent of NAICS 531311 and NAICS 531110 establishments that have revenues below $1 million and $5 million, respectively. The table also presents the percent of industry revenues and employment that can be attributed to these establishments.

[11] Includes establishments open year-round only.

Table 2-12: Small and Large Establishments as Percent of Industry				
NAICS Code	**Description**	**Percent of Establishments by Revenue Bracket**	**Percent of Industry Revenues by Revenue Bracket**	**Percent of Industry Employees by Revenue Bracket**
531311	**Residential Property Managers**			
	Establishments with Revenues < $1 million	85	35	40
	Establishments with Revenues of $1 million+	15	65	60
531110	**Lessors of Residential Buildings and Dwellings**			
	Establishments with Revenues < $5 million	99	82	86
	Establishments with Revenues of $5 million+	1	18	14
Source: U.S. Economic Census 2000a				

Based on 1997 data over 85 percent of NAICS 531311 establishments, and about 99 percent of NAICS 53110 establishments have revenues below the small business threshold defined by SBA. In the Residential Property Manager industry, these establishments contribute only 35 percent of the revenues, and employ only 40 percent of the workforce. The revenue and employment distribution is less skewed in the Lessor of Residential Buildings and Dwellings sector. Small establishments in this industry contribute about 82 percent of the revenues and employ 86 percent of the workforce (U.S. Census Bureau 2000a).

2.4.3 Industry Outlook

The market for lead-safe renovation activities will depend in part on the state of the rental housing market—an increase in rents would provide resources to construct new housing and/or renovate existing housing. According to Harvard University's Joint Center for Housing Studies (JCHS), "rents fell in 9 of the 27 metropolitan areas tracked by the federal government [in 2003]. Nationally, real contract and gross rents barely increased last year." The JCHS indicates that both the weak labor market and increased home ownership contributed to the softening of the rental market (JCHS 2004).

At the same time as rents fell, the nation-wide rental vacancy rate increased from 8.9 percent in 2002 to 9.8 percent in 2003. The vacancy rate was slightly above 10 percent during the first three quarters of 2004 (U.S. Census Bureau 2004e). None-the-less, the JCHS predicts a strengthening of the rental market over the next ten years due to the influx of immigrants and the aging of the "echo baby-boom generation." The strengthening of the market may also come from overall economic growth and a stemming of home ownership growth due to rising interest rates and/or house prices (JCHS 2004).

2.5 Training Providers

Impacts of the RRP regulations will be felt beyond the construction industry. Certified renovators will need accredited training. Both initial and refresher training courses will be required for certified renovators.

2.5.1 Definitions and Industry Characteristics

It is likely that lead-based paint training courses will be provided by establishments categorized as NAICS: Other Technical and Trade Schools. Census defines NAICS 611519 as "establishments primarily engaged in offering job or career vocational or technical courses (except cosmetology and barber training, aviation and flight training, and apprenticeship training). The curriculums offered by

these schools are highly structured and specialized and lead to job-specific certification" and these establishments are believed to currently provide training for lead abatement professionals (U.S. Census Bureau 2004a).

According to the 2002 Economic Census, there are a total of 3,323 establishments in the U.S. classified as Other Technical and Trade Schools (see Table 2-13). On average, each establishment employs 15.3 people. A striking characteristic is that about 19 percent of these establishments are exempt from the Federal Income Tax (FIT). Exempt establishments include non-profit organizations and educational institutions such as colleges or universities (U.S. Census 2004a).

Table 2-13: Number of Establishments in NAICS 611519

Industry	Number of Establishments	Total Number of Employees	Average Number of Employees
NAICS 611519 – Other Technical and Trade Schools	3,323	50,709	15.3
Source: U.S. Census Bureau 2004a			

Table 2-14 summarizes available financial information for establishments categorized under NAICS 611519. These include total revenues for the sector, average annual revenues per establishment, annual payroll for the sector, and payroll as percent of revenue. As Table 2-14 indicates, for Other Technical and Trade schools, annual payroll is equal to about 35 percent of establishment revenues.

Table 2-14: Summary Statistics for NAICS 611519 (By Tax Status)

Industry	Number of Establishments	Annual Sector Revenue (000)	Average Revenue per Establishment (000)	Average Payroll per Establishment (000)	Labor Cost as percent of Revenue
NAICS 611519 – Other Technical and Trade Schools	3,323	$ 4,118,995	$1,240	$429	35
Source: U.S. Census Bureau 2004a					

According to the U.S. Small Business Administration, in order to qualify as a small business, a firm categorized under NAICS 611519 must have annual revenues of $6 million or less (U.S. Small Business Administration 2004).[12] At the time of this report, the 2002 Economic Census did not provide data on the number of firms by revenue bracket. In 1997, however, 97 percent of the then 2,459 establishments classified as Other Technical and Trade Schools had revenues under $5 million (U.S. Census Bureau 2000b). This figure indicates that a large percentage of firms had revenues under the $6 million threshold and thus qualified for small business status. Per-establishment average revenues for 2002 indicate that a large percentage of firms have revenues of less than $6 million per year and would thus qualify for small business status.

2.5.2 Number and Type of Training Establishments

As mentioned in Section 2.5.1, there are over 3,000 establishments in the Other Technical and Trade school industry. It is likely that only a small portion of these establishments are involved in lead abatement training. To help characterize the lead training segment of the training provider industry, a random sample of firms that offer one or more of the courses required for EPA lead abatement

[12] Effective January 28th, 2004.

certification were identified. Since it is likely that these firms will also provide certified renovator training required by the RRP rule, the findings are briefly discussed in this section. The goal was both to collect tuition data for currently offered lead abatement training courses (used to estimate tuition rates for certified renovator training; see Chapter 4) and to learn what types of institutions (private establishments, non-profits, unions, etc.) offer these classes.

The sample consisted of 83 establishments selected from the Lead Listing[13] directory of 194 training providers.[14] Data were collected from company web sites (when available) and/or over the phone. Information was obtained from 68 training providers; a total of 15 providers could not be reached. Seven of the 68 contacted providers no longer offered lead abatement training.

There were five types of training providers in the sample: private for-profit establishments, non-profit establishments, educational institutions, trade unions and public/government training institutions. Trade unions provide tuition-free training to their members. Public/government providers train state employees and workers who qualify for financial assistance through government programs. They do not offer training to the general public.

Table 2-15 summarizes the number of private establishments, educational institutions, non-profits, unions and public/government providers that appeared in the sample. The table also presents the estimated national number of providers that fall into each of these categories. More than a third of lead hazard reduction training providers are private, for-profit establishments. The next largest group of providers are labor unions, followed by educational institutions (colleges and universities). None of the unions, however, are certified to offer the Project Designer course. About 13 percent of certified providers either do not offer training at this time, or have permanently stopped offering lead courses.

More than half of the privately owned, for-profit establishments in the sample (19 out of 35) offer environmental consulting services in addition to training. Thirteen of the 35 privately-owned providers specialize in training and do not offer other services. All of these 13 firms offer both lead and asbestos training courses, as well as, in most cases, OSHA safety, HAZ-MAT and/or mold classes. Although there was not enough information to determine the services provided by the remaining three companies, these findings indicate that lead-based paint training providers generally participate in several lines of business.

[13] The Lead Listing (www.leadlisting.org) website was run for the U.S. Department of Housing and Urban Development's Office of Healthy Homes and Lead Hazard Control that contained a directory of lead service providers. It is no longer in operation (as of late 2004).

[14] The sample included all the establishments on the list that are certified to offer a Project Designer course (42 total), as well as a random sample of 41 establishments that are not certified to offer this class. The data were weighted by the inversed probability of selection into the sample (P=1 for providers that offer a Project Designer course and P=.270 for providers that do not offer this class). It was assumed that there was no non-response bias.

Table 2-15: Estimated Number of Training Providers			
Type of Provider	**Number in Sample**	**National Estimates[a]**	
		Total	**Percent**
Private Providers	35	74	38
Educational Institutions	11	27	14
Non-Profit	4	19	10
Union	9	42	22
Pub/Gov Providers	2	6	3
No Longer Offer Training	7	26	13
Total Companies	68	194	

a. Adjusted for non-response assuming no non-response bias and weighted based on the probability of selection into the sample.

Source: EPA Calculations, see Section 4.4 of Chapter 4

REFERENCES

Farzad, Roben. "A Housing Boom Brings Jobs and, Sometimes, Abuse." *The New York Times* 07 Jul. 2005.

Federal Reserve Bank of New York Staff Reports. Gyourko, Joseph and Joseph Tracy. "Using Home Maintenance and Repairs to Smooth Variable Earnings" May, 2003.

Joint Center for Housing Studies of Harvard University. 1999. *Improving America's Housing.*

Joint Center for Housing Studies of Harvard University. 2000. "Impact of Changes in Household Composition on Home Improvement Decisions." Working Paper W00-6.

Joint Center for Housing Studies of Harvard University. 2001. *Remodeling Homes for Changing Households.*

Joint Center for Housing Studies of Harvard University. 2003. *Measuring the Benefits of Home Remodeling.*

Joint Center for Housing Studies (JCHS) at Harvard University. 2004. *The State of the Nation's Housing*. Available at: http://www.jchs.harvard.edu/publications/markets/son2004.pdf. (January 21, 2004).

Joint Center for Housing Studies of Harvard University. 2005. *The State of the Nations Housing: 2005.*

U.S. Census Bureau. 2001. North American Industry Classification System - Revisions for 2002. Available at: http://www.census.gov/epcd/naics02/ (Accessed 6/30/2005).

U.S. Census Bureau. 2000a. *Establishment and Firm Size (Including Legal Form and Organization). 1997 Economic Census: Subject Series for Real Estate and Rental and Leasing. Subject Series.* EC97F53S-SZ. Available at: http://www.census.gov/prod/ec97/97f53-sz.pdf.

U.S. Census Bureau. 2000b. *Establishment and Firm Size (Including Legal Form and Organization). 1997 Economic Census: Subject Series for Educational Services. Subject Series.* EC97S61S-SZ. Available at: http://www.census.gov/prod/ec97/97s61-sz.pdf.

U.S. Census Bureau. 2004a. *2002 Economic Census: Industry Series* (For NAICS 61). Available at: http://www.census.gov/econ/census02/guide/INDSUMM.HTM. (January 12, 2004).

U.S. Census Bureau. 2004b. "Sector 53: Industry Series: Summary Statistics for the US: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=53&ds_name=EC0200A1&_lang=en&_ts=141736463723 (Downloaded 8/3/2005)

U.S. Census Bureau. 2004e. *Housing Vacancy Survey*. Available at: http://www.census.gov/hhes/www/housing/hvs/annual03/ann03t1.html. (January 21, 2004).

U.S. Census Bureau. 2005a. "Sector 23: Industry Series: Employment Statistics for Establishments by State: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005b. "Sector 23: Industry Series: Detailed Statistics for Establishments: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005c. "Sector 23: Industry Series: Selected Statistics for Establishments by Value of Business Done: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005d. "Sector 23: Industry Series: Value of Construction for Establishments by Type of Construction: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005e. "Sector 23: Construction: Industry Series: Selected Statistics for Establishments by Specialization in Types of Construction: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005f. 2002 Economic Census: Industry Series: Residential Remodelers EC02-23I-236118 (RV). Available at: http://www.census.gov/prod/ec02/ec0223i236118.pdf (Accessed 8/3/2005).

U.S. Census Bureau. 2005i. 2002 Economic Census: Construction: By Industry. Available at: http://www.census.gov/econ/census02/data/us/US000_23.HTM (Accessed 8/3/2005).

U.S. Census Bureau. 2005j. "Number of Establishments: General Definition." Census Data Information. American Fact Finder. Available at: http://factfinder.census.gov/servlet/MetadataBrowserServlet?type=dataItem&id=ESTAB&dataset=EC0223I02&dsspName=ECN_2002&_lang=en (Accessed 8/3/2005).

U.S. Department of Commerce. 2004a. *Current Construction Reports: Expenditures for Residential Improvements and Repairs, 2nd Quarter.*

U.S. Department of Commerce. 2004b. *Current Construction Reports: Value of Construction Put in Place.*

U.S. Department of Commerce. 2005. *Real Gross Domestic Product, 3 Decimal*. GDP C96. Last updated: June 29, 2005.

U.S. Small Business Administration. 2004. "Small Business Size Standards matched to North American Industry Classification System." Available at: http://www.sba.gov/size/sizetable2002.html. (January 21, 2004).

U.S. Small Business Administration. 2005. "Non-Employer Statistics." *Firm Size Data*. Available at: http://www.sba.gov/advo/research/data.html. (Downloaded 8/3/2005).

3. Problem Definition and Regulatory Options

This chapter begins by characterizing the lead contamination problem to be addressed under the RRP regulations. The various sources of exposure, along with related adverse health effects, are presented in Section 3.1. This is followed by a discussion of how the market failures of incomplete information and external costs have resulted in inefficient levels of lead containment and control in renovation activities. Section 3.2 summarizes existing federal, state and local regulations and argues that additional federal regulation is a reasonable solution for these market failures. Alternative regulatory options are presented in Section 3.3.

3.1 Lead Contamination Problem

Despite recent reductions in air, water, and food contamination, important sources of lead exposure remain, due largely to the widespread presence of lead-based paint in home environments. Exposure to lead results in increased blood lead levels associated with various adverse health effects, including reductions in IQ and other negative cognitive effects, particularly in children. In addition, exposure to lead can result in a variety of adverse health effects in adults.

3.1.1 Exposure Sources

As described in Appendix 5A, lead may cause adverse health effects in any individual, exposed at any stage of life (*in utero* through adulthood) (U.S. EPA 2005c). However, young children are particularly susceptible to lead hazards because their central nervous systems are rapidly developing, and because their behavior is likely to result in greater exposure than older groups experience. The benefit analysis presented in Chapter 5 includes benefits of protecting both adult and child occupants of renovated housing units from the resulting lead hazards.

Currently the most significant high-dose source of lead exposure in children under school age is lead-based paint. Through the 1940's, paint manufacturers used lead as a primary ingredient in many oil-based interior and exterior house paints. During the 1950's and 1960's, the usage gradually decreased as new paints were developed, and in 1978 the Consumer Product Safety Commission (CPSC) ruled that paint used for residences, toys, furniture, and public areas must not contain more than 0.06% lead by weight. Nevertheless, about 50 percent of housing units built before 1980 still contain lead-based paint (U.S. HUD 2000). Children's exposure to lead from lead-based paint is likely to be high when the paint is in a deteriorated state or is found on accessible, chewable, impact, or friction surfaces, making the lead paint available to children who ingest paint chips. This "pica" behavior appears to be rare, but is the likely cause of a many of the highest blood lead levels observed in children. Renovation activities can create lead-based paint hazards for children by making paint chips more accessible for ingestion. These hazards can occur both within and outside the housing unit being renovated.

In addition to being a source of direct exposure, lead-based paint can be the source of lead contamination in soil and dust. Children are exposed to lead from soil or dust in their homes as a result of typical hand-to-mouth activities. Lead-contaminated dust and soil are thought to be the major pathway through which most young children are exposed to lead from lead-based paint hazards. Renovation activities increase the level of lead dust in the housing unit and potentially in the soil, thereby increasing the risk of lead ingestion in young children.

Occupational exposure is the primary exposure pathway to lead for adults. Several occupations put adults in direct contact with lead including: plumbing, lead mining, auto repair, glass manufacturing, shipbuilding, printing, lead smelting and refining, battery manufacturing, and bridge reconstruction work. Other common exposure pathways for teenagers and adults include gardening, housework, drinking water and certain hobbies such as creating objects from stained-glass and making pottery.

Individuals (children, teenagers and adults) are also exposed to a variety of other lead sources, some of which are localized in nature. Airborne lead is present in emissions from lead smelters, battery manufacturing plants, and solid waste incinerators. The phase-out of leaded gasoline has substantially reduced airborne lead. Drinking water may become contaminated with lead after it leaves the treatment plant. Although lead levels in drinking water generally do not have a statistically significant effect on blood-lead concentrations as a result of the 1986 Safe Drinking Water Act, water is still considered an important localized exposure source where lead solder and/or brass plumbing fixtures are present because of the high absorption rate of lead in water. Lead exposure through food ingestion has declined greatly in importance due to the phase-out of lead-soldered food cans and public education. With these improvements in exposure from air, water, and food, lead-based paint remains as the largest wide-spread source of lead exposure.

3.1.2 Health Effects of Lead Exposure

Most studies of the health effects of lead use body-lead burden as a biomarker for lead exposure. Although blood lead level reflects a mixture of recent and past exposure, it has the advantage of being easily and inexpensively measured. Other measures of body-lead burden include lead in bones, teeth, and hair. Each of these options, however, has disadvantages as measures of lead in the body, including poor sensitivity and external surface contamination problems.

Increased blood lead levels are associated with an assortment of deleterious health effects. See Appendix 5A for a discussion of the adverse health effects resulting from lead exposure.

EPA exposure data (EPA 1997) indicate that renovation activities potentially increase both short-term and long-term lead exposure levels. Lead concentrations are greatest in the area where the renovation work is performed, but lead does settle into other areas of the housing unit and potentially the surrounding housing units, causing longer-term exposure. The study found that, with the exception of carpet removal and drilling into plaster, all renovation activities examined deposited significant amounts of lead onto the floors in the area where the work was being performed, ranging from 480 micrograms per square foot for sawing to 15,500 micrograms per square foot for paint removal. This lead may be ingested or inhaled by occupants if proper containment and clean-up practices are not used. The study found that sweeping and shop-vacuum clean-up, considered to be standard practice in the industry, reduced the total amount of lead available to occupants. However, as the distance from the activity increased, the cleanup left more of the lead behind so that lead hazards remained following cleanup. These findings demonstrate that these practices do not adequately reduce risks from lead dust generated by renovation activities. Lead dust settled in carpeted areas or in soil is the most difficult to remove with simple broom and vacuum clean-up and thereby creates the longest lasting exposure pathway for household occupants.

3.2 Justification for Federal Regulations of Lead Exposure during Renovation

Executive Order 12866 calls for three findings to justify the need for a federal regulation. First, there should be a description of the market failure that can be corrected or other social purpose that can be met through regulation. Second, there should be n explanation of why the regulation should be carried out at the federal level. Finally, there should be a discussion of why current regulatory initiatives are not sufficient to correct the market failure.

3.2.1 Market Failure

From an economic perspective, a necessary condition for regulations is the existence of an inefficiency in the allocation of resources. This inefficiency is commonly labeled a market failure since the market is the mechanism assumed to make efficient resource allocations possible. A market failure can come from one or more of several sources. These include poorly defined property rights (such as negative externalities, common property resources, and public goods); imperfect markets for trading property rights (because of a lack of perfect information or of contingent markets; monopoly power; distortionary taxes and subsidies and other inappropriate government regulations); and the divergence of private and social discount rates.

The occurrence of any of these conditions justifies further inquiry into the need for government regulation to reduce inefficiencies in the allocation of society's resources. This section considers whether any of these conditions are linked to excess exposures from lead contamination resulting from renovation in target housing. If so, understanding the nature of the inefficiencies involved facilitates the design of more effective regulations. The specific regulatory approach considered here involves the promulgation of certification, training and accreditation requirements for firms that perform renovations that disturb lead-based paint in certain types of housing, as well as the establishment of containment, clean-up and cleaning verification practices to be used during regulated renovation projects.

Economic efficiency suggests that "lead-safe" renovation will occur as long as the property owners' willingness-to-pay for reduced lead risks exceeds the cost of reducing these risks. If the property owners are aware of the risks and are aware of the availability and costs of reducing these risks, then arguably they will be able to accurately trade off risk and cost without the aid of government regulation. However, there are two arguments for why individual households may not trade off risk and cost efficiently.

Incomplete/Incorrect Information

The strongest case for the existence of a market failure can be built on the lack of reliable information. Correct information is an important prerequisite to the demand for containment and clean-up practices that reduce lead exposure during renovation projects. In deciding whether lead-safe work practices or well-trained contractors are worth the extra cost, the property owner has to know whether there is lead in the work area, what risks are implied by having renovation done in areas with lead-based paint, the significance of these risks, what can be accomplished in reducing those risks through specific containment and clean-up practices, and how much these practices cost.

Misinformation can lead to inefficient outcomes. Without knowing there is a lead problem, or how renovation might create lead hazards, the owner will have too low a demand for proper work practices and may be unwilling to pay additional costs for contractors who voluntarily abide by these containment and clean-up standards. Furthermore, a great deal of uncertainty can exist if the consumer is unsure about the quality of lead-safe renovation services being purchased and their likely benefits. If consumers do not

have any guarantee that the contractor is qualified to identify and control lead-based paint hazards, his/her demand for these services is likely to be lower than in the presence of such a guarantee. On the supply side, contractors may be unaware of the risks they are creating and/or the methods they can use to reduce risks of lead exposure.

External Costs and Public-Good Characteristics of Lead-Safe Renovation

Another major cause of market failure stems from the external cost of poorly performed renovation projects in housing units with lead-based paint. An efficient outcome is achieved when the marginal willingness-to-pay for a service is equivalent to the marginal cost of providing that service. Because the use of lead-safe work practices is likely to benefit not only the consumer of the renovation (the head of a household, for example) but his/her children, neighbors and/or tenants, lead-safe renovation services are, in part, a public good. As such, even with perfect information, the maximum amount that the individual consumer of the renovation would be willing to pay for lead-safe work is likely to be lower than the total amount that that particular consumer plus the other beneficiaries (including children, neighbors, etc.) would be willing-to-pay for the service. Children, for example, cannot testify to their willingness-to-pay for risk reduction and thus rely on their parents' or the property owners' willingness-to-pay. Similarly, neighboring housing units may also experience an increased exposure to lead and may be willing-to-pay to reduce or eliminate this exposure but may not be consulted by the property owner making the decision.

A typical external cost market failure example is that of a landlord's decision to hire contractors to perform renovation in his/her rental units. Contractors that provide lead-safe renovation services are likely to charge more for their work than establishments that do not use lead-safe practices. Lead-safe work practices may also increase the duration of the project because contractors need to take additional steps to prevent the spread of lead dust. Since a landlord pays for the renovation, but not necessarily for the consequences of a tenant's lead exposure, he is faced with powerful short-term incentives (lower cost and a faster turn-around) to hire a contractor that does not use lead-safe work practices. Because the tenant, and not the landlord (the decision maker in this situation) pays for the consequences lead exposure, this scenario is likely to result in a socially inefficient outcome of too little lead-safe renovation services provided.

A similar external cost problem also leads to inefficiencies on the supply side of this market. Renovators that use lead-safe work practices incur higher costs than other contractors and contractors are faced with the incentives to keep their costs as low as possible. Similar to landlords, contractors may not incur the costs of consumer lead exposure resulting from unsafe renovation work. Because the legal/liability system is not perfect, the landlord's and contractor's financial responsibilities in terms of costs related to tenant/customer lead exposure are not clear and consistently enforced. This, in turn, may result in an inefficient outcome of either too much or too little lead-safe renovation services, depending on the risk-averseness of the landlord or contractor and his/her understanding of the risks and responsibilities involved. Given the other factors confronting landlords and contractors, there is likely to be too little lead-safe services.

Impacts of the Regulation on Demand for Lead-Safe Renovation Services

The general market failure relationships discussed above are illustrated in Exhibit 3-1 as three markets for close substitutes. A consumer's demand for renovation services is a function of the price of these services, the characteristics of the services (e.g., quality, lead safety etc.), and the characteristics of consumers. Assume that all renovation services are identical except that some are performed using lead-safe containment and clean-up practices and some are not. Assume for illustration purposes that there is only one consumer and one supplier in the market. Of the services that are performed not using these

lead-safe practices, some are done by the supplier, while others are do-it-yourself projects performed by the consumer. Figure (a) represents the market for lead-safe renovation projects, Figure (b) represents the professional market for "standard or non-lead-safe practice" renovation, and Figure (c) represents the do-it-yourself market for "standard practice" renovation. In each market, S_0 represents the supply of renovation services and D_0 represents the demand for renovation services in the baseline with incomplete information. Note that, moving from left to right, each supply curve is lower than the prior one, corresponding to the lower cost in terms of materials and time combined. The area under the demand curve in each market represents the consumer's willingness-to-pay for renovation services.

Exhibit 3-1: Impact of Proposed Regulation on Markets for Renovation/Remodeling Services

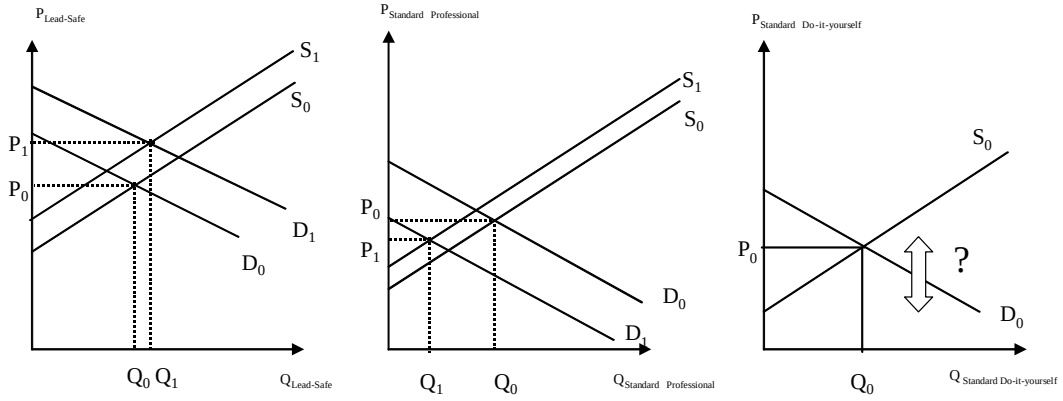


Figure (a) Market with Lead-Safe Work Practices

Figure (b) Professional Market with "Standard" Work Practices

Figure (c) Do-it-Yourself Market with "Standard" Work Practices

The proposed regulatory options alter the nature of these three markets by providing information to the consumer and contractor about the risk associated with lead-based paint renovation activities and by requiring lead-safe containment and clean-up practices for professional projects. EPA's §406(b) regulations already require that compensated renovators distribute a lead awareness pamphlet to owners and occupants of most pre-1978 target housing before beginning renovations. The proposed RRP rule builds on §406(b) by providing additional information to the consumer that will help to establish a more structured market for lead-safe renovation services. As discussed earlier in this section, prior to the rule, consumers of renovation services had no guarantee that a contractor who claimed to provide lead-safe renovation services would actually perform the project in a lead-safe manner. The implementation of work practice standards and training/certification requirements is likely to increase consumer confidence in the quality of the work provided by certified contractors, increasing their willingness-to-pay for these services.

EPA's targeted outreach program is also likely to increase demand for lead-safe renovation services by raising consumer awareness about the dangers of unsafe work. Although contractors that currently provide well-trained staff and perform lead-safe work practices are expected to find it in their vested interest to provide the kinds of information cited above, this possibility has not closed the information gaps for the public. One impediment may be public uncertainty about the reliability of information that contractors themselves provide. Their information may be considered unreliable because they are not fully competent to assess the lead contamination and what needs to be done, because the businesses are subject to moral hazard (which occurs, for example, when a firm tells a homeowner that there is a lead problem that warrants certain practices at an additional cost), or both. Since many property owners may lack easy access to independent sources of information to motivate their decisions, doing nothing may be the likely response. When provided with reliable information, however, consumers are likely to avoid the dangers posed by unsafe renovation and hire a qualified contractor to perform the work in a lead-safe manner.

The increased demand discussed above is shown by an upward shift of the demand curve in Figure (a) from D_0 to D_1 and an associated increase in price. Simultaneously, the demand for "standard practice"

renovation services decreases with an associated decrease in price. Given scarce resources for enforcement, it is expected that some "standard practice" professional work will continue, even in homes where there is the potential for lead exposure. The effect of the regulation on the do-it-yourself market is ambiguous. Some households that might have hired a professional to perform "standard practice" renovation work in the baseline may decide to perform this work themselves rather than pay the additional costs for lead-safe work practices. This would increase demand in Figure (c). However, some households that would have performed do-it-yourself "standard practice" renovation in the baseline may decide to either forgo renovation altogether or hire a lead-safe professional rather than incur the risk of lead exposure, thus reducing do-it-yourself demand.

Impacts of the Regulation on the Supply of Lead-Safe Renovation Services

The proposed regulation will increase both the costs of supplying lead-safe services and standard services. In Figures (a) and (b), S_1 represents the supply of services with the proposed regulations. A contractor that already uses lead-safe practices will also incur the costs of training, certification and cleaning verification. A contractor that continues to provide standard (not lead-safe) renovation services will have higher costs of operation due to potential enforcement actions, and potentially higher liability. The relative size of the shifts in the two submarkets will affect the final changes in quantity and price of both lead-safe and standard renovation services.

The net impact on the quantity of renovation projects performed is also ambiguous. If all households are willing to pay the full amount for lead-safe work practices, then the total quantity performed across all three markets will remain constant but the average price will rise. However, if some households are not willing to pay for the risk reduction they may chose to forgo renovation services altogether, resulting in a net decline in renovation services provided after regulation.[1]

Conclusions

As demonstrated in this review, due to the lack of perfect information and the existence of externalities, the quantity of lead-safe RRP services currently provided is likely to be inefficiently low. The results of the market failures discussed in this review are significant in both qualitative and quantitative terms. Childhood lead exposure continues to be a major public health problem among young children in the United States. During 1999 through 2002, approximately 310,000 children aged 1 to 5 years , had blood-lead levels greater than 10 μg/dL, despite the removal of lead from gasoline and the banning of lead-based paint in 1978 (CDC 2005). Most children with blood-lead levels in excess of CDC's current level of concern have been exposed to lead in non-intact paint, interior settled dust, and dust and soil in and around deteriorating older housing. According to the Center for Disease Control (CDC), "renovation and remodeling activities that disturb lead-based paint can create substantial amounts of lead dust in the home; such dust can then be inhaled or ingested by children" (CDC 1997). An insufficient number of lead-based paint interventions have occurred to remove the dangers posed by uncontrolled renovation activities; renovation activity thus continues to pose a significant risk of lead exposure.

3.2.2 Justification for Regulation at the Federal Level

In the Residential Lead-Based Hazard Reduction Act of 1992 (Title X), the United States Congress stated that the elimination of lead-based paint hazards was a national goal. Congress found that the Federal

[1] The amount by which price and quantity change in each of these markets is a function of both the amount by which the supply and/or demand functions shift and the relative elasticities of the two functions. See Appendix 3A for a discussion of how these factors affect the price of renovation services and the quantity provided by the market. Appendix 3B presents price elasticity estimates for construction and RRP.

Government must take a leadership role in building the required infrastructure, including an informed public, State and local delivery systems, certified inspectors, contractors, and laboratories, and trained workers (§1002(8)). The proposed rule under the authority of §402(c) helps the Federal Government achieve these objectives by establishing training, certification and accreditation requirements plus containment and clean-up standards for renovation work.

As written by Congress, various sections of Title X address different parts of the imperfect information problem. By setting hazard standards, §403 helps consumers identify situations that subject them to risk. Without this information, consumers are more likely to not value an intervention properly. They may either underestimate or overestimate its value. Hazard standards provide necessary, although not sufficient, information for making an informed choice. In addition, the consumer needs information on the cost and effectiveness of the various lead hazard control options available (e.g. removal of lead-based paint or lead contaminated soil, encapsulation of lead-based paint, dust clean-up). This information need is addressed by the RRP rule, which assures that trained and certified personnel are qualified to identify and control lead-based paint hazards, including hazards resulting from renovation activities. In addition, §1018 and §406 provide information about lead-based paint hazards to the population in general and in particular at the time of property transactions and prior to compensated renovations. Finally, the RRP rule reduces transaction costs by assuring consumers that the information provided to them about their particular situation will be accurate and complete. The RRP rule addresses a special case – renovation activities that may disturb lead-based paint and thus expose the workers, occupants and potentially their neighbors to lead.

Lead hazards are found in residences in all parts of the nation, and renovation activities which disturb lead-based paint will likely create lead hazards. Federal regulations can promote cost savings by encouraging coordination among jurisdictions with resulting economies of scale. For example, training and certification costs are reduced where states share the same requirements and provide for certification reciprocity. Federal regulations also promote partnerships in developing the most cost-effective ways to address lead-paint hazards. Establishing training, certification and accreditation requirements, as well as containment and clean-up standards, at the federal level does not preempt states from addressing needs peculiar to their situation. States are granted the power to administer and implement the federal guidelines and are encouraged to do so. It is the Agency's belief that states and localities are in a better position to determine how the hazard standards are used and how to adapt their implementation to local circumstances. In addition, states have the option of imposing requirements that are more stringent than the federal procedures.

3.2.3 Regulatory Background

This section outlines the extensive history of lead-based paint regulations at the federal, state and local levels and shows that current regulations are not sufficient to correct the market failure outlined in Section 3.2.1. While these regulations cover a wide-range of lead-related issues, no single regulation, nor combination of regulations, adequately closes the information gap for lead exposure from renovation projects.

The Federal Lead-based Paint Program.

Title X and the Federal goal

Primarily in response to the persistent health threat posed by lead-based paint, in 1992 Congress enacted Title X. Congress found that low-level lead poisoning was widespread among American children, affecting, at that time, as many as 3,000,000 children under age 6; that the ingestion of household dust containing lead from deteriorating or abraded lead-based paint was the most common cause of lead poisoning in children; and that the health and development of children living in as many as 3,800,000 American homes was endangered by chipping or peeling lead paint, or excessive amounts of lead-contaminated dust in their homes. Congress determined that the prior Federal response to this crisis was insufficient and established, in Title X, a national goal of eliminating lead-based paint hazards in housing as expeditiously as possible. Congress decided that the Federal government would take a leadership role in building the infrastructure necessary to achieve this goal.

The stated purposes of Title X are:

- To develop a national strategy to build the infrastructure necessary to eliminate lead-based paint hazards in all housing as expeditiously as possible.
- To reorient the national approach to the presence of lead-based paint in housing to implement, on a priority basis, a broad program to evaluate and reduce lead-based paint hazards in the Nation's housing stock.
- To encourage effective action to prevent childhood lead poisoning by establishing a workable framework for lead-based paint hazard evaluation and reduction and by ending the current confusion over reasonable standards of care.
- To ensure that the existence of lead-based paint hazards is taken into account in the development of Government housing policies and in the sale, rental, and renovation of homes and apartments.
- To mobilize national resources expeditiously, through a partnership among all levels of government and the private sector, to develop the most promising, cost-effective methods for evaluating and reducing lead-based paint hazards.
- To reduce the threat of childhood lead poisoning in housing owned, assisted, or transferred by the Federal Government.
- To educate the public concerning the hazards and sources of lead-based paint poisoning and steps to reduce and eliminate such hazards (Residential Lead-Based Paint Hazard Reduction Act of 1992).

To accomplish this ambitious goal, a number of agencies were assigned specific responsibilities under Title X, including HUD, CDC, OSHA, the National Institute for Occupational Safety and Health (NIOSH), and EPA.

The elimination of lead-based paint hazards in the nation's housing remains an important goal for the Federal government. In 1997, President Clinton created the President's Task Force on Environmental Health Risks and Safety Risks to Children in response to increased awareness that children face disproportionate risks from environmental health and safety hazards. Co-chaired by the Secretary of HHS and the Administrator of the EPA, the Task Force consisted of representatives from 16 Federal departments and agencies. The Task Force set a Federal goal of eliminating childhood lead poisoning by the year 2010. This proposed rule is an important component of the Federal strategy for achieving this goal. In October 2001, President Bush extended the work of the Task Force for an additional 18 months beyond its original charter (President's Task Force on Environmental Health Risks and Safety Risks to Children 2000). Reducing lead poisoning in children was the Task Force's top priority.

Childhood lead exposure continues to be a major public health problem among young children in the United States. Most children with blood lead levels in excess of CDC's current level of concern have been exposed to lead in non-intact paint, interior settled dust, and dust and soil in and around deteriorating older housing (CDC 2004). The nature and extent of the problems associated with residential lead-based paint have been thoroughly investigated. Approximately 40% of all U.S. housing units (about 38 million homes) have some lead-based paint. Use of leadsafe work practices during renovation can advance the goal of primary prevention of lead poisoning (CDC 2004).

EPA's lead-based paint program

Under Title X, EPA is directed to take actions that can be divided into 4 key categories:

- Establishing a training and certification program for persons engaged in lead-based paint activities, accrediting training providers, establishing work practice standards for the safe, reliable, and effective identification and elimination of lead-based paint hazards, and developing a program to address exposure to lead-based paint hazards from renovation and remodeling activities.
- Ensuring that, for most housing constructed before 1978, lead-based paint information flows from sellers to purchasers, from landlords to tenants, and from renovators to owners and occupants.
- Establishing standards for identifying dangerous levels of lead in paint, dust and soil.
- Providing information on lead hazards to the public, including steps that people can take to protect themselves and their families from lead-based paint hazards. Each of these categories is discussed in more detail in the following sections.

a. Training and certification, accreditation, and work practice standards. Title X added a new title to TSCA entitled ''Title IV Lead Exposure Reduction.'' Most of EPA's responsibilities for addressing lead-based paint hazards can be found in this title, with section 402 being one source of the rulemaking authority to carry out these responsibilities. TSCA section 402(a) directs EPA to promulgate regulations covering lead-based paint activities to ensure persons performing these activities are properly trained, that training programs are accredited, and that contractors performing these activities are certified. These regulations must contain standards for performing lead-based paint activities, taking into account reliability, effectiveness, and safety.

On August 29, 1996, EPA promulgated final regulations under TSCA section 402(a) governing lead-based paint inspections, lead hazard screens, risk assessments, and abatements in target housing (U.S. EPA 1996). TSCA section 401 defines ''target housing'' as any housing constructed prior to 1978, except housing for the elderly or persons with disabilities (unless any child who is less than 6 years of age resides or is expected to reside in such housing for the elderly or persons with disabilities) or any 0-

bedroom dwelling. These regulations also apply to ''child-occupied facilities,'' which are defined at 40 CFR 745.223 as buildings constructed before 1978, or portions of such buildings, where children under age 6 are regularly present. TSCA section 402 defines lead-based paint activities in target housing as inspections, risk assessments and abatements. The 1996 regulations cover lead-based paint activities in target housing and child-occupied facilities, along with limited screening activities called lead hazard screens. The regulations also established an accreditation program for training providers and a certification program for individuals and firms performing these activities. Training providers who wish to provide lead-based paint training for the purposes of the Federal lead-based paint program must be accredited by EPA. Implementing regulations at 40 CFR 745.225 describe in detail the requirements for each course of study, how training programs must be operated, and the process for obtaining accreditation. Training programs must have a training manager with experience or education in a construction or environmental field, and a principal instructor with experience or education in a related field and education or experience in teaching adults. Training programs must also have adequate facilities and equipment for delivering the training. To become accredited, an application for accreditation must be submitted to EPA on behalf of the training program. The application must either include the course materials and syllabus, or a statement that EPA model materials or materials approved by an authorized State or Tribe will be used. The application must also include a description of the facilities and equipment that will be used, a copy of the test blueprint for each course, a description of the activities and procedures that will be used during the hands-on skills portion of each course, a copy of the quality control plan, and the correct amount of fees. If EPA finds that the program meets the regulatory requirements, it will accredit the training program for 4 years. To maintain accreditation, the training program must submit an application and the correct amount of fees every 4 years.

Individuals and firms that perform inspections, lead hazard screens, risk assessments, or abatements in target housing or child-occupied facilities must be certified. Certification requirements and the process for becoming certified are described in 40 CFR 745.226. A firm that wishes to become certified must submit an application, along with the correct amount of fees, attesting that it will use only certified individuals to perform lead-based paint activities and that it will follow the work practice standards in 40 CFR 745.227. An individual who wishes to become certified must take an accredited training course in at least one of the certified disciplines: Inspector, risk assessor, project designer, abatement worker, and abatement supervisor. The risk assessor, project designer, and abatement supervisor disciplines have additional requirements for education or experience in a construction or environmental field. The inspector, risk assessor, and abatement supervisor disciplines also require the applicant to pass a certification examination administered by a third party.

The regulations at 40 CFR part 745, subpart L, also contain work practice standards for performing inspections, lead hazard screens, risk assessments and abatements in target housing and child-occupied facilities. The regulations contain specific requirements for conducting paint sampling during an inspection and specify information that must be gathered and samples that must be taken as part of a lead hazard screen or risk assessment. The requirements for abatements are also set forth in the regulations. When conducting abatements, an occupant protection plan must be prepared by a certified supervisor or project designer; certain work practices such as open-flame burning, machine sanding or abrasive blasting without high-efficiency exhaust control, dry scraping, and heat guns at high settings are prohibited; and a visual inspection and dust clearance sampling must be performed after the abatement is finished to ensure that the area is ready for re-occupancy. Any samples collected during any of these regulated lead-based paint activities must be analyzed by a laboratory recognized by EPA as being capable of analyzing paint chips, dust, and soil for lead. Requirements for inspection, lead hazard screen, risk assessment or abatement reports are also described in this section.

Recognizing the importance of States and Territories in achieving the goal of eliminating lead-based paint hazards in housing, Congress specifically directed EPA to establish a model State program and a process for authorizing States to operate such programs in lieu of the Federal program. Concurrently with the subpart L rulemaking in 1996, EPA codified, at 40 CFR part 745, subpart Q, a model training and certification program and a process for enabling States, Territories, and Tribes to apply for authorization to administer their own lead-based paint activity programs. Providing Indian Tribes with this opportunity is consistent with EPA's Policy for the Administration of Environmental Programs on Indian Reservations (U.S. EPA 1984). EPA also provides grants under TSCA section 404 to States, Territories, and Tribes to assist them in developing and administering these programs, as well as programs implementing TSCA section 406(b), discussed in this Unit. On June 9, 1999, the subpart L regulations were amended to include a fee schedule for training programs seeking EPA accreditation and for individuals and firms seeking EPA certification (U.S. EPA 1999). These fees were established as directed by TSCA section 402(a)(3), which requires EPA to recover the cost of administering and enforcing the lead-based paint activities requirements in unauthorized States. The most recent amendment to the subpart L regulations occurred on April 8, 2004, when notification requirements were added to help EPA monitor compliance with the training and certification provisions and the abatement work practice standards (U.S. EPA 2004a).

As of December 2005, 44 programs comprised of 39 States, 3 Tribes, Puerto Rico, and the District of Columbia were authorized to administer lead-based paint activity programs. In the remaining jurisdictions, where EPA is responsible for administering the subpart L regulations, there were approximately 55 accredited training course providers, 1,300 certified firms, 500 certified inspectors, 1,400 certified risk assessors, 60 certified project designers, 1,000 certified abatement supervisors, and 2,800 certified abatement workers. EPA believes that, in most areas of the country, there is an adequate supply of accredited courses and certified firms and individuals available to meet the demand for leadbased paint services. This is a significant part of the national infrastructure necessary to achieve the goal of eliminating lead-based paint hazards in housing.

In addition, Congress directed EPA, in TSCA section 405, to establish protocols, criteria, and minimum performance standards for analysis of lead in paint, dust, and soil. TSCA section 405 further directed EPA, in consultation with HHS, to develop a program to certify qualified laboratories. The National Lead Laboratory Accreditation Program (NLLAP) provides the public with a list of laboratories that have met EPA requirements and demonstrated the capability to accurately analyze paint chip, dust, or soil samples for lead. All laboratories recognized by NLLAP must pass on-site audits conducted by one of the two accrediting organizations currently participating in NLLAP, the American Industrial Hygiene Association (AIHA), and the American Association for Laboratory Accreditation. Recognized laboratories must also perform successfully on a continuing basis in the Environmental Lead Proficiency Analytical Testing (ELPAT) Program established by NIOSH, AIHA, and EPA.

b. Lead-based paint information for purchasers, renters, owners, and occupants of target housing. Another of EPA's responsibilities under Title X is to require that purchasers and tenants of target housing and occupants of target housing undergoing renovation are provided information on lead-based paint and lead-based paint hazards. As directed by TSCA section 406(a), CPSC, HUD, and EPA, in consultation with CDC, jointly developed a lead hazard information pamphlet entitled ''Protect Your Family From Lead in Your Home'' (''PYF'') (U.S. EPA et al 2003). The availability of this pamphlet was announced on August 1, 1995 (U.S. EPA 1995). This pamphlet was designed to be distributed as part of the disclosure requirements of section 1018 of Title X and TSCA section 406(b), to provide home purchasers,

renters, owners, and occupants with the information necessary to allow them to make informed choices when selecting housing to buy or rent, or deciding on home renovation projects. The pamphlet contains information on the health effects of lead, how exposure can occur, and steps that can be taken to reduce or eliminate the risk of exposure during various activities in the home.

Pursuant to the authority provided in section 1018 of Title X, on March 6, 1996, HUD and EPA jointly promulgated regulations requiring persons who are selling or leasing target housing to provide the PYF pamphlet and information on known lead-based paint and lead-based paint hazards in the housing to purchasers and renters (HUD and U.S. EPA 1996). These joint regulations, codified at 24 CFR part 35, subpart A, and 40 CFR part 745, subpart F, describe in detail the information that must be provided before the contract or lease is signed and require that sellers, landlords, and agents document compliance with the disclosure requirements in the contract to sell or lease the property. Title X does not provide for these requirements to be administered by States or Tribes in lieu of the Federal regulations. Therefore, HUD and EPA are responsible for administering and enforcing these disclosure obligations.

TSCA section 406(b) directs EPA to promulgate regulations requiring persons who perform home renovations for compensation to provide a lead hazard information pamphlet to owners and occupants of target housing being renovated. These regulations, promulgated on June 1, 1998, are codified at 40 CFR part 745, subpart E (U.S. EPA 1998). The term ‘‘renovation’’ is defined, at 40 CFR 745.83, as the modification of any existing structure, or portion of a structure, that results in the disturbance of painted surfaces. Lead-based paint abatement projects are specifically excluded, as are small projects that disturb 2 square feet (ft2) or less of painted surfaces, emergency projects, and renovations affecting components that have been found to be free of lead-based paint, as that term is defined in the regulations, by a certified inspector or risk assessor. Like the regulations regarding disclosure during sales or leases, these regulations require the renovation firm to document compliance with the requirement to provide the owner and the occupant with the PYF pamphlet. One important difference from the disclosure requirements in section 1018 of Title X is that TSCA section 404 allows States to apply for, and receive authorization to administer, the TSCA section 406(b) requirements. Two States are currently authorized to operate this program.

c. Standards for lead in paint, dust, and soil. Another responsibility assigned to EPA by Title X is the development of standards for identifying dangerous levels of lead in paint, dust and soil. These standards, promulgated pursuant to TSCA section 403 on January 5, 2001 and codified at 40 CFR part 745, subpart D, provide various Federal agencies, including HUD, and State, local and Tribal governments with uniform benchmarks on which to base decisions on remedial actions to safeguard children and the public from lead-based paint hazards (U.S. EPA 2001b). These standards also allow certified inspectors and risk assessors to easily determine whether a particular situation presents a lead-based paint hazard and whether to recommend remedial actions such as lead-based paint abatement, cleaning of dust, or removal of soil. The standards define lead-based paint hazards in target housing and child-occupied facilities as paint-lead, dust-lead, and soil-lead hazards. A paint-lead hazard is defined as any damaged or deteriorated lead-based paint, any chewable lead-based painted surface with evidence of teeth marks, or any lead-based paint on a friction surface if lead dust levels underneath the friction surface exceed the dust-lead hazard standards. A dust-lead hazard is surface dust that contains a mass-per-area concentration of lead equal to or exceeding 40 micrograms per square foot (µg/ft2) on floors or 250 µg/ft2 on interior window sills based on wipe samples. A soil-lead hazard is bare soil that contains total lead equal to or exceeding 400 parts per million (µg/ g) in a play area or average of 1,200 parts per million of bare soil in the rest of the yard based on soil samples.

d. Public outreach and education. Among other things, TSCA section 405(d) directs EPA, along with the Agency for Toxic Substances and Disease Registry (ATSDR) and HUD, to sponsor public education and outreach activities to increase public awareness of the health effects of lead, the potential for exposures, the importance of screening children for elevated blood lead levels, and measures that can be taken to reduce or eliminate lead-based paint hazards. Accordingly, EPA has worked to provide the public with information and increase public awareness of such matters. To date, these activities have included web site management, development of public outreach strategies, development of partnership agreements, distribution of materials, participation in national conferences and exhibits, and developing hazard information documents (and other media, such as videos), as necessary to implement Title X. EPA has collaborated closely with other Federal agencies and its State, Tribal, and local government partners in developing outreach campaigns targeted for the Women, Infants and Children (WIC) program, Little League Baseball, and Spanish-speaking populations. Recently, EPA worked with the National Head Start Association to develop a lead poisoning prevention campaign entitled ‘‘Give Your Child a Chance of a Lifetime.’’ The campaign consisted of a number of lead awareness documents, including a brochure for parents, fact sheets for Head Start staff, and a curriculum for Head Start teachers. Lead awareness outreach materials were provided to Head Start Centers in New York, Chicago, Philadelphia, Houston, and Los Angeles. The material was also distributed at the National Head Start Association Training Conferences. EPA has also been involved in developing model tool kits of various educational tools to provide to partners, such as slogans and graphic materials for public buses, trains, and mass transit stations.

EPA has used its authority under TSCA section 10 to award grants to Tribes to support Tribal educational outreach and to conduct baseline assessments of Tribal children’s existing and potential exposure to lead. In fiscal year 2005, EPA began a new targeted grant program aimed at reducing the incidence of childhood lead poisoning in vulnerable populations (U.S. EPA 2004b). These grants are providing funding for proven or innovative programs in areas with high rates of childhood lead poisoning, and in areas where rates are unknown but other conditions suggest high rates may exist.

TSCA section 405(e) further directs EPA to establish, in connection with HUD, CDC, other Federal agencies, and State and local governments, a clearinghouse for information on lead-based paint and a hotline for the public to use for questions and requests for information on lead-based paint. This clearinghouse, the National Lead Information Center, handles approximately 50,000 calls per year, and disseminates up to 500,000 documents per year to the public.

Lead-based paint programs at other Federal agencies

In addition to EPA, other Federal agencies have important roles in achieving the goals of reducing or eliminating lead-based paint hazards in housing, as well as the national goal of eliminating childhood lead poisoning by 2010. Other agencies specifically assigned tasks in Title X include HUD, CDC, and OSHA.

The Federal agencies have long realized that they must work together to develop and implement Federal strategies for addressing lead-based paint hazards in order to be efficient and effective. In 1989, HUD and EPA formed an inter-agency task force to work through issues associated with lead-based paint abatement. The Federal Interagency Lead Based Paint Task Force has remained active throughout the years and continues to meet on a quarterly basis. Participating agencies include the Department of Defense, the Veterans Administration, the National Institute of Standards and Technology (NIST), the U.S. Public Health Service, the National Aeronautics and Space Administration (NASA), the United States Department of Agriculture (USDA), the Government Accountability Office (GAO), the National

Institute for Environmental Health Sciences (NIEHS), ATSDR, CDC, CPSC, NIOSH, OSHA, HUD, and EPA. This Task Force serves as an important forum for coordinating the strategic plans of the Federal agencies who have responsibilities under Title X or who have responsibilities for maintaining and disposing of property that may contain lead-based paint.

Title X assigned certain responsibilities to HUD. One of HUD's functions is the administration of the Lead-Based Paint Hazard Control Grant Program established by the Act. This program provides grants of $1 million to $3 million to State and local governments for control of lead-based paint hazards in privately-owned, low-income owner-occupied and rental housing that is not receiving federal assistance. These grants are also designed to stimulate the development of a trained and certified hazard evaluation and control industry. Evaluation and hazard control work funded by the program must be conducted by either contractors who are certified by EPA or an EPA-approved State or Tribal program, or by contractors trained in lead-safe work practices, in the case of interim controls. Through these requirements, HUD hopes to create infrastructure that will last beyond the life of the grant. In awarding grants, HUD promotes the use of cost-effective approaches to hazard control that can be replicated across the nation. Since 1993, approximately $971 million has been awarded to over 200 local and State jurisdictions across the country. The work approved to date will lead to the control of lead-based paint hazards in more than 70,000 homes where young children reside or are expected to reside. Other HUD lead grant programs include the Lead Hazard Reduction Demonstration program, the Lead Elimination Action Program (LEAP), the Lead Outreach program and the Lead Technical Studies program.

HUD was also given regulatory authority over some aspects of leadbased paint hazard control. As noted previously, on March 6, 1996, HUD and EPA jointly promulgated regulations requiring the disclosure of lead-based paint information during sale or lease transactions involving target housing. The HUD disclosure regulations are codified at 24 CFR part 35, subpart A. Subparts B through R of 24 CFR part 35 are known as the ''Lead Safe Housing Rule,'' initially promulgated on September 15, 1999, and updated in June 2004 (HUD 2004b). This rule was designed to protect young children from lead-based paint hazards in target housing that is being sold by the Federal government or receives financial assistance from the government. The requirements generally depend upon the level of assistance being provided, and may include such things as inspections, risk assessments, abatement, paint stabilization, or interim controls, which are temporary measures to reduce potential exposure to lead-based paint hazards. The emphasis is on reducing lead-based paint hazards, so, after paint is disturbed, a visual assessment for surface dust, debris, and residue and dust clearance testing is required to ensure that no dust lead hazards were created or left in the work area or, for rehabilitation projects of moderate or substantial scope, in the entire housing unit. More information on the Lead Safe Housing Rule is available on the HUD website at http:/ /www.hud.gov/offices/lead/leadsaferule/index.cfm or by calling (202) 755–1785, extension 104.

Section 1017 of Title X required HUD to issue ''guidelines for the conduct of federally supported work involving risk assessments, inspections, interim controls, and abatement of lead-based paint hazards.'' In response to this directive, HUD completed the Guidelines for the Evaluation and Control of Lead-Based Paint Hazards in Housing (Guidelines), in June 1995 (HUD 1995). The Guidelines provide detailed, comprehensive, technical information on how to identify lead-based paint hazards in housing and how to control such hazards safely and efficiently.

Other core activities of HUD's lead-based paint program include providing technical assistance to housing authorities, nonprofit housing providers, local and State agencies, other Federal agencies, housing developers, inspectors, real estate professionals, contractors and financiers, and public health authorities; evaluating the hazard reduction methods used in the grant program to measure their

effectiveness, cost and safety; and maintaining a community outreach program in coordination with the other Federal agencies involved in lead-based paint hazard reduction.

CDC also provides significant funding for the prevention of childhood lead poisoning. CDC provides funding to support State, city and county programs in the areas of primary prevention, case management and screening, surveillance, strategic partnerships, and program evaluation. Since 2002, CDC has recommended that a blood lead level of 10 micrograms per deciliter (µg/dL) be used as a threshold for individual intervention (CDC 2002). Additional CDC recommendations address the type and intensity of individual intervention strategies that should be undertaken, depending upon the child's blood lead level. These strategies range from nutritional and educational interventions, along with more frequent testing, for a child with a blood lead level of 10–14 µg/dL, to medical and environmental interventions for children with blood lead levels above 45 µg/dL (CDC 2002). CDC has established a national surveillance system for children with elevated blood lead levels. In addition, CDC works with HUD and EPA to coordinate outreach and education campaigns.

OSHA is another agency with regulatory authority under Title X. As directed by the Act, OSHA promulgated an interim final standard on May 4, 1993, which regulates lead exposures in the construction industry (OSHA 1993). This standard, codified at 29 CFR 1926.62, limits worker exposures to 50 micrograms of lead per cubic meter of air averaged over an 8–hour workday. Employers must use a combination of engineering controls and work practices to reduce employee exposure as much as possible, using appropriate respiratory protection where necessary to achieve the exposure limit. Employees must receive training on the health effects of lead and how to limit exposure through proper work practices and personal protective equipment. Exposure monitoring and medical monitoring, including blood lead testing, are also required. This standard remains in effect and OSHA retains the authority to protect workers from occupational exposure to lead.

Many Federal agencies have been working to reduce or eliminate lead-based paint hazards in housing and to end childhood lead poisoning. EPA, HUD, and other Federal agencies have been working for many years on the problem of lead-based paint hazards that can be created during renovation and remodeling activities in housing. This rulemaking is an important component of the Federal strategy for eliminating childhood lead poisoning.

State Programs

As of August of 2005, 44 states, territories and tribes administer their own lead-based paint abatement programs. The programs vary in terms of the stringency of training, work practice standards and notification requirements, although all must be at least as protective of citizen well-being as the federal §402/404 regulations. In general, the programs focus on the prevention of lead-based paint poisoning via blood-lead level screenings, regulation of lead-based paint inspection, risk assessment, abatement and post-abatement clearance procedures, educational outreach and funding for lead-hazard reduction activities. Different state agencies may handle different aspects of a lead-based paint poisoning prevention program.

The majority of state lead-based paint regulations explicitly exclude renovation and remodeling activities from their training and work practice standards requirements. Several states, however, have promulgated regulations that require contractors to either take precautions when working with lead-based paint, or to be trained in and use lead-safe work practices when disturbing paint in certain types of housing. Other state programs include voluntary training and outreach initiatives meant to educate contractors on the

importance of using lead-safe work practices. EPA identified eight states with state-level regulations that address RRP activities in pre-1978 housing, as well as several states that have implemented voluntary programs. These state regulations and programs are summarized in Table 3-1. Due to time limitations, it was not possible to survey all states in detail. There may thus be additional states that have regulations pertaining to RRP projects in pre-1978 housing. It is unlikely, however, that these states have regulations that are more stringent than those discussed in this section. In general, identified state regulations address RRP activities in one of four ways: by prohibiting the creation of a lead hazard or lead threat/contamination (California and Maine), by prohibiting the use of certain work practices (Indiana and Oregon), by requiring the use of certain work practices (Massachusetts and exterior renovations in Rhode Island), and by setting forth training and work practice requirements for jobs performed in some, but not all, target housing (Rhode Island, New Jersey and Vermont). In addition, states may address renovation work in rental units indirectly through rental housing standards.

Table 3-1: State RRP Regulations		
State	**Type of RRP Regulations and Applicability[a]**	**Comments**
CA	*Cannot create lead hazard* Applies to: All Pre-1978 Housing	Title 17 and SB 460 prohibit creation of lead hazard during RRP activity. Definition of lead hazard includes "disturbing lead-based paint without containment." If lead hazard is discovered and reported, it will have to be abated/mitigated using trained personnel and following abatement work practices. Title 17 does not establish training or additional work practice requirements. Under CalOSHA regulations (Section 1532.1), workers performing lead-related construction (which includes renovation of residential or public building) who are exposed to more than 50µg/m^3 average over 8-hour period must be trained and certified as abatement workers or supervisors.
ME	*Cannot allow lead to enter environment* Applies to: Pre-1978 housing	Title 38, Chapter 12-B requires RRP contractors to take precautions to prevent release of lead to the environment, "including cleanup, removal and appropriate disposal of all visible lead-based paint debris generated by the project." Lists certain practices that are likely to result in release of lead to the environment. If lead dust or lead debris resulting from project creates a threat to public health, commissioner may order an immediate end to the project and may force responsible party to mitigate the risk. There are no training requirements for renovation contractors.
IN	*Work Practices Prohibited* Applies to: Pre-1960 target housing	326 IAC 23-5-2: Prohibits the use of certain methods of lead-based paint removal during RRP activities that disturb over 20 sq. ft. on the exterior of a building, or 2 sq. ft. in any room on the interior. Prohibited practices include open flame burning, abrasive blasting and machine sanding. Also, in case of exterior renovations, prohibits leaving any visible dust/debris on soil/surroundings for over 48 hours. There are no training requirements for renovation contractors.
OR	*Work Practices Prohibited* Applies to: Pre-1978 housing	OAR 333-069: Anyone removing or stabilizing (remodeling/painting) lead-based paint must apply to the Department of Human Services for a permit. The permit application requires firm/contractor to agree not to use prohibited work practices (including hydro/other power blasting without containment), to post warning sign, and to notify occupant of potential risks. There are no training requirements for renovation contractors.
MA	*Work Practice Standards* Applies to: All pre-1978 residences	454 CMR 22.11: Requires that in pre-78 housing where no inspection/risk assessment showing absence of LBP has been conducted, all workers must have undergone OSHA Lead in Construction Standard training. Sets forth work practice standards including posting of signs, shutdown and coverage of HVAC systems, and prohibition of certain lead-based paint removal techniques.
RI	*Work practice standards and training requirements* Applies to: Increased blood lead cases	R23-24.6-PB: Owners of certain high-risk properties and owners of properties receiving HUD or other funding, who are disturbing more than 15 sq. ft. of paint in any unit, or 3 sq. ft. feet in any common area, must use a certified Lead Hazard Reduction Contractor or Lead Renovator/Remodeler unless an inspection/risk assessment conducted by a certified professional has shown that there is no LBP present.
	Work practice standards Applies to: All exterior renovations	Air Pollution Control Regulation No. 24: Contractors or owners removing LBP from exterior of buildings or structures must notify owners and occupants of buildings and businesses within 50 ft. of structure as well as principal and chief administrative officer of schools within 50 ft. of structure. Must follow work practice standards that include containment, clean-up and the prohibition of certain paint removal techniques.

Table 3-1: State RRP Regulations		
State	**Type of RRP Regulations and Applicability[a]**	**Comments**
NJ	*Work practice standards and training requirements.* Applies to: Pre-1978 rental housing	5:10-6.6: Requires that anyone disturbing over 2 sq. ft. of interior LBP or 20 sq. ft. of exterior LBP in multi-family housing be trained in and follow lead-safe work practices (including occupant protection, worksite preparation, avoidance of certain work practices and dust sampling). Dust sampling must be performed by a person trained as a Lead-Sampling Technician.
VT	*Work practice standards* Applies to: Pre-1978 rental housing	18 V.S.A. § 1759: Requires owners of rental target housing and child care facilities to "take all reasonable precautions to avoid creating lead hazards during… renovation, remodeling… or repair project." Lists prohibited paint removal techniques and requires use of lead-safe work practices such as limiting work area access to workers, covering work area with plastic sheeting and requiring protective clothing. Requires clean-up of work area following renovation work. Rental property owners, managers and their employees must be trained in essential maintenance practices.
OH	*Voluntary*	Renovation contractors can get trained and certified as Lead-Safe Renovators. There are currently no regulations requiring lead-safe work practices.
WI	*Voluntary*	Owner may certify property as Lead-Safe to obtain immunity from civil and criminal liability on his/her property. Chapter HFS 163: RRP projects on Lead-Safe properties may only be performed by trained lead-safe renovators using lead-safe work practices.
MI	*Voluntary*	Michigan Compiled Laws Service 333.5473a(2-3) "requires department to establish and conduct educational programs to educate homeowners and remodelers of lead-safe practices and methods of lead-hazard reduction activities."
IA	*Voluntary*	Iowa Code §135.105A requires creation of voluntary program for training of remodelers.

[a] Some regulations may also apply to Child-Occupied facilities. Since only residential structures are subject to the RRP rule, this table focuses on the residential housing affected by the state rules.

Sources: CA DHS 1999 and 2003; State of Maine 2004; Rhode Island Department of Health 1992; New Jersey Department of Community Affairs 2004; Lamberti 2005; Vermont Statutes Online 2005; Indiana State Department of Health 2001; The Commonwealth of Massachusetts 1999; Holston 2005; Wisconsin Department of Health and Family Services 2003; National Council of State Legislatures 2005; OR DHS; OR DHS 2003; RI DEM

Prohibition of Lead Hazards or Lead Threats

Emergency provisions of Maine's Lead Abatement regulations require that "a person engaged in any renovation, remodeling… or repair project involving lead-based paint not subject to the licensing and certification requirements… shall take reasonable precautions to prevent the release of lead to the environment, including cleanup, removal and appropriate disposal of all visible lead-based paint debris generated by the project." The regulations list examples of work practices that may result in the release of lead to the environment, and stipulate that if the commissioner finds that the location of lead dust or debris resulting from the project poses a danger to public health, the commissioner may order the responsible party to mitigate the threat, and may also order an immediate stop to the project (State of Maine 2004).

Similarly to Maine, the state of California does not dictate specific work practice standards for renovation and remodeling projects. California's Title 17 and Senate Bill 460, however, make it illegal to create a

lead hazard on either the interior or the exterior of any residential or public building. A "lead hazard" as defined in Title 17 is "deteriorated lead-based paint, lead contaminated soil, disturbing lead-based paint… without containment, or any other nuisance which may result in persistent and quantifiable lead exposure" (CA DHS 1999). As such, similarly to EPA's RRP regulations, California's regulations require the use of containment when disturbing more than a small area of lead-based paint. A small area is defined as less than 2 sq. ft. of paint on the interior or less than 20 sq. ft. of paint on the exterior of a building. If RRP activity results in the creation of a lead hazard, local and state agencies can "issue orders to abate or otherwise correct" the hazard. They can also order an immediate stop to the project (CA DHS 2003). Local and state agencies depend primarily on citizen complaints to enforce these regulations (Frazier 2005).

While Title 17 and SB 460 do not require training for renovation workers, CalOSHA's Construction Safety Orders (Section 1532.1) states that any employee performing lead-related construction work (which includes renovation of public or residential buildings) and is exposed to lead dust concentrations above the permissible exposure limit must be trained by an accredited training provider and certified by the California Department of Health Services. The permissible exposure limit (as specified in CalOSHA regulations) is equal to an average of 50μg/m^3 average over an 8-hour period. If an employee works more than 8 hours in a workday, the allowable exposure limit is reduced to 400μg/m^3 divided by the number of hours worked. Because little information is available on the dust concentrations generated during renovation, repair and painting projects, it is not possible to determine what percentage of California's RRP contractors are required to be trained under the CalOSHA regulations.

Prohibition of Certain Work Practices

Unlike California and Maine regulations, which do not explicitly require the use or avoidance of particular work practices, Indiana and Oregon seek to protect workers and occupants through the prohibition of certain lead-based paint removal techniques.

Indiana's 326 IAC 23-5-2 regulations prohibit anyone disturbing over 20 sq. ft. of exterior paint or 2 sq. ft. of interior paint in pre-1960 target housing or child-occupied facilities from using various methods of removing lead-based paint. Prohibited practices include, but are not limited to, open flame burning and machine sanding/grinding or abrasive blasting/sandblasting without high efficiency particulate air local exhaust control. For exterior renovations, the regulations also require that all visible lead-based paint on soil or other horizontal exterior surfaces be removed within 48 hours after the end of activity (Indiana State Department of Health 2001).

In Oregon, contractors hired to remove or stabilize lead-based paint must apply to the Department of Human Services for a permit. As part of the permit application, contractors pledge not to use prohibited work practices such as uncontained hydro/other power blasting or sanding and agree to post a sign warning the public of possible lead-based paint hazards. Other prohibited work practices include, but are not limited to open-flame burning/torching and dry-scraping unless combined with a heat gun (OR DHS, OR DHS 2003).

Work Practice Requirements Applicable to All Target Housing

Massachusetts regulations (454 CMR 22.11) also prohibit the use of open flame burning as a method of LBP removal during renovation projects. In addition, the state has promulgated work practice requirements that are relatively similar to EPA's proposed RRP standards. For example, Massachusetts requires that the HVAC system be shut down during renovations that disturb LBP and that any HVAC

ducts exposed to the work area be sealed off. All movable objects must be removed from the work area, while non-movable objects must be covered with plastic sheeting. Clean-up requirements include cleaning any surfaces contaminated with lead debris or dust using a HEPA vacuum, wet wiping or another acceptable method (Commonwealth of Massachusetts 1999).

While Massachusetts does not require lead-safe work practice training for renovation workers, minors may not work on projects involving lead-based paint, and all workers must be trained according to OSHA Lead in Construction Standard (29 CFR Part 1926.26(1)).

The Rhode Island Department of Environmental Management (DEM) regulates all work involving the removal of lead-based paint from the exteriors of buildings and structures. Air Pollution Control Regulation No. 24 establishes detailed work practice standards for exterior lead-based paint removal. Requirements include, but are not limited to, covering or removing any toys, furnishings or play equipment within 50 ft. of the structure, covering the ground within an impenetrable material to contain all debris, abrasives and paint, and using vertical containment if there is "visible movement of abrasive material, paint dust and/or other debris beyond ground sheeting." The regulations state that certain paint removal techniques may only be used in conjunction with a HEPA vacuum unit and/or vertical containment, while others (open flame burning) may not be used at all. Furthermore, the regulations list clean-up procedures to be conducted at the end of each day and at the end of the project (RI DEM).

In addition to these work practice requirements, DEM regulations require that anyone removing lead-based paint notify a) adults residing in or within 50 ft. of the structure from which the paint is being removed, b) the owner of the structure or of any building or business located within 50 ft. of the structure, and c) the principal and chief administrative officer of any school within 50 ft of the structure five days prior to the start of the project. The notification must provide the location, start and completion dates of the project, a description of lead-paint removal procedures, contact information for the firm conducting the project, and a warning statement regarding the dangerous nature of lead-based paint (RI DEM).

Although DEM regulations do not require training or certification, in April 2005 the Department implemented a voluntary certification program for contractors involved in removing exterior lead-based paint. To participate in the program, the contractor must read a Certification Workbook, complete a Participation Form and Certification Checklist stating that he/she abides by the Air Pollution Control Regulation No. 24, and present a completed copy of a project checklist to the owner/occupant of each structure the contractor conducts work on. As of August 2005, approximately 20 contractors have become certified with DEM through this program (RI DEM 2005 a-c).

Work Practice and Training Requirements for RRP in Certain Types of Housing

In addition to work practice standards/prohibitions, New Jersey, Vermont and Rhode Island regulations require the use of trained contractors and in the case of New Jersey, post-renovation dust testing. In New Jersey and Vermont, however, these regulations apply only to multi-family housing. In Rhode Island they apply mainly in cases involving a child with an increased blood lead level.

New Jersey regulations require that all work that may disturb painted surfaces (over 2 sq. ft. of paint on the interior and over 20 sq. ft. of paint on the exterior) in multi-unit housing (except owner-occupied units) be performed by trained workers in accordance with HUD rules 24 CFR 35. The regulations require that steps be taken to protect occupants and prepare the worksite, and prohibit the use of some work practices, including open flame burning, power sanding and uncontained water blasting. Training

options include the HUD-EPA Lead Safety for Remodeling, Repair and Painting course. Furthermore, following any project which disturbs lead-based paint, the dust sampling must be performed by a person trained as a Lead-Sampling Technician (NJ DCA 2004, Lamberti 2005).

Vermont requires owners and managers of rental target housing and child-care facilities be trained in and perform essential maintenance practices on their properties. These practices include "tak[ing] all reasonable precautions to avoid creating lead hazards during any renovation, remodeling, maintenance or repair project that disturbs a lead-based painted surface pursuant to guidelines issued by the department." Guidelines include the prohibition of work practices such as "burning, water blasting, dry scraping, power sanding, or sandblasting, unless authorized by the department." The regulations further require the use of good work practices, including, but not limited to "limiting access to work areas to workers, covering the work area with six mil polyethylene plastic … protecting belongings of occupants by covering or removing them from the work area." Finally, the regulations require specialized cleaning of the work area using recommended methods (Vermont Statutes Online 2005).

In Rhode Island, the Department of Health regulates Lead Hazard Reduction and Lead Hazard Control activities as well as renovation, repair and painting projects on certain properties.

Lead Hazard Reduction activities are defined as

> "any activity which reduces the risk of human exposure to lead-based paint or lead containing materials or substances in a regulated facility through environmental modification. Such activity includes, but is not limited to: repair, enclosure, encapsulation, removal and/or replacement of lead-based paint or painted surfaces, materials, or components in a building or structure (RI DOH 1992)."

Lead Hazard Reduction activities may only be performed by licensed Lead Hazard Reduction Contractors, who require 40 hours of training for certification. The regulations stipulate a variety of work practice standards, clean-up and clearance inspection/dust testing requirements. The regulations exclude activities that disturb less than 15 sq. ft. of paint in any one unit, or 3 sq. ft. of paint in any common area. Note that a Lead Hazard Reduction Contractor is not required for exterior abatement activity (RI DOH 1992).

Lead Hazard Control activities include paint stabilization and treatments of friction and impact surfaces where the lead levels are above the permitted standard. Window and door removal may also qualify as a Lead Hazard Control activity as long as the process does not involve paint removal and all resulting dust/debris are immediately cleaned up. Lead Hazard Control activities may only be performed by Lead Renovators/ Remodelers, who require eight hours of training. The regulations stipulate notification, work practice standards, clean-up and clearance inspection/ dust sampling requirements for Lead Hazard Control activities. Again, regulations exclude activities that disturb less than 15 sq. ft. of paint in any one unit, or 3 sq. ft. of paint in any common area (RI DOH 1992).

For the majority of residential units, Lead Hazard Reduction and Lead Hazard Control activities do not include renovation, repair and painting work (although Lead Hazard Reduction may be required if a renovation project results in the generation of lead dust). However, properties that:

- Have received a Notice of Violation or Order;

- Have been cited by the Department of Health for "significant childhood lead poisoning involving three or more children [under age 6] in the previous seven years at units in which the owner has or had a financial interest ";
- Receive funding from an agency that requires this level of protection; or
- Request this level of protection

and are disturbing more than the exempt amount of paint during an RRP project must either conduct an inspection to show that no lead-based paint is present, or assume that there is lead-based paint and conduct the renovation/remodeling activity as if it were a Lead Hazard Reduction activity, following all relevant regulations.

Similarly, properties that:

- Have received a Notice to Abate;
- Must comply with lead-hazard control requirements dictated by HUD;
- Receive funding from an agency that requires this level of protection; or
- Request this level of protection

and are disturbing more than the exempted amount of paint must either conduct an inspection to show that no lead-based paint is present, or assume that there is lead-based paint and conduct the renovation/remodeling project as if it were a Lead Hazard Control activity, following all relevant regulations (RI DOH 1992).

Additional Regulations that may Affect RRP Projects

In addition to the regulations discussed above, EPA identified two states (Rhode Island and Maryland) that have promulgated housing standards that may impact renovation events in rental units. In both states, owners of rental housing constructed prior to 1978 in Rhode Island and prior to 1950 in Maryland are required to bring their properties into compliance with certain standards for the maintenance of surfaces covered with lead-based paint. In addition, these owners are required to perform visual inspections and maintenance/clean-up at tenant turnover (RI HRC 2003, State of Maryland 1994). Maryland Housing Bill 760 also requires that if a repair project takes place while a unit is occupied, all children and pregnant women must be relocated and all other occupants must be kept out of the work area (State of Maryland 1994). Neither of the laws, however, explicitly dictates any work practices or training requirements for renovation, repair or painting projects. Thus, although these state laws are likely to result in thorough clean-up at the end of a project (so as not to violate the housing standards, which prohibit the presence of chipped or deteriorating lead-based paint in rental housing), they do not regulate the manner in which a renovation is performed.

State Voluntary Programs

Whereas some states have promulgated regulations that may limit lead exposure from renovation and remodeling activities, others have turned to voluntary programs as a way of encouraging contractor training and the use of lead-safe work practices.

In Ohio, for example, contractors may choose to take a 6-hour class and become trained as Lead-Safe Renovators. Lead abatement supervisors and lead abatement workers are automatically eligible for certification as lead-safe renovators. There are currently no work practice standards in place for certified

lead-safe renovators and no enforcement activities to ensure that the renovations are in fact performed safely. In the past, some lead-safe renovators had to submit a notification prior to starting a renovation project. The notifications are no longer required, but some renovators submit them voluntarily. Currently, there are approximately 900 - 1,000 certified lead-safe renovators in Ohio (Holston 2005).

In Wisconsin, a property owner may choose to certify his or her property as lead-safe. Lead-safe status is granted following an inspection conducted by a certified inspector/risk assessor. The Lead Safe certificate "provides the listed "Property Owner" and his employees and agents immunity from civil and criminal liability on this property. Also, they may not be subject to a DHFS proceeding, except under circumstances cited in ch. 254.173(2), Wis. Stats." Once a property is certified as lead-safe, however, any RRP activity performed on the property must be conducted by a trained Lead-Safe Renovator following lead-safe work practices (WI DHFS 2003). As of July 2004, the Wisconsin listing of lead-safe properties contained 39 residential structures (WI DHFS 2005).

Other voluntary initiatives include educational outreach in the form of suggested lead-safe work practices and periodic free training offered by health departments and housing agencies.

Local Initiatives

Similar to state programs, local lead-poisoning initiatives have had limited resources with which to carry out their programs. Differences between typical state and city programs lie more in the extent than in the substance of the activities. In general, city programs are more focused and seem to receive higher priority, which may be due to the urgency of the lead-paint problem in larger cities (HUD 1990).

In the *Comprehensive and Workable Plan for the Abatement of Lead-Based Paint in Privately Owned Housing* (HUD 1990), the Department of Housing and Urban Development outlined several distinguishing features of local programs as determined by studying ten selected cities:

- A city that is governed both by local ordinances and state regulations for lead-poisoning prevention and detection activities usually has local laws that are more stringent than state laws and may supersede the state requirements.
- In addition to providing intervention after cases of lead poisoning have been detected, local programs may require intervention as a result of targeted inspection of tenant complaints. Several cities, including Baltimore, Chicago, Louisville, New York, and Philadelphia, are authorized to take such preventive measures.
- In general, the city programs show more cooperation and coordination between agencies.
- City programs usually screen for high blood lead levels more systematically and target high-risk areas for screening.

Several cities have promulgated regulations that affect renovation, remodeling, and painting activities. These regulations are summarized in Table 3-2. Once again, it is possible that there are additional cities with similar regulations. However, similarly to state-level regulations, these rules are likely to fall short of correcting the market failure discussed in Section 3.2.1. and thus do not substitute for the proposed federal Renovation Rule.

Local regulations, which are most often promulgated as city ordinances, are similar to state regulations in that they address the dangers posed by RRP activities in pre-78 housing via prohibiting the creation of

lead hazards or the use of certain paint removal techniques, requiring the implementation of work practice standards, or requiring lead-safe work practices for projects in certain types of housing.

New York City currently has one of the most extensive local regulatory programs dealing with lead-based paint. The City recently promulgated a rule entitled Local Law 1, which applies to all units with a child under age 7 in pre-1960 multi-dwelling buildings and to common areas in these buildings. The regulations also apply to housing units in multi-dwelling buildings constructed between 1960 and 1978 where children reside and where the owner knows there is lead paint, as well as to common areas in these buildings. When disturbing between 2 sq. ft. and 100 sq. ft. of paint in the interior of these buildings, the owner must hire workers trained in lead-safe practices. Work practices must be no less stringent than Health Code §173.14 and dust tests must be performed. If work disturbs over 100 sq. ft. or more than one window within the interior of the building, the owner must hire an EPA-certified firm and follow the same work practices as for the disruption of areas between 2 sq. ft. and 100 sq. ft. Furthermore, notification is required for projects disturbing over 100 sq. ft. Relocation may be required for any project where work cannot be performed safely. According to the Department of Housing Preservation and Development's *Local Law 1/2004 – Section by Section Analysis*, it is not clear from the statute whether the over 100 sq. ft. project requirements apply to private dwellings (NYC DHPD 2004a-b).

Chapter 36 of San Francisco's Building Code, *Work Practices for Exterior Lead-based Paint*, is another example of a city-level regulation that addresses renovation and remodeling. It should be noted that Chapter 36 establishes far more detailed requirements than do California Title 17 and SB460. The San Francisco regulations apply to any work that disturbs over 10 sq. ft. of lead-based paint on the exterior of pre – 1978 buildings or steel structures. The regulations require the use of containment for all regulated jobs and prohibit the use of paint removal techniques such as "acetylene or propane burning and torching, hydroblasting or high pressure blasting without containment barriers [and] heat guns operating above 1,100 degrees Fahrenheit." The party responsible for the project must also perform a clean-up of all visible lead-based paint debris prior to finishing the project. The regulations further require that the owner notify all contract bidders of any paint inspection reports related to lead-based paint in the regulated area of the project. The owner or contractor must also notify the Department of Building Inspection and the tenants prior to the start of work, and must post a sign warning of the presence of lead-based paint (National Center for Healthy Housing, DBI 1999).

Although Cleveland's lead paint regulations focus primarily on lead abatement, they do provide requirements for safe work practices and clean-up during any type of lead-based paint removal. Ordinance 1027-04 applies to all pre-1978 buildings except residences of the elderly or disabled where children under six years of age do not and will not reside or any zero bedroom dwelling. The regulations prohibit all open flame burning as well as power-assisted paint removal techniques that do not immediately capture dust and debris in a closed container (this method is likely to involve power-assisted machines with HEPA vacuum attachments). The law requires that notification be given to occupants of the building and to any occupants of neighboring buildings within 30 ft. of the worksite. Preparation of an exterior worksite includes attaching plastic sheeting to the foundation of the structure and extending it 10 ft. from the foundation. For an interior paint removal task, preparation consists of laying plastic sheeting over an area "sufficiently large" to protect the surrounding environment from contamination and to capture dust and debris. Clean-up entails the rolling up and disposal of plastic sheeting along with the removal of all paint debris and dust (City of Cleveland, 2004).

The Kansas City Lead Ordinance (Article X: Lead Poisoning Control, Sec. 34-401 – 34-409) includes a general statement regarding renovations, remodeling projects, and demolitions. While it does not

mandate detailed guidelines, the ordinance makes it illegal for workers involved in these activities to create lead hazards and expose themselves, occupants of the building, or occupants of adjacent properties to lead-containing debris and dust. The rule applies to all housing types but is particularly important in areas where children under the age of six are likely to be exposed (Kansas City Health Department).

Similar to Kansas City, the Chicago Department of Public Health issued a nonspecific lead-based paint regulation. The law, as outlined in *Control and Mitigation of Lead Bearing Substances*, applies to facilities and premises that are frequented by children who are of age six or younger. It simply states that workers cannot create lead hazards while performing any work on lead bearing substances in these facilities and premises. This includes containing and removing "any visible dust, chips, or debris" from lead-based paint. The regulation further prohibits the use of certain work practices, as described in Table 3-2. Similar to the California regulations, this ordinance implicitly requires renovators to contain lead-based paint dust and debris (City of Chicago Department of Public Health, 2004).

Table 3-2: Local RRP Regulations

City, State	Type of RRP Regulations and Applicability	Comments
New York City, NY	*Training and work practices* Applies to: All Pre-1960 multiple dwellings; Multiple dwellings built between 1960 and 1978 with knowledge of lead paint (interior work)	NYC Local Law 1: Regulation applies to all units with a child under age 7 in pre-1960 (as well as buildings constructed between 1960 and 1978 where the owner knows there is lead paint) multi-dwelling buildings and to common areas in these buildings. When disturbing between 2 and 100 sq. ft. of LBP, owner must hire workers trained in lead-safe practices. Work practices must be no less stringent than Health Code §173.14 and dust tests must be performed. If work disturbs over 100 sq. ft., must hire EPA-certified firm and follow same work practices as for disruption of 2 to 100 sq. ft. Notification is required for projects disturbing over 100 sq. ft. The 100 sq. ft. regulations may or may not apply to private residential dwellings.
San Francisco, CA	*Work practices prohibited* Applies to: Pre-1978 buildings (exterior work)	Chapter 36 of the San Francisco Building Code: Regulation applies to any work disturbing over 10 sq. ft. of LBP on the exterior of buildings and steel structures. Requires containment barriers for all jobs disturbing more than the exempted amount of paint. Prohibits use of some paint removal techniques and requires clean-up of all visible LPB debris. Requires notification of the Department of Building Inspection and of tenants prior to start of work. Requires the postage of sign warning of presence of LBP. No specialized training is required.
Chicago, IL	*Cannot create lead hazard* Applies to: Pre-1978 buildings frequented by children six years old and younger	Chicago Department of Public Health prohibits the presence of lead hazards (definition of "Lead Hazard" includes uncontained lead dust or debris created during RRP activity) in residential housing and child-occupied facilities/premises. Prohibits use of work practices (including open flame burning, dry sanding, dry scraping, heat guns, mechanical paint removers without HEPA dust containment, uncontained hydro or abrasive blasting, and chemical strippers) that may create a lead hazard. City inspectors may order abatement or mitigation of any lead hazards. No specialized training is required.
Kansas City, MO	*Cannot create lead hazard* Applies to: Pre-1978 buildings, particularly areas where children under age 6 may be exposed to lead paint	Kansas City Lead Ordinance (Article X: Lead Poisoning Control, Sec. 34-401 – 34-409) makes it illegal for any person to "repair, renovate or demolish any dwelling in such a manner that any occupant, worker or any person on any adjacent property(ies) may be exposed or have access to the resulting dust, contaminants or debris from lead-bearing substances." No specialized training is required.
New Orleans, LA	*Cannot create lead hazard* Applies to: Pre-1978 buildings or metal structures	New Orleans City Ordinance No. 20345 regulates activities that disturb LBP on and in pre-1978 buildings and all steel structures. Prohibits the use of certain paint removal practices including scraping, hydro blasting or sandblasting without containment, heat removal and chemical removal. Requires containment for exterior work using power sanding. Requires notification of tenants and other affected parties and postage of signs if power sanding is used. Requires notification of the Director of the Department of Safety and Permits if power sanding is used on exterior of building or structure. No specialized training is required.

Table 3-2: Local RRP Regulations		
City, State	**Type of RRP Regulations and Applicability**	**Comments**
Cleveland, OH	*Work practices and prohibitions for paint removal* Applies to: Pre-1978 target housing	Cleveland Ordinance 1027-04 provides prohibitions and guidelines for paint removal. It prohibits open flame burning and power-assisted paint removal unless debris and dust are immediately captured in a closed container before being released into the environment. Plastic cloths are to be attached to the foundation and extended out 10 ft. for exterior paint removal and laid in an area "sufficiently large" for interior. Vents, windows, and ducts are to be closed. Upon completion of work, cloths are to be wet wiped, rolled up, and disposed of. All paint or paint dust is to be removed from the premises. The law requires that notification be given to occupants of the building and occupants within 30 ft. of paint removal. No specialized training is required.
[a] Some regulations may also apply to Child Occupied Facilities. Since only residential structures are subject to the RRP rule, this table focuses on the residential housing affected by the state rules. *Sources: National Center for Healthy Housing; NYC DHPD 2004a-b; DBI 1999; CDPH 2004; Kansas City Health Department; City of New Orleans 2001; City of Cleveland 2004.*		

Conclusions

While the regulatory and non-regulatory initiatives undertaken at the federal, state, and local level to reduce exposure to residential lead are extensive, they are not sufficient to ensure that lead exposure resulting from renovation activities is reduced to the levels of the RRP regulations. Very few of the existing programs address renovation or consider the release of lead into the surrounding environment that frequently occurs during renovation. Even childhood blood-lead screening programs, which should act as a monitoring system by identifying exposure problems that do develop, are not universal — many states and communities have yet to institute such testing programs and even where they exist, they often miss many children. Even if these blood-lead screening programs were more uniformly applied across states and at risk children, such an *ex-ante* approach to limiting exposure would only address the issue after it becomes a significant health concern (i.e., children will suffer from increased blood-lead before intervention occurs).

3.3 Regulatory Options for Reducing Lead Exposure Resulting from Renovation

In drafting the Renovation, Repair and Painting Rule, EPA considered various regulatory approaches, including, but not limited to: (1) information provision and labeling, (2) required work practice standards, (3) bans or restrictions on use, and (4) economic incentives. The first and second of these instruments are most closely linked to the problems contributing to the market failure described in Section 3.2. Consequently, directly addressing the lack of adequate information and external costs through information provision, and the establishment of work practice standards are the focus of this section and the analysis presented in this report.

3.3.1 Information Provision

The objective of the proposed regulation is to reduce exposure to lead from renovation projects and thereby protect children and adults from health hazards posed by lead. Due to the nature of the problem,

uncertainty currently exists on the part of consumers about the quality of lead-safe renovation services and their likely benefits. The lack of information regarding the benefits of and the lack of confidence in the quality of a good or service generally leads to a lower demand and a lower willingness-to-pay for that good or service. Thus, if consumers of renovation services (i.e. property owners) are not aware of the dangers posed by lead dust generated during renovation, or if they are not confident that a contractor who claims to use lead-safe work practices has been properly trained, they may not be willing to pay the additional costs of contractors who voluntarily abide by these work practice standards. The proposed rule will assure consumers that trained and certified personnel are qualified to control lead-based paint hazards. This provision of information will act as an important instrument in alleviating the problems contributing to undue lead exposure. An example of the market failure stemming from the lack of perfect information is presented in the previous section and is shown graphically in Exhibit 3-1.

An additional information flow will occur under these regulations. The teaching of safe work practices to contractors will provide them with information they need to undertake renovation activities in ways that will not expose their clients. The training course will also provide information about the hazards associated with lead and renovation activities, which contractors will pass along to their clients. Thus provision of information is likely to increase the demand for lead-safe work practices and assist in eliminating the market failure that currently exists due to incomplete or misinformation.

Information provision will occur in several ways under this rule, in conjunction with other sections of Title X. Consumers will be directly informed about lead-based paint hazards and risks associated with renovation work through educational programs. The aim of these programs will be to educate the property owner about the risks associated with lead-based paint hazards and having renovation work done in areas with such hazards, the significance of these risks, what can be accomplished to reduce those risks through specific work practices, and how much these practices cost. In addition, requiring training of professionals carrying out renovation projects will provide these individuals information about the hazards of lead exposure and the use of appropriate procedures to reduce exposure during their work. Similarly, the firm certification process will act as an indirect form of information provision to the consumer by assuring them that the services they are purchasing will reduce or eliminate lead exposure.

All these forms of information provision will aid in reducing the extent of the market failure that currently exists for lead-safe renovation services. However, relying solely on information provision is unlikely to be enough because of the nature of the lead problem. The lead in lead-based paint cannot be seen on visual inspection, and thus the consumer does not know if lead is present and whether a lead exposure hazard actually exists. Likewise, the adverse health effects are not noticeable for several years, and the source may not be recognized. In such situations, education may not be sufficient and other mechanisms are needed to ensure that if a potential risk exists, it is suitably addressed. The current rule introduces other mechanisms for the elimination of lead-hazards during renovation work. These include training requirements for personnel engaged in renovation work and standard practices for the containment and cleanup of lead dust and debris generated during the project.

3.3.2 Containment and Clean-up Work Standards

Flexible and prescriptive standards are two alternative regulatory approaches that were considered for the work practice standards component of this rule. Both options require the use of specific containment, clean-up and cleaning-verification practices[2] within the work area. Under the prescriptive option, EPA

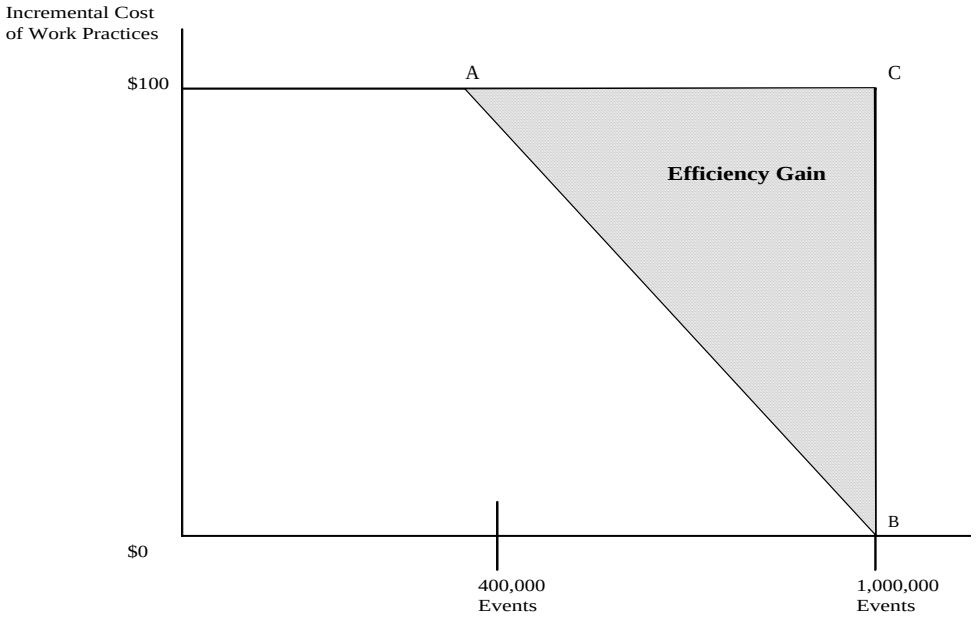
[2] Note that in the remainder of this discussion, the terms *clean-up* or *clean* is used to mean clean-up and cleaning verification work practices. Higher/lower level of containment/clean-up means the size of the work area that is

would define certain renovation projects as small and allow a smaller area to be contained and cleaned for these events; the remaining projects would be considered large and all rooms where work is performed would have to be contained and cleaned. Flexible standards, on the other hand, allow the certified renovator to determine the size of the work area that needs containment and cleaning for each project he/she performs.

The advantage of flexible containment work practices over prescriptive standards lie in higher efficiency and resultant cost savings. The expected superiority of flexible containment work practices rests on the assumption that the contractor on the site is a better judge of the dwelling area that might be exposed to lead dust (and should thus be contained and cleaned) than the rule writers. Contractors with perfect information would contain/clean the minimum area necessary to prevent the spread of lead dust and debris. This would lead to cost savings for some percentage of jobs where a greater level of containment is not required (but would have been prescribed), resulting an efficiency gain for society as a whole. Exhibit 3-2 provides a graphical example of the type of efficiency gain that could result from applying the flexible rather than the prescriptive option under conditions of perfect information. The incremental costs for each are calculated relative to a baseline where no protective measures are taken.

contained and cleaned using the work practices specified in the RRP rule.

Exhibit 3-2: Example of Cost Savings with Flexible Standards Under Perfect Information



In this example, 40% of events are assumed to require the maximum prescribed area to be contained and cleaned. The remaining 60% require containment and clean-up of a smaller area.[3] For simplicity, a linear decrease in the size of the work area that should be contained and cleaned is assumed, so that at the top margin projects require nearly the maximum area identified by the prescriptive and at the lower margin clearance is obtained using current industry practices only. The shaded area ABC represents the cost savings to be gained under flexible standards as compared to prescriptive option. Note that because all projects are assumed to attain the same level of lead hazard reduction, the benefits of the regulation remain unchanged, the costs decrease and the net benefits increase. In the example shown in Exhibit 3-3, the efficiency gain from using flexible work practices is $30 million (Area ABC = 0.5 × 600,000 × $100).

What if contractors do not have perfect information? If contractors cannot determine the exact area that should be contained and cleaned in a particular situation, then the full cost savings may not be realized. Depending on the type of imperfect information, the flexible, rather than prescriptive option may result in either smaller cost savings or result in greater costs savings with reduced benefits, as illustrated in the following two examples.

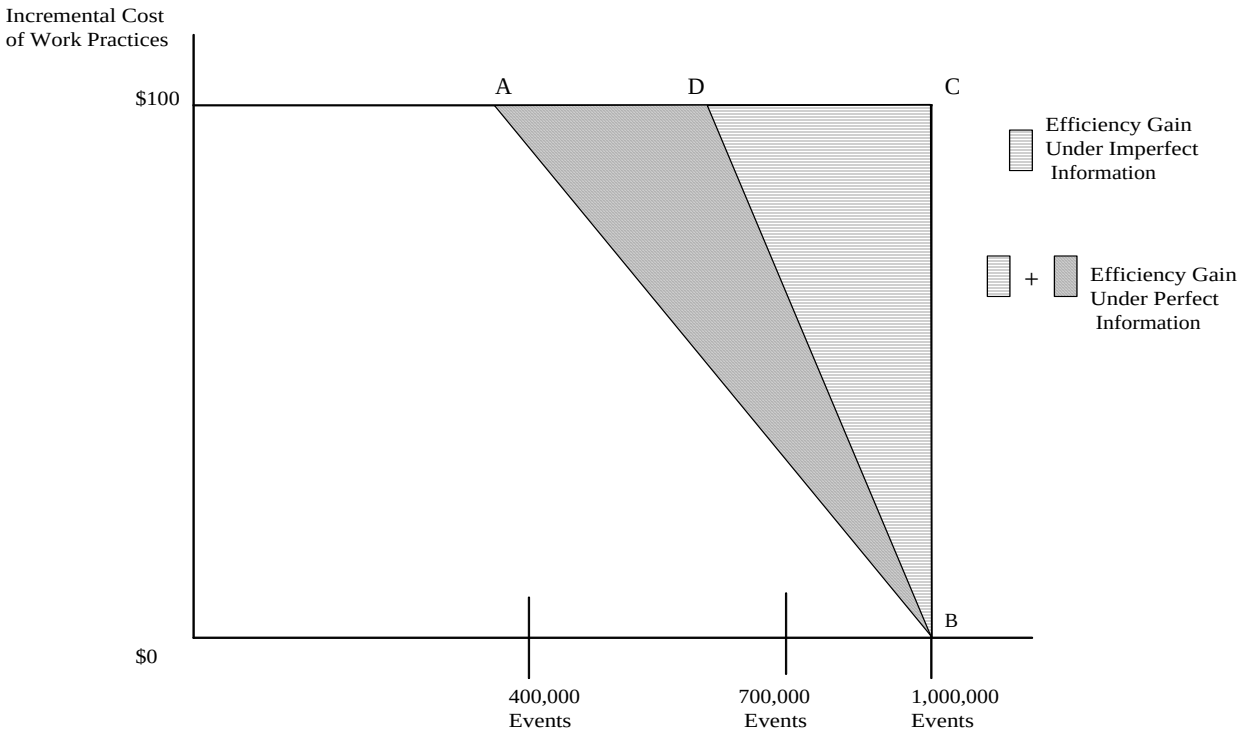
[3] Note that these percentages are assumptions only and are not based on housing data.

Example 1: Imperfect information results in using work practices that are too stringent

In this imperfect information scenario, contractors believe that the work area is larger than it actually is, resulting in a greater level of containment/clean-up than necessary. This situation is demonstrated graphically in Exhibit 3-3 below.

Exhibit 3-3: Cost Savings with Flexible Containment Standards under Imperfect Information

Doing More than Necessary



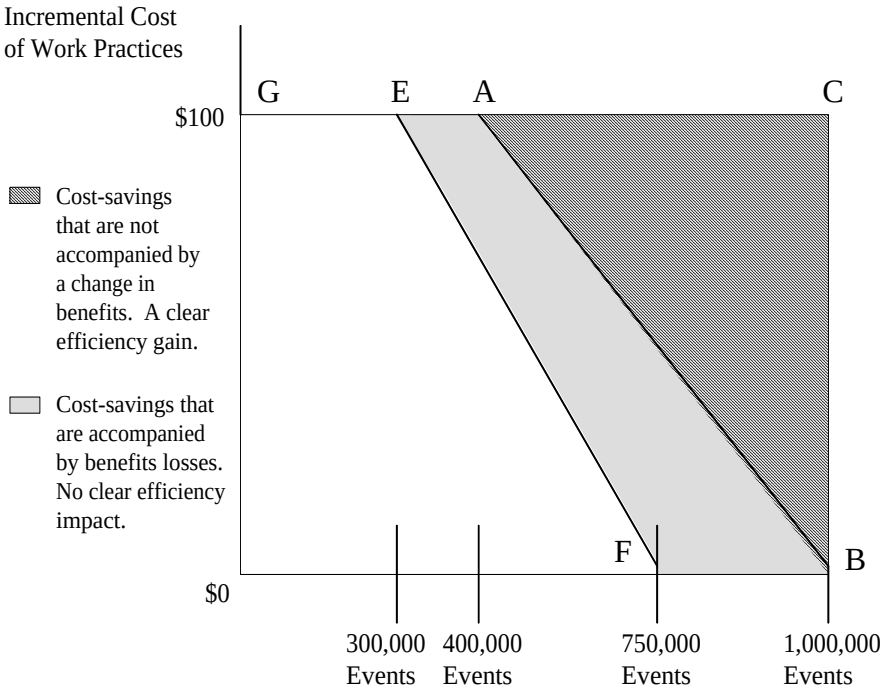
Under the illustration of perfect information presented in Exhibit 3-2 above, 600,000 events contained/cleaned a smaller area than required under the prescriptive option to attain the hazard reduction. If contractors are risk-adverse, or believe that a greater level of containment is necessary, then the number of events using less costly work practices is reduced. In the example presented in Exhibit 3-3, only 300,000 events contained/cleaned a smaller area. Because contractors are erring on the side of additional work practices, the benefits of the regulation are not reduced, the costs are reduced from the prescriptive option as represented by the area DBC and an efficiency gain occurs. Using the numeric example in Exhibit 3-3, the cost savings from applying the flexible option under imperfect information rather than the prescriptive option is $15 million, a smaller gain than would have occurred under perfect information (area ABC).

Example 2: Imperfect information results in using work practices that are too lax

Under the second scenario of imperfect information, it is assumed that contractors may err on the side of doing too little rather than too much. The effect of this scenario on the potential cost savings is demonstrated graphically in Exhibit 3-4 below.

Exhibit 3-4: Cost Savings with Flexible Standards Under Imperfect Information

Doing Less than Necessary



The efficiency impact of using the flexible option instead of the prescriptive option under this type of imperfect information is less clear. There is still an efficiency gain that results from cost-savings for projects where the EPA-recommended level of containment/clean-up is not required (area ABC). There is an additional cost savings that occurs on all projects that contained a smaller work area than was actually needed to achieve the hazard reduction (area EABF). In these cases, however, there is also a loss of benefits because the level of containment/clean-up used is not sufficient to prevent lead exposure. The net impact depends on the amount of benefits lost relative to the cost savings.

In conclusion, the conceptual framework outlined here can still be used to approximate the cost-savings from using the flexible option under an assumption of perfect information. Since EPA does not know the extent to which imperfect information will affect the efficiency of the flexible option, this approximation is made by estimating the percentage of events that that require containment/clean-up of a smaller area than prescribed by EPA and calculating the area of the efficiency gain as shown in Exhibit 3-2. However, qualitative information on the relative costs and benefits of the rule can be used to determine if the flexible costs savings might be outweighed by losses in benefits resulting from imperfect information.

3.3.3 Alternative Regulatory Options

In light of the prior discussion, the regulatory options analyzed attempt to provide flexibility while also providing information on what action contractors and property owners need to consider undertaking in order to contain and clean-up potential lead contamination. These work practices are combined with training to ensure that contractors will have the information they need to properly conduct RRP events in a protective manner.

Several alternative regulatory options are considered. First, EPA considered whether the regulations should apply to all housing units or only the housing units where children under the age of six reside and/or rental units. A focus on children is appropriate because they have the highest risk of exposure and adverse health effects. A focus on rental units is appropriate to address the agent problem – the person selecting the contractor and the containment/clean-up activities (i.e. the property owner) is not the person who will be affected by the resulting lead exposure (i.e. the tenant).

Perhaps the main difference among the options is the definition of the housing units subject to the regulation based on year built: between housing units built before 1978 and housing units built before 1960 or before 1950. With the ban on the use of lead-based paint in 1978, housing units built after that date are highly unlikely to present lead hazards, and thus are not included in the statutory definition of "target housing". Units constructed prior to 1978 make up 65 percent of the U.S. housing stock, while units constructed prior to 1960 and 1950 make up 34 and 22 percent of the housing stock, respectively. The use of lead-based paint declined rapidly during the 1950s and 1960s, so housing units built between 1960 and 1978 are much less likely to have lead-based paint than those built before 1960 (See Section 4.2.5 of Chapter 4 for further discussion).

Limiting the regulation to the earlier homes reduces costs with a less than commensurate reduction in benefits. This discrepancy arises from the difficulties associated with testing for lead-based paint in order to determine whether or not a particular project will need to comply with the regulations, which is likely to result in over-compliance, particularly in units constructed between 1960 and 1978. The RRP Rule allows contractors to use a lead-based paint (LBP) test kit to determine whether lead-based paint is present in a home, but test kits that are currently on the market have false positive rates that range from 47 to 78 percent. Because pre-1960 and pre-1950 units are more likely to contain lead-based paint than units constructed between 1960 and 1978, the LBP test kits will return more false positives for these newer units. EPA plans to develop a more accurate LBP test kit, which is expected to have a false positive rate of only 10 percent or less and to be available by the second year that the regulation is in effect. As such, by promulgating an option that applies only to older units in the first year and to all pre-1978 units in the second year, EPA can reduce the costs of the rule while incurring a significantly smaller reduction in benefits. EPA is thus considering several phase-in options, where the regulation will apply only to older renter-occupied target housing units or owner-occupied target housing units where children under the age of six reside in the first year and to all such pre-1978 units in the second year.

As discussed in Section 3.3.2, the third distinction among the options is the amount of flexibility given to contractors. Three of the regulatory options analyzed allow the contractor to exercise judgment as size of the work area that requires containment, clean-up and cleaning verification. The fourth option under consideration defines the size of the work area as either small or large and prescribes the amount of containment/clean-up accordingly.

The result is four options. By the second year of the regulation, all four options cover RRP events in renter-occupied target housing units built before 1978 and owner-occupied target housing units built before 1978 where a child under the age of six resides. One of the options also covers these same units in the first year, the other options cover smaller sets of housing units in the first year (two cover pre-60 housing and one covers pre-50 housing in the first year). Three of the options (flexible options) allow a certified renovator to define of the size of the work area while one option (prescriptive option) defines the area that must be contained and cleaned. More information on the options is provided in Chapter 4.

Appendix 3A: The Role of Elasticities in Determining the Impacts of a Rule

EPA is often faced with deciding on a regulatory policy in the absence of good information about the likely effects of the policy on consumers and producers. In particular, data on the own-price elasticity of supply and demand often are uncertain. This appendix provides background information on the likely effects of own-price elasticity of demand and supply on the outcomes of EPA's regulatory efforts. The bulk of the discussion focuses on the case of perfect competition, not because the majority of markets EPA is likely to affect will exhibit competitive behavior, but simply because the theory is clearly defined in this case. However, this appendix also examines the likely impacts of relaxing the assumption of perfect competition. It focuses on two general classes of regulatory options: regulations that alter the market outcome by imposing additional costs upon producers, and regulations that alter the market by providing information to consumers.

3A.1 Elasticities of Supply and Demand

The market equilibrium for a commodity (e.g., purchasing renovation, remodeling or painting (RRP) work that uses lead-safe work practices) is determined by the intersection of the aggregate demand and supply curves. The aggregate demand curve depicts consumer behavior and is based on consumer income and preferences. Likewise, the aggregate supply curve describes the behavior of producers in the market, and is dependent upon the costs of production. At market equilibrium, the price is referred to as market clearing. In other words, at this price, the quantity demanded by consumers and supplied by producers are equal and neither the consumer nor producer has any incentive to move away from this steady state as long as current demand and supply conditions prevail.

However, when demand and supply conditions do change, for example when new information causes consumers to adjust their preferences and thus shift the demand curve, or changes in input prices affect costs of production and shift the supply curve, the market gravitates to a new equilibrium. This new equilibrium is represented by a new combination of market clearing price and quantity. The magnitude of the change in price and quantity is dependent not only upon the extent of the shift in the demand or supply curve, but also on the own-price elasticity of demand and supply for the commodity.

The own-price elasticity of demand is defined as the ratio of the percent change in quantity demanded to the percent change in price, and is reflected in the slope of the demand curve, similarly for the own-price elasticity of supply. By determining the level of change in price and quantity, the elasticities of the two curves also determine the distribution of the burden or benefit between the consumer and producer resulting from a change in equilibrium conditions. Analyzing changes in consumer and producer surpluses provides a means for quantifying such distributional changes.

Figure 3A-1 below provides an hypothetical example of how the effects of regulation may impact consumer and producer surpluses. In the baseline, the supply curve is represented by S_1, and producers supply Q_1 at a price P_1. On all the inframarginal units supplied, producers receive a price above the cost of production. The difference between the price and the cost of production represents the producer surplus resulting from supplying Q_1 at price P_1 (triangle P_1CD). Similarly, in the baseline consumers demand quantity Q_1 at price P_1. For all the inframarginal units demanded, consumers would be willing to pay more than that price and thus receive a surplus. The difference between what consumers are willing to pay as measured by the height of the demand curve, and what they have to pay is the consumer surplus (triangle ACP_1).

So what are the effects of regulation? In Figure 3A-1, the upward shift in the supply curve to S_2 (say from a rise in production costs due to the implementation of the RRP rule which requires use of the more costly lead-safe work practices) results in a new equilibrium at the point B, with a new market price of P_2 and quantity of Q_2. Note that producer surplus decreases from P_1CD to EBP_2 and the consumer surplus also decreases from ACP_1 to ABP_2. Thus, in the arbitrary case drawn in Figure 3A-1, the social costs of the regulation are born by both consumers and producers of the pollution-generating good. This result turns out to be a function of the way the supply and demand curves have been drawn, and the distribution of costs between consumers and producers depends on the slope (elasticity) of the demand and supply curves.

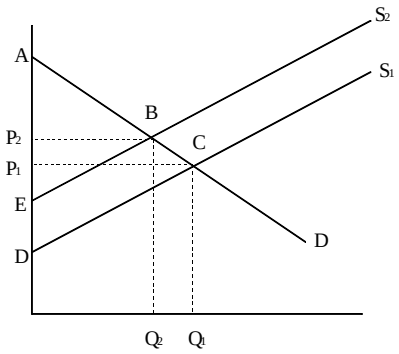


Figure 3A-1: Effect on consumer and producer surplus due to a supply curve shift

In general, for a given production cost increase, the more elastic the demand curve, the greater the inability on the part of the producers to pass the additional costs of production on to the consumers. As shown in Figure 3A-2 (a) and 3A-2 (b) below, the differing slopes of the demand curve lead to differential impacts on the consumer and producer surplus. In Figure 3A-2 (a) demand for the good is relatively price elastic, while in Figure 3A-2 (b) the good has a relatively inelastic demand. Notice that when demand is less elastic, the price increase resulting from a shift in supply is greater and consumers bear a greater share of the loss in consumer surplus. On the other hand, with a more elastic demand, the overall price increase is smaller and the share of total costs born by producers is larger.

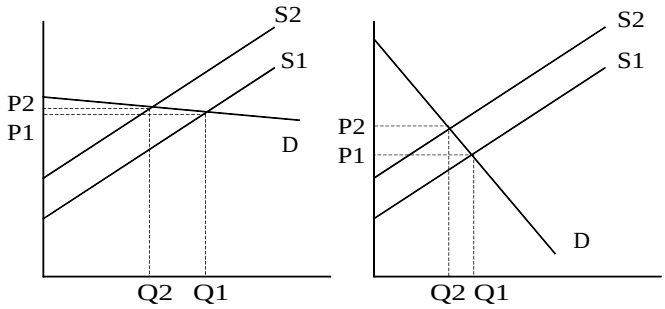


Figure 3A-2(a) **Figure 3A-2(b)**

2(a): Effect of a change in input prices when demand is elastic

2(b): Effect of a change in input prices when demand is inelastic

The elasticity of demand is determined in general by the existence of suitable substitutes for a commodity. If several commodities exist in the market that are considered to be close substitutes for each other, then a consumer is likely to have a great deal of choice available to him while making his consumption decision. This being the case, if the price of the commodity that he is presently consuming happens to rise, he is easily able to reduce his current consumption level of that commodity and switch over to consuming more of one of the substitutes. This flexibility limits the ability of the producer to pass on the burden of the cost increase on to the consumer. Thus, the availability of close substitutes in the market explains why the demand curve for a commodity will be relatively elastic, and why the rise in price will be relatively small. On the other hand, if substitutes are lacking for a commodity that experiences a price increase (and it is not a luxury good), then the consumer has little choice but to carry on consuming similar quantities of the same product. Thus, in this situation he will have to shoulder a larger share of the increased costs by paying a much higher price, and this rigidity in his consumption behavior explains the inelastic nature of the demand curve for that commodity.

Recognizing that most markets are not perfectly competitive, product differentiation allows firms to charge prices higher than marginal costs and charge different prices for similar goods. The degree to which producers can pass on the cost of production depends heavily on the degree to which they can convince consumers that their product is different from other products. In its limit this argument is just a restatement of the fact that markets with lower elasticities of demand will experience higher price increases. If "market demand" is defined to be the demand for a single brand of good, then the number of substitutes for the good affects its demand elasticity and thus affects the degree to which the producer can pass on cost increases. If the firm can convince consumers that the product is distinct then it in essence lowers the elasticity of demand for its product.

The own price elasticity of supply, on the other hand, is dependent on the degree of specialization of inputs. If the inputs are highly specialized or firms are locked into long term contracts then firms in this industry can be left with substantial sunk investments creating high transition costs which are reflected in an inelastic supply curve. However, if supply is highly elastic then firms can easily switch production to other uses and minimize the effect of the demand shock. In essence the elasticity of supply measures the amount of resources lost or tied up indefinitely when consumption patterns change suddenly.

The EPA seeks to reduce hazards from lead-based paint under the RRP rule by two separate pathways of regulatory impact. First, it hopes to reduce exposure to lead-based paint by regulating the "method of production" of RRP work in pre-1978 homes by establishing standards for such activities and through requiring certifications and/or training. This is likely to result in an increase in the "costs of production" of RRP work thereby affecting the supply curve for such activities. Second, the RRP rule will provide information to consumers. In this case EPA is likely to alter the market outcomes by changing the demand for products (lead-safe and non lead-safe work practices). To the extent that the demand and supply of RRP work will be affected by the rule, one must consider the price elasticities involved to determine the distributive impact of the rule on consumers and producers.

An important factor on which the price elasticity will depend is the number of substitutes that exist for the RRP service that is sought in the market. As previously explained, the greater the number of available substitutes, the more elastic the demand and lesser the burden of a production cost increase likely to fall on the consumer. Under this rule three classes of substitutes may be said to exist for RRP services. These are (1) professionals using lead-safe work practices, (2) professionals using non lead-safe work practices,

and (3) the do-it-yourself jobs. Thus, a certain amount of flexibility is available to the consumer when it comes to hiring RRP services.

Currently a sizeable number of RRP firms may not necessarily be following lead-safe work practices thereby limiting the size of the class of firms that do so. However, with the implementation of the RRP rule, a much larger number of firms are expected to adhere to these practices in the future, thus enlarging the size of this class. In addition, this increase in the number of professionals using lead-safe work practices will also have a geographical impact. Presently, the limited number of professionals who use lead-safe work practices are concentrated in a select number of locations where state and local regulations have fostered their development. As a result, in many parts of the country the choice of hiring "lead-safe" professionals currently does not exist. But this situation will change as a larger number of firms switch to lead-safe work practices once the RRP rule comes into effect.

However, if the increase in production costs from the rule is extremely high such a large transition of firms from using lead-unsafe to lead-safe work practices may not occur. This is because the cheaper option of using non-certified (non lead-safe work practice using) RRP workers or doing the work yourself will limit the ability of the certified (lead-safe work practice using) professional to charge the consumer for all or a large portion of this significant cost increase. In this situation a large number of lead-unsafe firms may remain in existence. Thus, one may assume that as long as an appreciable difference exists between "costs of production" of lead-safe and non lead-safe work practices, firms of both types will continue to exist. The continued existence of firms using non lead-safe practices also depends on the extent and effectiveness of enforcement activities. The greater the cost differential between lead-safe and non lead-safe practices, the greater the need for enforcement activities.

In addition to the number of substitutes, the closeness of substitutes in their ability to replace one another needs to be judged. The important question is whether RRP work done by uncertified professionals and the do-it-yourself efforts are substantially less safe than the services of certified professionals. To the extent an appreciable difference exists between the quality of service (in terms of preventing or reducing lead-based paint hazards) provided by the two groups, they will not be perceived as close substitutes for each other and their demand curves will not be as elastic as they would have been if they were considered close substitutes. In such a situation, consumers feel that a sufficiently differentiated product is being offered by the two groups, and thus their choice is limited.

This judgment on the degree of closeness of substitutes will to some extent depend upon the importance that lead safety holds with the homeowner compared to other priorities. To the extent that the priority assigned to lead exposure is relatively small, the uncertified professionals and do-it-yourself jobs will tend to be seen as closer substitutes for certified professionals, than if lead-based paint hazards are perceived as a larger threat by the household. Thus, the elasticity of demand will also vary according to homeowner priorities, and in this regard, the informational aspect of the RRP rule may in fact assist in raising more awareness, resulting in lead safety being assigned a higher priority.

Of a related nature, the firm certification aspect of the rule is likely to increase consumer ability to differentiate between the services being offered by the three classes of substitutes. The certification process will create a distinct divide which will permit the homeowner to get a better appreciation of the varied benefits to be gained from the alternatives at hand. This is likely to reduce to some extent the perceived closeness of the substitutes and thereby make the demand more inelastic for each class of RRP service.

3A.2 How Price Elasticity of Demand Affects the RRP Rule

As discussed above, EPA foresees two separate pathways by which the RRP rule will take affect; increasing costs of production leading to a shift in supply and provision of information to consumers leading to a shift in demand. The way these two effects will play out and the role that price elasticities will play in the adjustment of prices and quantities under the two scenarios is discussed below.

3A.2.1 Effect of RRP Rule on the Cost of Production (Supply Shift)

EPA seeks to reduce exposure to lead-based paint hazards by the introduction of lead-safe work practices during RRP work. These practices involve the use of increased precautions in situations where lead-based paint hazards may potentially be created during RRP work, and as a result costs of RRP work are likely to increase above current levels. Since producers seek to maximize profits and in the baseline will produce goods using the lowest-cost combination of inputs, a rule requiring producers to change their input mix will necessarily increase the cost of production. Thus, one impact of the rule will be to increase the production costs, leading the supply curve to shift upward and to the left.

Figures 3A-2(a) and 3A-2(b) demonstrate the distributional affects of such a hypothetical shift in supply in markets with different elasticities of demand. The price increase is much higher (P1 to P2) and the decrease in quantity demanded is much lower (Q1 to Q2) with a given shift in supply when demand is less elastic (as shown in Figure 3A-2(b)) as compared to the elastic demand scenario in Figure 3A-2(a). Thus, the consumers bear a higher share of the total social cost from the regulation (represented by the relatively larger decrease in the consumer surplus compared to that in the producer surplus). On the other hand, Figure 3A-2(a) shows that the higher the elasticity of demand, the lower the overall price increase, the larger the reduction in quantity demanded, and thus the larger the share of total costs to be born by producers (represented similarly by the larger decrease in producer surplus as compared to the consumer surplus).

3A.2.2 Effect of RRP Rule on the Provision of Information to Consumers (Demand Shift)

The alternative regulatory approach is to provide information to consumers in the hopes that they will make more environmentally friendly consumption choices. In this case EPA alters the market outcomes by changing the demand for products. Figures 3A-3(a) and 3A-3(b) depict such a hypothetical example. In these cases the commodity in question (non lead-safe work practices) has negative environmental effects (byproducts). By educating consumers about these byproducts and alternative products that have lower levels of adverse effects (lead-safe work practices), EPA can change consumer preferences and shift demand for the "bad product" inward and to the left. This lower demand curve would more accurately reflect the true "social" marginal benefits of consuming the product.

What are the likely distributional and efficiency effects of this type of regulatory policy? Figures 3A-3(a) and 3A-3(b) reveal that under both scenarios (for an elastic and inelastic supply curve), the downward shift in the demand curve will lead to a decrease in price and quantity demanded of the commodity. However, in the case of an elastic supply curve when the transition costs associated with switching to the production of other products is relatively low, the decrease in price of the commodity is smaller and the decrease in quantity demanded larger, as compared to the changes in the case of an inelastic supply curve involving high transition costs. Restated in terms of changes in producer and consumer surpluses, the producer surplus is reduced under each scenario, but the elastic supply curve causes a relatively smaller

burden to fall on the producer than the inelastic supply curve. Similarly, the consumer receives a reduction in social benefit under each scenario, however, the magnitude of this reduction is larger under the inelastic supply curve case.

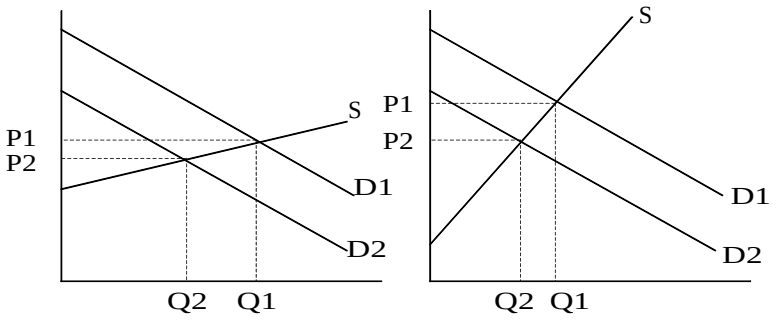


Figure 3A-3(a) **Figure 3A-3(b)**

3(a): Effects of a regulation-induced change in demand when supply is elastic

3(b): Effects of a regulation-induced change in demand when supply is inelastic

3A.2.3 Application to Renovation

In the Renovation, Repair and Painting Rule, EPA is both affecting production and providing information. The likely effects of the regulation on prices and welfare are difficult to discuss without more accurate information on the supply and demand elasticities. However, some general observations are warranted.

The welfare effects of the regulation will likely be driven by the supply side rather than the demand side. This is because the elasticity of supply for RRP services is likely to be relatively higher than the elasticity of demand. Supply elasticities are expected to be relatively high because there are relatively few barriers to entering or leaving this industry. Little capital equipment or specialized labor skills are needed for RRP work, and what is needed is easily transferred from non-compliant renovation to "lead-safe" projects. On the demand side, there are two primary categories of RRP events – those of a maintenance character and those of an improvement character. Maintenance activities usually cannot be postponed and thus are not particularly sensitive to price. Improvement projects, however, can more easily be postponed and thus tend to be more price elastic. Complicating matters, however, are the existence of different categories of purchasers. Some place a high premium on quality and timeliness, while others actively seek low prices. Appendix 3B discusses some of the empirical evidence on elasticities of demand and supply.

However, the analysis does not suggest that the education factor is unimportant. If the regulation is not accompanied by education efforts and enforcement, then EPA could unintentionally drive up demand for non-compliant renovation projects creating additional welfare losses. These losses are the result of the fact that if consumers were aware of the lead paint issues their true marginal valuation for the non-compliant projects is lower than the price of these projects. Thus, if enforcement is not perfect, education is essential. EPA can compensate for the fact that it is raising the costs of lead-free renovation on the supply side by educating consumers on the environmental effects of non-compliant renovations thereby making these cheaper, non-compliant projects less attractive.

Appendix 3B: Elasticities of Demand and Supply for Housing / Renovation Services

As described in Chapter 3 and Appendix 3A, the impact of increases in the cost of RRP services on demand for RRP will depend on both the size of the cost increase and the elasticity of demand for these services. Likewise, the impact on the supply of RRP services will depend on both the size of the cost increase and the elasticity of supply for these services. These impacts are expressed in terms of changes in price and in the quantity of services purchased. Chapter 4 estimates the cost increases due to the requirements of the various regulatory options, based on the increased labor and materials costs of complying with the containment and clean-up requirements, as well as the training and certification costs imposed by the requirements. This appendix reviews the existing literature on residential demand elasticities.

Unfortunately, RRP has received relatively little attention by housing economists. While there are many studies that estimate elasticities for new construction, these studies have only limited applicability to renovation and remodeling. The income elasticity of demand for housing is generally estimated to be somewhat inelastic (in the 1.0 to 0.8 range). This is consistent with housing being a necessity – expenditures on housing do not increase as rapidly as income (Green and Malpezzi 2003). Demand for housing is also considered to be somewhat price inelastic, with generally accepted values either in the range of -0.5 to -1.0 or -0.75 to -1.2 (Mayo 1981, Malpezzi and Maclennan 2001, Ellwood and Polinski 1979). One study is available that estimated a renovation demand elasticity (Gyourko and Saiz 2003). This study found renovation demand to be very inelastic, with an elasticity estimated to be –0.28.

On the other hand, housing supply appears to be very elastic – consistent with the highly competitive nature of the residential construction market and the large number of small contractors. Because it is very easy to enter (and to leave) the construction business, supply is very responsive to changes in prices, especially in the long run.[1] Based on the literature surveyed, estimates of housing supply elasticities tend to range from 1.0 to 4.0, but a couple of studies found elasticities as high as 13 or higher (DiPasquale and Wheaton 1994, Topel and Rosen 1988, Blackley 1999, Malpezzi and Maclennan 2001). No elasticity numbers specific to the supply of renovation services could be found.

Several characteristics of RRP tend to make its demand more price elastic than the demand for housing in general. For example:

- The existence of close substitutes to professional RRP. These substitutes include:
    - Do-It-Yourself RRP. One substitute for professional RRP (the regulated commodity) is Do-It-Yourself RRP (a non-regulated commodity)
    - Firms that do not complying with the regulations. These regulations may be difficult to enforce because of the large number of small contractors who may be hard to identify and monitor. If the regulations are not actively enforced, purchasers will be able to buy the services from non-compliant firms at a lower price.
    - Reductions in the scope of the projects to compensate for the price increase. Purchasers can reduce other RRP-related costs by substituting lower-priced appliances/fixtures and/or less extensive remodeling

[1] Note – stock adjustment models give lower elasticities than flow models. Malpezzi and Maclennan (2001).

    - Move instead of remodel. Purchasers can move to another dwelling that meets their needs/desires.
- Many RRP projects are discretionary. The price elasticity of discretionary projects (e.g. new family room or updated/expanded kitchen) is likely to be higher than replacement projects (e.g. new roof).For discretionary RRP projects, it is relatively easy for the purchaser to reduce the scale/scope of the project, postpone the project, or never do it.

Offsetting these characteristics that foster higher elasticities of demand, are ones that foster lower elasticities. The major one is that the product purchased cannot be separated from the firm providing the product, which is true of all services. In addition to the various RRP events analyzed in the subsequent chapters, RRP firms themselves are relatively differentiated. Some firms specialize in high-end, complicated projects (e.g. elaborate new kitchens) while other firms specialize in performing small routine tasks (repainting apartments at tenant turn-over). Some firms only work in historic or Victorian homes, while others will work on any type of home. Some firms do only one type of project (e.g. replacing siding) while other firms will do any and all types of RRP work. This differentiation results in lower demand elasticities, because producers are not considered particularly close substitutes.

- To the extent that lead-safe work can be distinguished from non-lead-safe work, a higher price can be charged for it.

- Many contractors already employ lead-safe practices (or at least control the dispersion of dust and clean well before leaving). The regulations will serve to reduce this differentiation.

Second, the nature of RRP projects may also reduce price competition. For relatively small jobs, homeowners frequently will not get multiple bids – the assumed cost of the job does not warrant the effort. In this case, the compliance cost can be passed on without fear of losing the work. In the case of large jobs, where home owners will get bids, compliance costs will make up a relatively small proportion of the total cost and, again, passing on the costs may be easy.

Characteristics of the purchaser of the RRP services may also affect their demand price elasticity. High-income purchasers are likely to be less price sensitive than low-income purchasers. In addition, owners of rental properties may be more price sensitive than owner occupants because they have different objective functions. Owner-occupants operate so as to maximize their utility (their enjoyment of the house) and asset growth is likely to enter their decision as a secondary factor. Owners of rental housing, on the other hand, are assumed to be maximizing their profits. It is reasonable to expect that the optimal level of capital of an absentee landlord's rental building is lower than that of an owner-occupier's house, since the landlord's marginal rent revenue from renovations is likely to be less than the homeowner's marginal utility.

Because of the lack of detailed price elasticity estimates for RRP, the analysis in the Chapters 4, 5 and 6 do not incorporate any reduction in professional RRP activities in response to the cost increases resulting from the regulation. The sensitivity analysis presented in Chapter 7 and the small entity analysis in Chapter 8 addresses these issues.

REFERENCES

Battelle. 1999. *Risk Assessment to Support Standards for Lead in Paint, Dust and Soil.* Prepared by Battelle, for National Program Chemicals Division, Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency. EPA 747-R-006, December.

Blackley, D.M. 1999. "The Long-Run Elasticity of New Housing Supply in the United States: Empirical Evidence for 1950 to 1994." *Journal of Real Estate Finance and Economics*, 18: 25-42.

California Department of Health Services (CA DHS). 1999. Title 17, California Code of Regulations, Division 1, Chapter 8: Accreditation, Certification, and Work Practices for Lead-Based Paint and Lead Hazards. Available at: http://www.dhs.ca.gov/childlead/pdfs/Title17.pdf

California Department of Health Services (CA DHS). 2003. Summary of California's Lead Hazard Reduction Enforcement: Senate Bill 460. Available at: http://www.lacity.org/lahd/SB460.pdf.

Center for Disease Control. 1997. "Children with Elevated Blood Lead Levels Attributed to Home Renovation and Remodeling Activities -- New York, 1993-1994." *Morbidity and Mortality Weekly Reports*. 45(51&52);1120-3. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00045033.htm.

Center for Disease Control. 2002. Managing Elevated Blood Lead Levels Among Young Children (March).

Center for Disease Control. 2004. Preventing Lead Exposure in Young Children: A Housing Based Approach to Primary Prevention of Lead Poisoning: Recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention (October).

Center for Disease Control. 2005. "Blood Lead Levels --- United States, 1999—2002." *Morbidity and Mortality Weekly Reports.* 54(20);513-516. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5420a5.htm#tab1.

City of Cleveland. 2004. *Ordinance No. 1027-04*. Available at: http://www.ehw.org/Lead/documents/finalleadordinance.pdf

City of New Orleans. 2001. *Ordinance No. 20345 Mayor Council Series*. Available at: https://secure.cityofno.com/resources/portal47/finordin.pdf

City of New Orleans. *Work Practices for Renovations to Buildings Containing Lead-Based Paint*. Available at: https://secure.cityofno.com/resources/portal37/leadpaint.pdf

Chicago Department of Public Health (CDPH). *City of Chicago Department of Public Health Control and Mitigation of Lead Bearing Substance.* Available at: http://egov.cityofchicago.org/webportal/COCWebPortal/COC_EDITORIAL/LeadReg.5.19.04_3.pdf.

Commonwealth of Massachusetts. 1999. *454 CMR 22.00: Deleading Regulations.*

President's Task Force on Environmental Health Risks and Safety Risks to Children. 2000. Eliminating Childhood Lead Poisoning: A Federal Strategy Targeting Lead Paint Hazards (February).

DiPascale, Denise and William C. Wheaton. 1994. "Housing Market Dynamics and the Future of Housing Prices." Journal of Urban Economics, 35: 1-27.

Ellwood, David and Mitchell Polinski. 1979. "An Empirical Reconciliation of Micro and Grouped Estimates of the Demand for Housing," Review of Economics and Statistics, 61:199-205.

Green, Richard K. and Stephen Malpezzi, 2003, A Primer on U.S Housing Markets and Housing Policy, AREUEA Monograph Series No. 3, The Urban Institute Press, Washington DC.

Gyourko, Joseph and Albert Saiz. 2003. *Urban Decline and Housing Reinvestment: The Role of Construction Costs and the Supply Side.* Federal Reserve Bank of Philadelphia. Working Paper 03-9.

Indiana State Department of Health. 2001. Article 23. Lead-based Paint Program. Available at: http://www.ai.org/legislative/iac/T03260/A00230.PDF.

Kansas City Health Department. *Article X. Lead Poisoning Control.* Available at: http://www.kcmo.org/health.nsf/web/ordinance?opendocument.

Malpezzi, Stephen and Duncan Maclennan. 2001. "The Long-Run Price Elasticity of Supply of New Residential Construction in the United States and the United Kingdom," Journal of Housing Economics, 10: 278-306.

Mayo, Steven K. 1981. "Theory and Estimation in the Economics of Housing Demand, Journal of Urban Economics, 10 (January) 95-116.

National Council of State Legislatures. 2005. *State Lead Statutes*. Available at: http://www.cdc.gov/nceh/lead/Legislation%20&%20Policy/State%20Lead%20Statutes%20Jan%205,%202005%20NCSL.PDF.

New Jersey Department of Community Affairs (NJ DCA). 2004. Regulations for Lead-Safe Maintenance of Rental Property. Available at: http://www.state.nj.us/dca/codes/lead_safe/combined_lead_regs.pdf.

New York City Department of Housing Preservation and Development (NY DHPD). 2004. *Local Law 1/2004 – Section by Section Analysis.*

New York City Department of Housing Preservation and Development (NY DHPD). 2004. *Local Laws of the City of New York for the Year 2004: No. 1*. Available at: http://dhfs.wisconsin.gov/waldo/Registry/index.htm.

Oregon Department of Human Services Office of Public Health Systems (OR DHS). 2003. *Oregon Administrative Rule (OAR) 333-069.* Available at: http://arcweb.sos.state.or.us/rules/OARs_300/OAR_333/333_069.html.

Oregon Department of Human Services Office of Public Health Systems (OR DHS). Lead-Based Paint Permit Application. Available at: http://www.oregon.gov/DHS/ph/leadpaint/docs/permitapp.pdf.

Residential Lead-Based Paint Hazard Reduction Act of 1992, Pub. L. no. 102-550. 106 Stat. 3672 (1992).

Rhode Island Department of Environmental Management (RI DEM). Air Pollution Control Regulation No. 24: Removal of Lead Based Paint from Exterior Surfaces. Available at: http://www.dem.ri.gov/pubs/regs/regs/air/air24_93.pdf.

Rhode Island Department of Environmental Management Office of Technical and Customer Assistance (RI DEM). 2005a. Exterior Lead Paint Removal Certification Program (Brochure). Available at: http://www.dem.ri.gov/programs/benviron/assist/extlead/pdfs/mailer.pdf.

Rhode Island Department of Environmental Management Office of Technical and Customer Assistance (RI DEM). 2005b. *Environmental Compliance Certification Program: Certification Checklist Package for Exterior Lead Paint Removal Contractors*. Available at: http://www.dem.ri.gov/programs/benviron/assist/extlead/pdfs/cheklist.pdf

Rhode Island Department of Environmental Management Office of Technical and Customer Assistance (RI DEM). 2005c. *Certified Contractor List*. Available at: http://www.dem.ri.gov/programs/benviron/assist/extlead/pdfs/conlist.pdf.

Rhode Island Department of Health (RI DOH). 1992. *Rules and Regulations for Lead Poisoning Prevention [r23-24.6-pb]*. Available at: http://www.rules.state.ri.us/rules/released/pdf/DOH/DOH_3357.pdf.

Rhode Island Housing Resources Commission. 2003. Lead Hazard Mitigation Regulations. Available at: http://www.hrc.ri.gov/pdf/LeadHazard_Mitigation_Regs.pdf.

San Francisco Department of Building Inspection. (DBI) 1999. Chapter 36 of the *San Francisco Building Code*. Available at: http://www.centerforhealthyhousing.org/SF_Lead_Ordinance.pdf.

State of Maine. 2004. Title 38, Chapter 12-B, Lead Abatement (Heading: PL 1997, c.375, @14(new)). Available at: http://janus.state.me.us/legis/statutes/38/title38ch12-B.pdf.

State of Maryland. 1994. *The Lead Poisoning Prevention Program. Environmental Article 6-8 (Housing Bill 760).*

Topel, R. and S. Rosen. 1988. "Housing Investment in the United States." *Journal of Political Economy*, 96: 718-740.

U.S. Department of Housing and Urban Development (HUD). 1990. *Comprehensive and Workable Plan for the Abatement of Lead-Based Paint in Privately Owned Housing: Report to Congress.* Washington, DC, February.

U.S. Department of Housing and Urban Development (HUD). 1995. Guidelines for the Evaluation and Control of Lead-Based Paint Hazards in Housing (June).

U.S. Department of Housing and Urban Development (HUD). 1997. *Moving Toward a Lead-Safe America. A Report to the Congress of the United States*. Office of Healthy Homes and Lead Hazard Control, Washington, DC, February.

U.S. Department of Housing and Urban Development (HUD). Data as of August, 2000. *National Survey of Lead and Allergens in Housing.* Office of Healthy Homes and Lead Hazard Control, Washington, DC.

U.S. Department of Housing and Urban Development (HUD). 2004b. Requirements for Notification, Evaluation, and Reduction of Lead-based Paint Hazards in Housing Receiving Federal Assistance and Federally Owned Residential Property Being Sold (Lead Safe Housing Rule); Final Rule, Conforming Amendments and Corrections. Federal Register (69 FR 34262, June 21, 2004).

U.S Department of Housing and Urban Development (HUD) and U.S. EPA. 1996. Lead; Requirements for Disclosure of Known Lead-Based Paint and/or Lead-Based Paint Hazards in Housing; Final Rule. Federal Register (61 FR 9064, March 6, 1996)

U.S. Department of Labor, Occupational Safety and Health Administration (OSHA). 1993. Lead Exposure in Construction; Interim Final Rule. Federal Register (58 FR 26590, May 4, 1993).

U.S. EPA. 1984. EPA Policy for the Administration of Environmental Programs on Indian Reservations (November 8).

U.S. EPA. 1995. Lead Hazard Information Pamphlet; Notice of Availability. Federal Register (60 FR 39167, August 1, 1995).

U.S. EPA. 1996. Lead; Requirements for Lead-Based Paint Activities in Target Housing and Child-Occupied Facilities: Final Rule. Federal Register (61 FR 5778, August 29, 1996).

U.S. EPA. 1998. Lead; Requirements for Hazard Education Before Renovation of Target Housing; Final Rule. Federal Register (63 FR 29908, June 1, 1998).

U.S. EPA. 1999. Lead; Fees for accreditation of Training Programs and Certification of Lead-based Paint Activities Contractors; Final Rule. Federal Register (64 FR 31092, June 9, 1999).

U.S. EPA. 2001b. Lead; Identification of Dangerous Levels of Lead; Final Rule. Federal Register (66 FR 1206, January 5, 2001)

U.S. EPA. 2004a. Lead; Notification Requirements for Lead-Based Paint Abatement Activities and Training; Final Rule. Federal Register (69 FR 18489, April 8, 2004)

U.S. EPA. 2004b. Targeted Grants to Reduce Childhood Lead Poisoning; Notice of Funds Availability. Federal Register (69 FR 69913, December 1, 2004).

U.S. EPA, Consumer Product Safety Commission, U.S. Department of Housing and Urban Development (HUD). 2003. Protect Your Family From Lead in Your Home (EPA 747-K-99-001, June 2003).

Vermont Statutes Online. 2005. *Title 18: Health. Chapter 38: Lead Poisoning.* Available at: http://www.leg.state.vt.us/statutes/fullchapter.cfm?Title=18&Chapter=038

Wisconsin Department of Health and Family Services (WI DHFS). 2003. *Chapter HFS 163. Certification for the Identification, Removal and Reduction of Lead-Based Paint Hazards.* Available at: http://www.legis.state.wi.us/rsb/code/hfs/hfs163.pdf.

Wisconsin Department of Health and Family Services (WI DHFS). 2005. *Lead-Free/Lead-Safe Registry.* Available at: http://dhfs.wisconsin.gov/waldo/Registry/index.htm.

Personal Communication with David Holston, Ohio Department of Health Lead Poisoning Prevention Program. August 2005.

Personal Communication with Kendra Frazier, California Department of Health Services, Compliance and Enforcement. August 2005.

Personal Communication with Paul Lamberti, Supervisor, Lead/Asbestos Unit at the New Jersey Department of Community Affairs. August 2005.

4. Compliance Costs of the Renovation, Repair, and Painting Rule

The costs associated with the regulatory impact of the §402(c) Renovation, Repair, and Painting (RRP) Rule are divided into three categories for the purposes of this analysis: (1) training costs, (2) work practice costs, and (3) certification costs (which include the firm's paperwork burden and EPA administrative and enforcement costs). The general approach of the analysis is to first estimate the number of affected activities or entities, then estimate the incremental regulatory cost per-activity or entity affected. Finally, the incremental costs and the number of affected activities and entities are combined to estimate the total costs. The analysis first estimates the total costs associated with the first three years of regulation; then, the analysis extrapolates to the costs of the regulation over a fifty year period—estimated with three and seven percent discount rates.

The chapter is organized as follows: Section 4.1 defines the regulatory options considered in this analysis; Section 4.2 estimates the number of regulated renovation, repair, and painting events under the various regulatory scenarios; Section 4.3 presents the estimated number of affected establishments and personnel; Section 4.4 presents the estimated incremental training costs; Section 4.5 presents the per-event work practice costs; Section 4.6 presents the administrative and enforcement cost estimates; and Section 4.7 presents the total costs of the regulation.

4.1 Definitions of Options

The four options considered in this analysis differ by the type of housing units they affect and whether they are flexible or prescriptive. In each case, the differences in the types of housing units affected by the rule produces differences in the numbers of housing units affected by the rule. Table 4-1 summarizes the options considered in this analysis; they are described in more detail below.

Options A, B, and C are described as flexible, which means that certified renovators can rely upon their training to determine how much containment is necessary and practical in any particular situation. Thus, when the analysis refers to the flexible options, it refers to Options A, B, and C together; these options differ in terms of the universe of housing units subject to the rule's requirements during the first year of the rule. In addition to these three options, a more prescriptive option is considered, referred to as Option D. The containment, cleaning, and verification practices required under Option D are the same as those in the flexible options; however, Option D prescribes the size of the work area that must be contained, cleaned, and verified. Therefore, Option D is referred to as prescriptive. The proposed rule is Option B.

Table 4-1: Summary of Options			
Option Name	**Universe**		**Containment, Cleaning, and Verification**
	Year 1	**Years 2+**	
Option A	All Pre-1978 renter-occupied target housing units and pre-1978 owner-occupied target housing units where a child under the age of six resides	All Pre-1978 renter-occupied target housing units and pre-1978 owner-occupied target housing units where a child under the age of six resides.	Flexible: Flexible containment practices, required cleaning and verification methods
Option B	All Pre-1960 renter-occupied target housing units and pre-1960 owner-occupied target housing units where a child under the age of six resides [a]	All Pre-1978 renter-occupied target housing units and pre-1978 owner-occupied target housing units where a child under the age of six resides.	Flexible: Flexible containment practices, required cleaning and verification methods
Option C	All Pre-1950 renter-occupied target housing units and pre-1950 owner-occupied target housing units where a child under the age of six resides [a]	All Pre-1978 renter-occupied target housing units and pre-1978 owner-occupied target housing units where a child under the age of six resides.	Flexible: Flexible containment practices, required cleaning and verification methods
Option D	All Pre-1960 renter-occupied target housing units and pre-1960 owner-occupied target housing units where a child under the age of six resides [a]	All Pre-1978 renter-occupied target housing units and pre-1978 owner-occupied target housing units where a child under the age of six resides.	Prescriptive: Required containment practices, required cleaning and verification methods

[a.] In Year 1, also includes all pre-1978 housing units where a child with an increased blood-lead level resides, where increased is defined as greater than or equal to 10 µg/dL or a State or local government level of concern, if lower.

The proposed rule is Option B.

4.1.1 Affected Universe, by Option

The term "target housing" is defined in TSCA Section 401 as any housing constructed before 1978, except housing for the elderly or persons with disabilities (unless any child under 6 resides or is expected to reside in such housing) or any 0-bedroom dwelling. EPA is not proposing to modify this definition in any way. For Options B, C, and D, the type of housing units affected by the rule differs in the first year of the rule but are the same in all subsequent years of the rule thereafter.

Option A

During all years of the rule, the requirements in Option A would apply to renovation projects performed for compensation in:

- All renter-occupied target housing.
- All owner-occupied target housing, unless the firm performing the renovation obtains a statement signed by the owner that the renovation will occur in the owner's residence and no child under 6 resides there.

Option B

During the first year, the requirements in Option B apply to renovation projects performed for compensation in:

- All pre-1960 renter-occupied target housing.
- All pre-1960 owner-occupied target housing, unless the firm performing the renovation obtains a statement signed by the owner that the renovation will occur in the owner's residence and no child under 6 resides there.
- All pre-78 target housing units where a child with an increased blood-lead level resides.

For all subsequent years:

- Option B is identical to Option A.

Option C

During the first year, the requirements in Option C apply to renovation projects performed for compensation in:

- All pre-1950 renter-occupied target housing.
- All pre-1950 owner-occupied target housing, unless the firm performing the renovation obtains a statement signed by the owner that the renovation will occur in the owner's residence and no child under 6 resides there.
- All pre-78 target housing units where a child with an increased blood-lead level resides.

For all subsequent years:

- Option C is identical to Option A.

Option D

During the first year of the rule:

- The type of housing units affected during the first year of the rule under Option D is the same as the type of housing units affected during the first year of the rule under Option B.

For all subsequent years:

- The housing stock affected under Option D is identical to the housing stock affected during subsequent years of the rule under Option B.

For each option, the proposal would apply to housing that is currently being rented, as well as housing being offered for rent and housing that the owner intends to offer for rent. Renovations to prepare housing for the rental market would have to be performed in accordance with this proposal.

For the purposes of this proposal, children reside in the primary residences of their custodial parents, foster parents, and legal guardians. In addition, EPA is proposing to apply this regulation to housing where a child resides and sleeps most of the time, even if this housing is not the residence of the child's legal custodians. This means that a child may have more than one residence; this requirement should ensure that the primary residences of all children under 6 are covered by the proposal.

4.1.2 Proposed Containment, Cleaning, and Verification Standards, by Option

The proposed containment, cleaning, and verification standards mentioned in this section are the same for all options. Options A, B, and C allow those who are performing the RRP activity to decide the extent of containment necessary. Contrastingly, Option D specifies the area to be contained.

Occupant protection

Under proposed Section 745.85(a)(1), work areas must be clearly defined with signs warning occupants and other persons not involved in renovation activities to remain outside of the work area. These signs must be posted before beginning the renovation and must remain in place until the renovation has been completed and the work area has been verified to have been adequately cleaned. If warning signs have been posted in accordance with HUD's Lead Safe Housing Rule (24 CFR §35.1345(b)(2)) or OSHA's Lead in Construction Standard (29 CFR §1926.62(m)), additional signs are not required by this proposal.

Containing the work area

Under proposed Section 745.85(a)(2), a firm must contain the work area so that no visible dust or debris leaves the work area while the renovation is being performed. Containment refers to methods of preventing leaded dust from migrating beyond the work area. It includes everything from the simple use of disposable plastic drop cloths to the sealing of openings with plastic sheeting.

Interior renovations

When planning a renovation project, special consideration should be given to determining the type of work site preparation necessary to prevent dust and debris from leaving the work area. Renovation projects generate varying amounts of leaded dust, paint chips, and other lead-contaminated materials depending on the type of work, area affected, and applied work methods. For example, repairing a small area of damaged drywall would likely generate less lead-contaminated dust and debris than sanding a large area in preparation for painting. Similarly, a higher containment level would be necessary for demolition work than for scraping a small area. To address these differences, Option D specifies that all rooms where RRP is being performed must be contained except for events that are considered small. A small event is defined under Option D as an event where dust or debris from a disturbed painted surface are unlikely to migrate further than five feet from the disturbed area. The flexible options (Options A, B, and C) allow certified renovators to rely on their training and experience to determine the area that requires containment. The certified renovator is responsible for determining which level of containment is appropriate for a particular renovation.

Under the current regulations for lead-based paint abatement activities, certain practices are prohibited. These practices are open flame burning or torching of lead-based paint; machine sanding, grinding, abrasive blasting, or sandblasting of lead-based paint except when done with HEPA exhaust control; dry scraping of lead-based paint except around electrical outlets or for any area no more than 2 square feet in any one room, hallway, or stairwell, or for any area no more than 20 square feet on exterior surfaces; and operating a heat gun at 1100 degrees Fahrenheit or higher.

Unlike with abatement, EPA is proposing to allow the use of these practices during renovation activities. The Agency understands that, because these practices are commonly used during renovation work, prohibiting such practices could make certain jobs, such as preparing a surface for new painting, extremely difficult, if not impossible. For example, contractors have indicated there may be no practical way to restore old and historic millwork other than open flame burning, and that prohibiting dry scraping and sanding would cause many problems because wet sanding tends to raise the grain of wood surfaces preventing a smooth finish which consumers demand. The Agency believes that proper training, in

combination with appropriate containment and cleanup requirements, adequately addresses the introduction of new hazards.

Exterior renovations

For exterior projects, the firm preparing the work area would be required to close all doors and windows within and below the area undergoing renovation, and to cover the ground with plastic sheeting or other disposable impermeable material extending out from the edge of the structure a sufficient distance to collect falling paint debris. In addition, doors within the work area that must be used while the job is being performed would have to be covered with plastic sheeting to prevent dust and debris from entering the building.

Waste from renovations

Renovation projects can generate a considerable amount of waste material. Lead-contaminated building components and work area debris must be handled carefully to prevent the release of lead-contaminated dust and debris. EPA is concerned that allowing the storage of lead contaminated waste where it may be accessible to residents could result in exposure to a lead-based paint hazard. Therefore, under proposed Section 745.85(a)(3), a firm would be required to contain the waste from renovation activities to prevent releases of dust and debris before the waste is removed from the work area for storage or disposal. If a chute is used to remove waste from the work area, it must be covered. At the conclusion of each work day and at the conclusion of the renovation, waste that has been collected from renovation activities must be stored under containment, or behind a barrier that prevents release of dust and debris out of the work area and prevents access to dust and debris.

In addition, transporting lead-based paint waste in uncovered vehicles is a possible source of releases of paint chips or dust. Therefore, lead-based paint waste from RRP activities would be required to be transported under containment that prevents identifiable releases (e.g., inside a plastic garbage bag).

Cleaning the work area

Under proposed Section 745.85(a)(4), a firm would be required to clean the work area until no visible dust, debris, or residue remains. EPA is also proposing to require more thorough cleaning, which would remove both visible debris and dust particles too small to be seen by the naked eye. All renovation activities that disturb painted surfaces can produce dangerous quantities of leaded dust. Because very small particles of leaded dust are easily absorbed by the body when ingested or inhaled, a small amount can create a health hazard for young children. Unless this dust is properly removed, a work area will be more hazardous after the work is completed than it was originally. Therefore, careful cleaning is required. Improper cleaning can increase the cost of a project considerably because additional cleaning may be necessary during post-renovation cleaning verification. Although it may not be possible to remove all leaded dust generated by the renovation, it is possible to reduce it below the EPA floor hazard level, 40 $\mu g/ft^2$.

The special cleaning methods and procedures required by the proposed option are typically not standard operating procedures for general home improvement contractors. Therefore, this proposal seeks to train renovators and establish containment and cleaning procedures to ensure no lead-based paint hazards are introduced as a result of a renovation.

Cleaning verification

EPA is proposing to require an additional cleaning verification step following the visual inspection. This step would involve wiping the windowsills and floors with specialized cleaning cloths and comparing them to a cleaning verification card developed and distributed, or otherwise approved, by EPA for the

purpose of determining, through comparison of disposable cleaning cloths with the card, whether postrenovation cleaning has been properly completed.

4.2 Estimating the Number of Regulated Renovation, Repair, and Painting Events

To achieve the rule's objective of controlling lead exposure through containment, cleanup, and verification, most of the compliance costs associated with the RRP rule's work practices pertain to the room or area where the renovation work is performed. Therefore, this analysis defines a regulated event as any group of renovation tasks where two or more square feet of a painted surface are disturbed in a specific room or area of a housing unit. The 2003 American Housing Survey (AHS) is the primary data source for the estimates of regulated RRP events that occur in owner-occupied housing. The 1995 Property Owners and Managers Survey (POMS) is the primary data source utilized for estimating the number of regulated events in renter-occupied housing.

Event counts are estimated separately for single- and multi-family units since compliance costs for the two types of housing differ (primarily because the average unit size differs). In addition, the counts of exterior events for multi-family housing units are adjusted to correspond to building-specific compliance costs.[1]

Available renovation data do not include information specific enough to determine when a renovation task disturbs a painted surface, or when renovation tasks are performed together in the same room or area. Thus, it was necessary to make some assumptions about which types of renovation tasks are likely to disturb painted surfaces and which sets of tasks are likely to be performed together as part of one renovation project.

4.2.1 Data Sources

U.S. Census: American Housing Survey

According to the U.S. Census (2005g):

> The survey is conducted by the Bureau of the Census for the Department of Housing and Urban Development (HUD).
>
> The American Housing Survey (AHS) collects data on the Nation's housing, including apartments, single-family homes, mobile homes, vacant housing units, household characteristics, income, housing and neighborhood quality, housing costs, equipment and fuels, size of housing unit, and recent movers. National data are collected in odd numbered years, and data for each of 47 selected Metropolitan Areas are collected currently about every six years.

The surveys utilized in this analysis, 1997 and 2003, have sample sizes of 45,932 and 55,452, respectively. Of the housing units sampled, 33,549 and 35,996, for the 1997 and 2003 surveys respectively, have at least one bedroom, are not public housing, receive no rent subsidies, and were built before 1980. The 2003 AHS groups housing units built in the 1970's as units built between 1970-74 or 1975-1979, so this analysis counts all housing units built before 1980 in the pre-1978 regulated universe.

[1] For example, when siding is replaced on the outside of a three-unit building, the analysis accounts for this as *one* siding replacement event rather than the siding replacement outside of *three* units.

The sample weights provided by the U.S. Census for analyzing the AHS data were designed so that estimates using the provided sample weights would represent the population of housing in the nation. However, the U.S. Census weights were not designed to correct for underreporting within housing units—such as information reported on occupants living in the housing units. Since there is underreporting within-housing units, estimates of the number of individuals calculated using the U.S. Census weights results in lower population estimates than those estimated using other U.S. Census population data sources. In addition, according to Harvard's Joint Center for Housing Studies (personal communication with Kermit Baker August 2005), it appears that the 2003 survey labels too many housing units as vacant; these units are actually occupied by individuals that did not respond to the survey. To correct for this bias, the Joint Center for Housing Studies has adjusted the weights provided by the U.S. Census for the 2003 AHS. These adjusted weights provided by the Joint Center for Housing Studies are utilized for all of the calculations using the 2003 AHS in this analysis; population estimates calculated from the AHS are more closely aligned with other U.S. Census population estimates when calculated with these adjusted weights.

U.S. Census: Property Owners and Managers Survey

According to the U.S. Census (2005h):

> The Property Owners and Managers Survey (POMS) was designed to learn more about rental housing and the providers of rental housing. The purpose was to gain a better understanding of the property owners and managers on whom the nation depends to provide affordable rental housing and what motivates their rental and maintenance policies. Interviewing for the survey was done between November 1995 and June 1996.
>
> A nationwide sample of approximately 16,300 housing units which were rented or vacant-for-rent in the 1993 American Housing Survey National Sample (AHS-N) was selected, and a questionnaire was mailed to the property owner, manager, or other agent of the owner of each property containing a selected unit. Detailed information was collected on maintenance, management practices, tenant policy, financial aspects of rental property ownership, owner characteristics, and related topics.
>
> **POMS Sample Areas**
> The addresses included in the POMS sample were limited to counties and independent cities in the 438 sampling areas used for the Census Bureau's 1993 American Housing Survey (AHS) National Sample.
>
> **Units Included**
> A unit (and the property containing the unit) was included in the survey if it was a privately owned rental unit in the 1993 AHS-N, and was still rental at the time of the POMS (November 1995 to June 1996). A unit was considered rental if it was either rented for cash rent, occupied by someone other than the owner without payment of cash rent, or vacant but available for rent.

Since the POMS survey is relatively old (1995), this analysis first calculates the percentage of rental-housing units performing renovations according to the POMS and then applies these percentages to the corresponding number of rental-housing units in 2003 according to calculations using the AHS. This is described in greater detail in the section below.

4.2.2 Number of Regulated Events in Owner-Occupied Housing Units

The 2003 AHS is the primary data source used for estimating the number of RRP events in owner-occupied housing for which compliance costs will be incurred. The 1997 AHS is also used for estimating the number of RRP events since it contains some more specific renovation information that was not included in the 2003 survey. AHS respondents report information about the ages of householders, who are defined by the survey as persons who live or sleep there most of the time. Thus, child-occupied households are defined as those households that report having a householder under the age of 6. This section describes how the numbers of events are estimated from the renovation module of the AHS and the methodology for estimating the number of Interior Painting and Exterior Painting events using data from the (one-time) 1997 lead paint module of the AHS.

AHS Renovation Tasks

The 2003 AHS allows respondents to report 40 different renovation tasks; this analysis categorized 24 of these 40 as tasks that may disturb more than 2 square feet of a painted surface. Since tasks performed within two years of the survey can be reported, it is assumed that half occurred in the first year and half occurred in the second (i.e. the total number of events counted for the two year period is divided by two).

Table 4-2 lists these 24 renovation tasks by their event category. The seven event categories (bathroom event, kitchen event, addition event, non-room-specific window/door event, non-room specific wall/ceiling event, whole exterior event, contained exterior event) are defined based on the room or area where each renovation task is likely to be performed. When a household reports multiple tasks listed under the same event category, it is assumed that these tasks are performed together in the same area; therefore, one set of compliance costs are assumed to apply to each event. For example, a household reporting replacing their air conditioning system and replacing their heating system is assumed to incur the compliance costs associated with one Non-Room-Specific event.[2] Similarly, when a household reports a Non-Room-Specific task as well as a room-specific task—e.g. remodeling the kitchen (specific to the kitchen) and replacing water pipes (non-room-specific), the analysis accounts for the costs associated with one Non-Room-Specific event (rather than one Non-Room-Specific event plus one Kitchen event). In other words, when tasks specific to a room are reported together with tasks that are not specific to a room, it is assumed that the Non-Room-Specific work area includes the specific rooms where other tasks are reported.[3] However, if a household reports multiple room-specific events (such as remodeling the kitchen and bathroom), all of the room-specific events are counted.

As shown in Table 4-2 and discussed above, some tasks are not necessarily confined to a specific room or area of the unit. In these cases, the tasks are assigned to a Non-Room-Specific event. Of the tasks that are not specific to any room, the analysis differentiates between tasks that are likely to only disturb painted surfaces on walls or ceilings and those that involve adding and/or replacing windows and/or

[2] A Non-Room Specific Event is an interior event that is not a bathroom, kitchen, or addition event.

[3] When the compliance costs are estimated for Non-Room-Specific events, it is assumed that the work area that must be contained, covered with plastic sheeting, and cleaned makes up 50 percent of the housing unit. When a household reports adding/replacing windows/doors together with at least one Non-Room-Specific Wall/Ceiling task, this is counted as a Non-Room-Specific Window/Door event, which has the same large event compliance costs as a Non-Room-Specific Wall/Ceiling events, but higher small event compliance costs. The small event cost associated with Non-Room-Specific Window/Door events is based on specific window/door-removal practices used to remove windows and doors from the exterior of the unit. A small interior event is one that affects only one side of a room and a large interior event affects the entire work area, which could include one or more rooms.

doors. This distinction is made because lead-based paint (LBP) is more likely to be found on windows and doors; therefore, a LBP test kit result is more likely to be positive for LBP when testing these surfaces.

As stated above, the 2003 AHS did not explicitly ask respondents whether a renovation task involved disturbing a painted surface. Therefore, assumptions are made about which tasks might disturb paint in order to estimate the number of events subject to the rule's requirements. In general, when a reported task will sometimes involve disturbing a painted surface, it is assumed that compliance costs are incurred each time that task is reported. For example, replacing internal water pipes will sometimes, but not always, require disturbing painted walls to access old pipes and replace them with new ones. However, the analysis makes no adjustment to account for the instances where no painted surfaces are disturbed (or when less than two square feet of a painted surface is disturbed). Sufficient data for making such an adjustment are not available. Thus, these assumptions may lead to an overestimate of the number of regulated events.

In the case of adding or replacing heating equipment (AHS task 58) and/or central air conditioning equipment (AHS task 57)—Heating Ventilation and Air Conditioning (HVAC) tasks—it is assumed that only a fraction of these HVAC tasks require disturbing a painted surface. In addition, 18 percent of the households reporting tasks listed in Table 4-2 reported at least one HVAC task without reporting any other Non-Room-Specific task. Therefore, assuming that all HVAC work requires disturbing painted surfaces is likely to result in a substantial overestimate of regulated Non-Room-Specific Wall/Ceiling events.

The percentages of HVAC tasks that are assumed to disturb painted surfaces are estimated using the 1997 AHS. Unlike the 2003 AHS, the 1997 AHS distinguishes between installing new HVAC equipment and replacing existing equipment. Since disturbing a painted surface is most likely to occur while performing work on the HVAC ducts (which often are behind painted walls), it is assumed that this occurs when new systems are installed but not when existing systems are replaced.[4]

In summary, when a household's only reported Non-Room-Specific tasks are HVAC tasks, it is assumed that this disturbs a painted surface some percentage of the time, depending on which combination of HVAC tasks are reported. For households reporting a HVAC task and a room specific task, it is assumed that a Non-Room-Specific event occurs when a new HVAC system is added, and the room event(s) occurs the remaining percentage of the time (since the analysis only counts the Non-Room-Specific event when both a Non-Room-Specific and a room specific task are reported).

In addition to these seven event definitions, Interior Painting events and Exterior Painting events are also estimated. The remodeling module of the 2003 AHS data does not cover these types of activities, so data from the 1997 (one-time) lead module are utilized to estimate the number of these events.

[4] When heating equipment work (but not air conditioning work) is reported, 7 percent and 9 percent of these tasks involve adding a new system for single- and multi-family units, respectively. When air conditioning equipment work (but not heating work) is reported, 36 percent and 17 percent of these tasks involve adding a new system for single- and multi-family units, respectively. When both heating and air-conditioning equipment work is reported, 52 percent and 29 percent of the households install a new system for single- and multi-family units, respectively.

Table 4-2: List of 2003 AHS Renovation Tasks, Grouped by Room or Area	
AHS Task ID	**Task Description**
Bathroom Event	
71	Remodeled bathroom
Kitchen Event	
72	Remodeled Kitchen
Addition Event	
7	Added Bathroom onto home
8	Added Kitchen onto home
9	Added Bedroom onto home
10	Added other inside room onto home
35	Bedroom created through structural changes
36	Other room created through structural changes
73	Bathroom created through structural changes
Non-Room-Specific Window/Door Event	
45	Added/Replaced doors/windows to home
Non-Room-Specific Wall/Ceiling Event	
40	Added/replaced internal water pipes in home
42	Added/replaced electrical wiring, fuse boxes, or breaker switches in home
47	Added/Replaced plumbing fixtures in home
55	Installed paneling or ceiling tiles
57	Added/replaced central air conditioning
58	Added/replaced built-in heating equipment
64	Other major improvements or repairs (up to three could be reported)
74	Added/replaced security system in home
Whole Exterior Event	
38	Added/replaced siding on home
Contained Exterior Event	
11	Added attached garage onto home
12	Added porch onto home
13	Added deck onto home
14	Added carport onto home
69	Added/replaced shed, detached garage, or other building

Interior Painting Events

In the 1997 AHS, respondents were asked two questions related to painting activities that are used to estimate the number of Interior Painting events. Respondents were asked:

- Was there any painting done on the inside of the unit?
- Before painting, did anyone sand or scrape off any of the old paint?

Unfortunately, obtaining a count of the number of Interior Painting events is not as simple as adding up the number of respondents that answered yes to both of these questions. It is also necessary to estimate: (1) how many of the respondents that had painting done with sanding or scraping hired a professional to do the work, and (2) how many of these events occur in conjunction with other professional events

reported (so the analysis does not double count if, for example, someone painted with sanding or scraping in their kitchen and reported both painting with sanding or scraping and remodeling their kitchen).

To avoid the double counting problem, the analysis only counts an interior painting job as an event if no other in-scope renovation task was reported. That is, if a household reports remodeling their kitchen and painting with sanding and scraping, it is assumed that this is one event. Therefore, this will result in undercounting when the room painted was not where the reported task occurred.

More formally, the number of Interior Painting events is the number of professionally performed in-scope 2003 RRP events multiplied by the 1997 ratio of [number of units reporting painting with sanding or scraping—includes do-it-yourself painting] to [number of lead-disturbing renovation events—includes do-it-yourself events]. Thus, there are two critical assumptions: (1) the ratio of exclusive interior painting renovations to other renovations is the same in 1997 and 2003, and (2) the professional share of interior painting work is the same as the professional share of other renovation work. Since painting is one of the more popular do-it-yourself jobs, this second assumption may lead to an overstatement of the number of Interior Painting events.

Exterior Painting Events

This analysis assumes that exteriors of 100 percent of homes with some paint on their exterior are painted with sanding or scraping every eight years.[5] Since data on the percentage of homes with some paint on their exteriors are not available, it is assumed that 75 percent of homes have some exterior paint; this assumption is based on data from HUD's (2000) *National Survey of Dust Lead Hazards and Allergens in Housing*, which indicates that 70 percent of pre-1960 homes have some lead paint on their exterior. Since nearly all exterior painted surfaces on pre-1960 homes are likely to have some lead paint, it was assumed that slightly more, 75 percent, of all pre-1978 homes have exterior painted surfaces. The annual number of Exterior Painting events is estimated as one eighth of the number of regulated structures with exterior paint.

4.2.3 Number of Regulated Events in Renter-Occupied Housing Units

The 1995 POMS is the primary data source used for estimating the number of RRP events in renter occupied housing where compliance costs will be incurred. The 1997 and 2003 AHS are also used for estimating the number of renter-occupied RRP events, since these data contain more current estimates of the number of potentially regulated households as well as some other information not available from the POMS.

This section first describes how the POMS data are used to obtain the annual percentage of renter-occupied housing units where there is a regulated RRP event. Second, it describes the methods employed for combining the percentages estimated from the POMS and the AHS data to obtain an estimate of regulated RRP events in renter-occupied units for the first year the rule is in effect.

[5] According to the Painting and Decorating Council, exteriors of homes are usually painted every 4-12 years; thus, the analysis uses the midpoint, eight, for estimating the number of Exterior Painting events.

POMS Data

The POMS data generally has less detail then the AHS but is still the best source of renter-occupied renovation information available. The POMS asked property owners or managers about 12 or 13 types of maintenance and repair activities (for single-family and multi-family units respectively) and about 11 types of capital improvements that may have been made to one of their units. It is likely that 12 of these maintenance, repair, or upgrade activities require disturbing painted surfaces; these activities are listed in Table 4-3 according to the event category that they are classified by in this analysis.

The percentage of units where at least one of the RRP activities listed under each event was performed is calculated by type of unit (single- or multi-family). Similarly to the owner-occupied event estimate, if a Non-Room-Specific activity was reported together with a room specific activity, the Non-Room-Specific event was counted and the room specific event was not. Unlike in the AHS data, respondents were not asked whether sanding or scraping was performed before painting (and painting without sanding or scraping is not subject to the rule's requirements). Therefore, it is assumed that 40 percent of the households reporting interior painting are subject to the rule's requirements; this is based on the percentage of rental households that reported sanding or scraping before painting in the AHS.[6]

Since the POMS does not ask respondents about replacing windows or doors, the frequency that these tasks are performed is assumed to be the same in rental units as observed in owner-occupied units; 3.7 and 3.4 percent of owner-occupied single- and multi-family units, respectively, replace windows or doors each year. Since these improvements are likely to be reported in the POMS data as 'other major upgrades,' the numbers of these tasks that are reported are adjusted downward to reflect this. In summary, 37 and 23 percent of 'other major upgrades' reported in the POMS are assumed to be window or door replacements, for single- and multi-family units respectively.

In contrast to the methodology employed for estimating owner-occupied events, when Interior Painting is reported along with a room-specific activity, only the Interior Painting event is counted—only the room-specific event is counted for the owner-occupied estimates. This distinction between owner- and renter-occupied units is made because interior painting is more likely to occur throughout the unit in rental units than in owner-occupied units— since painting in rental units is generally a maintenance-related activity, whereas painting in an owner-occupied unit is more likely to be part of an improvement.

Similarly to the methodology for the owner-occupied RRP event estimates, it is assumed that HVAC related activities do not always incur compliance costs. The analysis assumes that compliance costs are incurred 28 percent and 15 percent of the time, for single- and multi-family units respectively, which is the percentage of the time new equipment is installed when HVAC work is performed in owner-occupied units according to the 1997 AHS.

[6] The 40 percent of rental units that reported sanding or scraping before painting in AHS compares to the 35 percent of owner-occupied units units that reported sanding or scraping before painting.

Extrapolating from the POMS and AHS Data

After calculating the percentages of rental units that performed RRP in the event categories listed in Table 4-3, the number of renter-occupied events in these categories are calculated by applying the percentages calculated with the 1995 POMS data to the number of rental-units according to the 2003 AHS. It is assumed that Whole Exterior events and Contained Exterior events occur in rental units with the same frequency as they do in owner-occupied units (since data on these types of events are not available in the POMS). Addition events are not estimated for rental units since these renovation activities in these rooms are fairly uncommon in rental units and likely to already be reported as 'other major upgrade' and counted as a Non-Room-Specific event.

Table 4-3: List of 1995 POMS RRP Activities that are Grouped by a Room or Area Specific Event
Interior Painting Event
Any Interior Painting in 1995
Bathroom Event
Upgraded Bathroom in 1995
Kitchen Event
Upgraded Kitchen in 1995
Non-Room-Specific Wall/Ceiling Event
Unit Rewired in 1995
Other major repairs in 1995[a]
Upgraded Plumbing in 1995
Upgraded Security System in 1995
Other Major Upgrade in 1995
Repaired Heat or AC in 1995
Upgraded Heat in 1995
Upgraded AC in 1995
Non-Room-Specific Window/Door Event
Other Major Upgrade in 1995[a]
Exterior Painting Event
Any Exterior Painting in 1995 (single-family units only)
[a] Some 'Other Major Upgrades' are counted as Non-Room-Specific Wall/Ceiling events, others are counted as Non-Room-Specific Window/Door events. See text above for a description of how the task is apportioned.

4.2.4 Number of Regulated Events in Compliance During First Year of Regulation

Table 4-4 presents the estimated number of regulated events in compliance with the rule the first year the requirements come into effect. These are estimated using the methodology outlined above along with the assumption that 75 percent of the RRP events subject to the rule's requirements comply with the requirements. This assumption is based on compliance rates observed for the Occupational Safety and Health Administration's (OSHA) regulations for the construction industry (Gilkeya 2003 and Weil 1999). The variation in the number of regulated events in compliance under the different options reflects the variation in the regulated universe. Thus, Table 4-4 shows that the number of regulated events is highest under Option A, where all pre-1978 renter-occupied target housing units and pre-1978 owner-occupied target housing units where a child under the age of six resides are subject to the requirements. Under Options B and D, pre-1960 renter-occupied target housing units and pre-1960 owner-occupied target housing units where a child under the age of six resides are subject to the requirements in the first year. Under Option C, pre-1950 renter-occupied target housing units and pre-1950 owner-occupied target housing units where a child under the age of six resides are subject to the requirements in the first year. Note that since the regulated universe will be the same under all four options after the first year, the number of regulated events in compliance will be the same under all the options in subsequent years. Also, for Options B, C, and D, the estimated number of events covered by the rule does not account for the events that are regulated because a child with an increased blood-lead level is living in a unit built before 1978. It would be difficult to estimate this because triggers for increased blood lead levels vary from community to community. This provision of the rule is estimated to account for a very small number of events—less than 0.2 percent for Options B and D.[7]

Since it is assumed that certified renovators always use a test kit to detect the presence of LBP before performing any RRP, the number of events presented in Table 4-4 represents the estimated number of tests performed using LBP test kits during the first year the rule goes into effect. About 40 percent of all events include renovation tasks that disturb walls and/or ceilings, but are not specific to any room (Non-Room Specific Wall/Ceiling Events). Exterior Painting accounts for nearly 20% of all events (note that this is the number of buildings where exterior painting is performed, so the number of units where there is exterior painting is larger). Additions account for the smallest share of the events, which reflects the fact that they are not reported for rental-units where they are likely to occur only rarely.

[7] For example, there are an estimated 310,000 children with blood-lead levels greater than 10 µg/dL, a common community action threshold, and only about 75,000 are aware of their condition (MMWR 2003). If these children were equally likely to reside in housing units built in any year pre-1978, then about 46 percent would reside in units built between 1960 and 1980, and of these about 30 percent would have an RRP event in a year. Thus, under these assumptions, 10,000 additional events would be covered in the first year. This is likely to be a substantial overestimate, however, since other data show that children with an increased blood lead level are more likely to be living in older homes. Based on NHANES data for 1991-1994, about 8.6 percent of children living in pre-46 housing units had an increased blood lead level, while only 4.6% of children living in units built between 1946 and 1973 did (MMWR 1997). Thus the actual number of events due to children with increased blood lead levels living in housing units built between 1960 and 1980 is likely to be well below 10,000.

Table 4-4: Number of Events where Compliance Costs Are Incurred, First Year of Regulation				
Event Type	**Option A**	**Option B**	**Option C**	**Option D**
Kitchen	848,766	438,199	333,187	438,199
Bathroom	582,256	305,193	229,762	305,193
Additions	14,080	6,208	4,501	6,208
Non-Room-Specific Wall/Ceiling	4,385,000	2,332,696	1,743,874	2,332,696
Non-Room-Specific Window/Door	980,233	537,820	387,996	537,820
Interior Painting	1,727,358	924,003	691,317	924,003
Whole Exterior	207,960	118,542	82,005	118,542
Contained Exterior	150,358	87,301	60,429	87,301
Exterior Painting	1,831,884	1,069,018	765,265	1,069,018
Total	**10,727,895**	**5,818,980**	**4,298,336**	**5,818,980**

Note: Events where compliance costs are incurred include those that are: (1) subject to the rule's requirements, and (2) in compliance. Thus, this includes some events where LSWP are not required because a test kit indicates that LBP is not present. It excludes the 25% of regulated events that are assumed to be noncompliant.

Option Descriptions: Option A: All pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option B: All pre-1960 renter-occupied target housing units and all pre-1960 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option C: All pre-1950 renter-occupied target housing units and all pre-1950 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option D: All pre-1960 renter-occupied target housing units and all pre-1960 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are prescriptive.

Source: U.S. Census Bureau 1997 and 2003; U.S. Census Bureau 1995; EPA Calculations.

4.2.5 Number of Events Employing Lead-Safe Work Practices

Likelihood of Positive Test Kit Result for LBP

It is assumed that all certified renovators use a test kit for LBP before performing any RRP, because performing the relatively inexpensive test may allow the renovator to avoid the costs of using Lead-Safe Work Practices (LSWP) that are required when LBP is disturbed. Since LBP is most likely to be found on certain components of housing units—and therefore most likely to be disturbed during certain types of renovations—the analysis accounts for this by estimating LBP likelihoods specific to each event type. These LBP likelihoods are estimated using data from HUD's 2000 National Survey of Lead and Allergens in Housing (HUD 2000).[8] These data include information on approximately 630 housing units built before 1978, including data on the presence of LBP in certain rooms (e.g. kitchen) and on certain components or surfaces (e.g. floors, walls, ceilings, doors and windows).

The probability that LBP is disturbed during a RRP event is estimated as the probability of LBP in any of the rooms where RRP is performed or on any of the components that might be disturbed during the RRP

[8] In addition to the likelihood of lead-based paint varying by age of housing, there is evidence that the concentration of lead in the paint varies by the age of housing. A review of the data in HUD 2000 is presented in EPA 2005c. This document is available in the docket for this rulemaking.

event. This assumption leads to an upward bias in the estimates of the number of events where LSWP are required. For example, if there is LBP in the kitchen, it is assumed that a kitchen remodeling will disturb LBP. However, the LBP component(s) will not necessarily always be disturbed. For example, the LBP in the kitchen may be on the window trim, but the renovation may not disturb the window trim. Unfortunately, there is no reasonable basis for correcting this bias using currently available data. For the purposes of this analysis, data from HUD (2000) are used to estimate event-specific likelihoods of positive test kit results based on the estimated likelihood of disturbing LBP for each event type, as Table 4-5 describes.

Table 4-5: Types of Estimates Used for Calculating the Likelihood of Disturbing LBP for Each Event Type

Event Type	Estimate of Likelihood of Disturbing LBP
Kitchen	Likelihood of LBP in the kitchen
Bathroom	Likelihood of LBP in 'other room' (up to two 'other rooms' were inspected for LBP in each housing unit; these rooms might be bathrooms, living rooms, dens, or laundry rooms)
Additions	Likelihood of LBP on the interior or exterior of the unit (since these events typically require some demolition of the interior and exterior)
Non-Room-Specific Wall/Ceiling	Likelihood of LBP on any walls, floors or ceilings of the housing unit
Non-Room-Specific Window/Door	Likelihood of LBP anywhere on the interior or exterior of windows and doors
Interior Painting	Likelihood of LBP anywhere in interior of unit
Whole Exterior	Likelihood of LBP anywhere on exterior of unit
Contained Exterior	Likelihood of LBP anywhere on exterior walls of unit (since Contained Exterior events—such as replacing a porch—are likely to disturb exterior walls, but not very likely to disturb other exterior components such as windows
Exterior Painting	Likelihood of LBP anywhere on exterior of unit
EPA estimated LBP Likelihoods with room and component/surface specific data from HUD (2000).	

Test kits for LBP that are currently available have false positive rates that range from 47 percent to 78 percent; this analysis assumes a false positive rate of 63 percent, the midpoint, for the first year that the rule's requirements are effective. By the end of the first year of regulation it is assumed that an improved test kit will be developed that will have a false positive rate of 10 percent or less.[9] Thus, the likelihood of a positive test kit result in the first year is estimated as the likelihood of LBP plus 63 percent of the percentage of homes without LBP. In the second year, the likelihood of a positive test kit result is estimated as the likelihood of LBP plus 10 percent of the percentage of homes without LBP. Table 4-6 shows the likelihoods of LBP and positive test kit results that are used to estimate the percentage of events where LSWP will be employed.

[9] EPA believes that the sensitivity of test kits can be adjusted so the results reliably correspond to one of the two Federal standards for lead-based paint (1.0 mg/cm^2 and 0.5% by weight). EPA is planning to conduct research to further the development of test kits that accurately identify both the presence and absence of lead in paint at levels that exceed the Federal standards. EPA is confident that improved test kits can be commercially available within the next three years, i.e., by the time the second stage of the rule becomes effective. This timing will coincide with the expansion of the regulatory universe to include housing units built between 1960 and 1978. Alternatives for the test kit costs described in Section 4.5.1 and the development time-frame for the improved test kits are considered in sensitivity analyses presented in Chapter 7.

Table 4-6: Likelihood of LBP and Positive Test Kit Results for LBP									
Year Built	**Kitchen**	**Bathroom**	**Addition**	**Non-Room-Specific Wall/ Ceiling**	**Non-Room-Specific Window/ Door**	**Interior Painting**	**Whole Exterior**	**Contained Exterior**	**Exterior Painting**
Likelihood of LBP									
Pre-1950	50%	31%	83%	35%	77%	74%	70%	47%	70%
1950-1959	23%	12%	67%	16%	56%	38%	55%	27%	55%
1960-1979	6%	4%	22%	5%	14%	14%	13%	10%	13%
Likelihood of Positive Test Kit Result for LBP in First Year (63% False Positive Rate)									
Pre-1950	82%	75%	94%	76%	92%	90%	89%	80%	89%
1950-1959	71%	67%	88%	69%	84%	77%	83%	73%	83%
1960-1979	65%	65%	71%	65%	68%	68%	68%	67%	68%
Likelihood of Positive Test Kit Result for LBP after First Year (10% False Positive Rate)									
Pre-1950	55%	38%	84%	41%	79%	77%	73%	52%	73%
1950-1959	30%	21%	70%	24%	60%	44%	60%	34%	60%
1960-1979	15%	14%	30%	14%	23%	23%	21%	19%	21%
Source: EPA calculations using HUD (2000)									

In cases where a household performed more than one interior event, the likelihood of disturbing LBP is estimated as the likelihood of LBP anywhere in the interior of the unit. There are two exceptions to this: (1) when one of the events is an Addition, the Addition likelihood is used, and (2) when the sum of the individual event probabilities is less than the likelihood of LBP anywhere in the interior of the unit, the sum of the event probabilities is used. These simplifying assumptions are necessary because the data are not sufficient for calculating the joint probabilities that would be necessary for relaxing this assumption. As a result, the estimates of the number of events where LSWP are used will be biased upward. That is, for a housing unit performing multiple interior events, it is assumed that if there is LBP in the housing unit, all the interior events in that unit require LSWP. However, the LBP component(s) may be disturbed only in certain areas throughout the house, requiring less containment than is assumed. Similar to the assumptions pertaining to households performing multiple interior events, for households performing multiple exterior events the likelihood of disturbing LBP is assumed to be the maximum likelihood for the events performed. Unlike for interior events, this is always the same as the largest and most costly exterior event that determines the housing unit's exterior compliance costs.

Number of Events Where Lead-Safe Work Practices are Employed When the First Year Rule is Effective

Table 4-7 shows the estimated number of events where LSWP are used during the first year the rule is in effect. These estimates are calculated by applying the test kit likelihoods described above to the number of events presented in Table 4-4. The percentage of test kit results indicating the presence of LBP increases from Option A to Options B&D to Option C because the prevalence of LBP increases with the age of the housing.

Table 4-7: Number of Events where LSWP are Employed, First Year of Regulation								
	Option A				Option B			
Event Type	Single-Family Owner-Occupied	Single-Family Renter-Occupied	Multi-Family	All Housing Units	Single-Family Owner-Occupied	Single-Family Renter-Occupied	Multi-Family	All Housing Units
Kitchen	21,754	190,655	414,984	627,393	10,651	121,341	225,739	357,731
Bathroom	20,617	145,229	258,298	424,144	11,184	91,021	140,123	242,328
Additions	11,047	na	263	11,310	5,708	na	na	5,708
Non-Room-Specific Wall/Ceiling	194,795	1,288,758	1,714,667	3,198,220	112,285	811,194	920,332	1,843,811
Non-Room-Specific Window/Door	137,571	338,687	307,125	783,383	87,967	220,341	172,497	480,805
Interior Painting	104,557	481,715	766,505	1,352,777	71,208	309,905	422,582	803,695
Whole Exterior	38,202	107,428	18,345	163,975	21,334	69,628	12,523	103,485
Contained Exterior	28,351	81,920	na	110,271	16,944	51,285	na	68,229
Exterior Painting	299,693	978,912	172,109	1,450,714	183,382	634,475	116,810	934,667
Total	**856,587**	**3,613,304**	**3,652,296**	**8,122,187**	**520,663**	**2,309,190**	**2,010,606**	**4,840,459**
	Option C				Option D			
	Single-Family Owner-Occupied	Single-Family Renter-Occupied	Multi-Family	All Housing Units	Single-Family Owner-Occupied	Single-Family Renter-Occupied	Multi-Family	All Housing Units
Kitchen	6,779	89,695	184,816	281,290	10,651	121,341	225,739	357,731
Bathroom	6,887	66,964	114,820	188,671	11,184	91,021	140,123	242,328
Additions	4,212	na	na	4,212	5,708	na	na	5,708
Non-Room-Specific Wall/Ceiling	72,794	596,823	751,691	1,421,308	112,285	811,194	920,332	1,843,811
Non-Room-Specific Window/Door	54,443	160,573	140,353	355,369	87,967	220,341	172,497	480,805
Interior Painting	47,310	230,057	347,253	624,620	71,208	309,905	422,582	803,695
Whole Exterior	12,036	50,372	10,571	72,979	21,334	69,628	12,523	103,485
Contained Exterior	11,173	37,446	na	48,619	16,944	51,285	na	68,229
Exterior Painting	123,851	459,008	98,199	681,058	183,382	634,475	116,810	934,667
Total	**339,485**	**1,690,938**	**1,647,703**	**3,678,126**	**520,663**	**2,309,190**	**2,010,606**	**4,840,459**

Notes: It is assumed that test kits have a false positive rate of 63% in the first year of regulation.
See Table 4-4 for option descriptions.

Source: U.S. Census Bureau 1997 and 2003; U.S. Census Bureau 1995; EPA Calculations.

Number of Events Where Lead-Safe Work Practices are Employed During Second Year Rule is Effective

Table 4-8 shows the estimated number of events where LSWP are used during the second year the rule is in effect; the number is the same across all options after the first year since the options do not differ from the second year forward in terms of the regulated universe of housing. The percentage of positive test kit results is substantially lower in the second year because it is assumed that tests with a lower false positive rate (10 percent) will be available at that time.

Table 4-8: Number of Events where LSWP are Employed, Second Year of Regulation

Event Type	All Options			
	Single-Family Owner-Occupied	**Single-Family Renter-Occupied**	**Multi-Family**	**All Housing Units**
Kitchen	9,470	95,925	203,623	309,018
Bathroom	8,405	64,255	124,186	196,847
Additions	7,201	0	110	7,311
Non-Room-Specific Wall/Ceiling	79,185	614,421	798,488	1,492,093
Non-Room-Specific Window/Door	88,895	221,119	189,342	499,355
Interior Painting	64,685	297,093	451,091	812,869
Whole Exterior	21,790	66,881	11,883	100,554
Contained Exterior	13,181	39,453	0	52,633
Exterior Painting	180,468	609,434	111,102	901,004
Total	473,281	2,008,580	1,889,823	4,371,683

Notes: It is assumed that test kits have a false positive rate of 10% after the first year of regulation.

Source: U.S. Census Bureau 1997 and 2003; U.S. Census Bureau 1995; EPA Calculations.

4.2.6 Number of Regulated Events over 50-Year Period

The stock of regulated housing units is expected to slowly decline over time as some older housing is demolished or destroyed by disasters and as housing units are merged or converted to nonresidential structures.[10] Likewise, EPA expects the number of regulated events to decline as the regulated housing stock declines. EPA estimated the decline in the number of regulated events based on the decline in the pre-1980 housing stock according to 1990 and 2000 Decennial Census data from the U.S. Census Bureau (1990 and 2000c). Since the pre-1980 housing stock declined at an annual rate of 0.41 percent, it is assumed that the number of regulated events will decline at this rate as well.

[10] Housing where lead abatements are performed also shrinks the stock of regulated housing; however, this is not accounted for in the analysis since its impact is negligible—less than .05% of the housing stock (EPA Calculations using the Federal Lead-Based Paint Program (FLPP) Database, the U.S. Census (2003b) American Community Survey Profile, data collected from 8 non-EPA administered states and the U.S. Department of Housing and Urban Development's (2000) National Survey of Lead and Allergens in Housing). See Appendix 4A.

4.3 Estimating the Number of Establishments and Personnel Seeking Certification and Training

The RRP rule requires all entities that conduct RRP activities in regulated housing to become certified under the rule. The regulations also require firms to ensure that all persons performing renovation activities on behalf of the firm are either certified renovators or have been trained by a certified renovator in a manner specified by the rule. It is expected that two types of construction businesses will perform regulated RRP work – businesses with employees and non-employer, or self-employed, contractors. In addition, rental companies are likely to perform some, if not all of the RRP work on the properties they manage rather than hire an outside contractor. The regulation requires that a certified renovator be physically present when warning signs are being posted, the work site is being contained, and when the post-renovation cleaning is being done. The certified renovator must be available, either on-site or by telephone, at all other times when regulated renovation activities are being performed. In addition, only a certified renovator may perform the cleaning verification step required by the rule. As such, each certified establishment with employees will need to have at least one certified renovator on staff. All self-employed contractors performing regulated RRP work will need to be trained as renovators, and upon satisfying the training requirements, will need to be certified as firms.

4.3.1 Estimating the Number of Construction Establishments with Employees Seeking Certification

The RRP rule requires firms that conduct RRP activities in regulated housing to become certified under the rule. Because the majority of firms involved in construction work are likely to be small, single establishment businesses, this analysis assumes that firms will seek certification at the establishment level. As demonstrated in Chapter 2, the eleven potentially affected construction sectors (Residential Remodelers and ten specialty contractor sectors: Plumbing and HVAC, Tile and Terrazzo, Painting and Wall Covering, Finish Carpentry, Glass and Glazing, Drywall and Insulation, Siding, Other Building Equipment, Other Building Finishing, and Electrical contractors) include over 357,000 establishments. Because these establishments are involved in a variety of construction and non-construction activities, in all likelihood only some of them will seek certification under the RRP rule. For example, only 54 percent of Residential Remodeling establishments specialize in residential work (i.e. derive at least 51 percent of their revenues from residential work). In addition, only 56 percent of the revenues of Residential Remodelers come from residential RRP activities. Establishments are likely to incur the cost of certification and of training their employees only if they derive a substantial portion of their revenues from residential Renovation, Repair, and Painting in housing affected by the regulations. Businesses that derive the majority of their revenues from new construction or from RRP activities in non-target housing are not likely to invest in certification.

Unfortunately, the U.S. Economic Census does not provide data on the number of establishments that specialize in residential RRP. The number of establishments that will perform regulated residential RRP was estimated by applying each industry sector's ratio of RRP residential revenues to total construction revenues (obtained from the U.S. Economic Census, see Table 2.6 of Chapter 2) to that industry's total number of establishments. The resulting estimated number of RRP establishments was further reduced to account for the fact that only some of these entities will perform RRP work in regulated housing.[11] The latter adjustment was made for each option based on data obtained from the American Housing Survey on the percent of U.S. households residing in regulated housing (by age of housing stock) and on the percent of RRP events that take place in renter-occupied housing units and in owner-occupied housing units

[11] This assumption is relaxed in a sensitivity analysis in Chapter 7.

where children reside.[12] Thus, for each industry the estimated number of certified establishments in the first year was calculated as follows:

Number of establishments seeking certification =
[(number of establishments in industry) x (value of residential RRP/total construction revenues)]
x (% of households living in regulated and compliant housing)

It is worth noting that 25 percent of regulated renovations are assumed to be out of compliance (i.e., performed by firms and individuals without training and certification). It is also worth noting that after the first year, the total number of certified establishments in each industry will be the same under all options since all establishments performing work in pre-1978 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides will need to be certified. In the first year, however, only those establishments working in pre-1960 and pre-1950 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides are likely to seek certification under Options B (D) and C, respectively.

The estimation methodology used in this analysis makes several assumptions regarding the number of establishments that perform RRP work in regulated residential housing. These assumptions imply that most certified firms will specialize in regulated renovations. Since there may be less specialization than these assumptions imply, the analysis considers, as part of the sensitivity analysis, higher estimates for the regulated universe of certified firms and renovators.

The assumptions made in this analysis involve a significant amount of uncertainty. The estimation approach based on these assumptions may lead to an underestimate of the number of establishments involved in RRP since the proportion of businesses performing RRP may be greater than the portion of revenues derived from these activities. Furthermore, if residential RRP projects are less profitable than new construction or RRP projects in non-residential structures, then the marginal revenue of each RRP project would be lower than the marginal revenue derived from other projects. This implies that an industry would need to perform more RRP projects (and would thus devote a larger portion of the workforce to these projects) in order to obtain the same amount of revenues from RRP as from other activities.

On the other hand, the numbers presented here may overestimate the number of establishments seeking certification under the regulations. The residential RRP revenue figure obtained for nine out of eleven affected sectors includes revenues from RRP activities in single-family homes and "Other buildings" – a category that may include apartment buildings as well as other non-residential (and thus not regulated) structures. As such, the ratio of residential RRP revenues to the total value of construction for these industries is likely to overstate the true amount of residential Renovation, Repair, and Painting work performed by the industry.

The resulting estimates of the number of establishments with employees likely to seek certification in the first year under Options A, B, C and D are presented in Table 4-9. Estimates of the total number of

[12] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied housing units and owner-occupied housing units where children reside. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing.

establishments with employees certified in the second and third years are presented in Table 4-14. Note that the number of self-employed firms seeking certification is estimated similarly and described in 4.3.3.

Table 4-9: Estimated First-Year Number of Establishments with Employees Seeking Certification Under the RRP Rule

NAICS Code	Description	Total Number of Establish-ments	Residential RR as Percent of total value construction	Number of Establishments Certified		
				Option A[a]	Options B & D[a]	Option C[a]
236118	Residential remodelers	82,747	56	13,207	6,970	4,798
238170	Siding contractors	6,632	50	945	499	344
238350	Finish carpentry contractors	35,087	50	5,000	2,639	1,817
238290	Other building equipment contractors	6,087	33	572	302	208
238390	Other building finishing contractors	3,729	30	319	168	116
238340	Tile and terrazzo contractors	8,950	28	714	377	260
238220	Plumbing and HVAC contractors	87,501	27	6,734	3,554	2,447
238150	Glass and glazing contractors	5,294	26	392	207	143
238320	Painting and wall covering contractors	38,943	25	2,775	1,465	1,008
238210	Electrical contractors	62,586	23	4,103	2,165	1,490
238310	Drywall and insulation contractors	19,598	21	1,173	619	426
Total		**357,154**	**31**	**35,933**	**18,964**	**13,054**

[a] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing. Of the regulated housing, 75 percent are assumed to comply with the regulations.

See Table 4-4 for option descriptions.

Source: U.S. Census Bureau 2003; U.S. Census Bureau 2005b,d,f; EPA Calculations.

4.3.2 Estimating the Number of People who will Seek Renovator and Worker Training

The RRP rule requires certified firms to ensure that employees involved in RRP activities are trained as either certified renovators or workers. This section discusses the methodology used to estimate the number of construction workers employed by certified establishments that are expected to seek renovator or worker training under the rule.

Estimating the Total Number of People Trained

The number of employee establishment personnel expected to seek training as either certified renovators or workers was estimated by applying the same approach used for the estimation of the number of establishments that will seek certification under the regulations (note: employee establishment personnel does not include the self-employed). EPA assumed that the number of people who perform RRP work in each of the affected industries is proportional to the ratio of residential RRP revenues to the total construction revenues in that sector. In other words, it was assumed that since 28 percent of construction revenues in the Tile and Terrazzo contractor industry come from residential RRP, then 28 percent of the construction employees perform residential RRP work. EPA then adjusted the number of people who perform any type of residential RRP by the percent of U.S. households living in regulated and compliant housing to obtain the estimated number of construction employees who will be trained as either renovators or workers under each regulatory option. Estimates of the number of construction employees seeking training in the first year are presented in Table 4-10. Note that, similar to the number of certified firms, the total number of trained individuals in each industry will be equal under all options starting with the second year, when the regulations require all firms performing work in pre-1978 renter or child occupied housing to ensure that only trained employees are involved in these projects.[13]

[13] Note that alternative estimates of the number of individuals seeking training and certification are considered in sensitivity analyses in Chapter 7.

Table 4-10: Number Of Construction Employees That Will Seek Training Under The RRP Rule in the First Year						
NAICS Code	**Description**	**Number of Construct. Employees in Industry**	**Number of Construct. Employees Performing RRP**	**Number of Construction Employees Performing RRP in Regulated Housing**		
				Option A[a]	**Options B & D[a]**	**Option C[a]**
236118	Residential remodelers	207,633	116,274	33,140	17,489	12,039
238170	Siding contractors	30,284	15,142	4,316	2,278	1,568
238350	Finish carpentry contractors	129,888	64,944	18,510	9,769	6,725
238290	Other building equipment contractors	90,504	29,866	8,513	4,493	3,092
238390	Other building finishing contractors	37,353	11,206	3,194	1,685	1,160
238340	Tile and terrazzo contractors	44,729	12,524	3,569	1,884	1,297
238220	Plumbing and HVAC contractors	712,452	192,362	54,826	28,934	19,918
238150	Glass and glazing contractors	34,086	8,862	2,526	1,333	917
238320	Painting and wall covering contractors	184,328	46,082	13,134	6,932	4,772
238210	Electrical contractors	606,403	139,473	39,752	20,979	14,441
238310	Drywall and insulation contractors	261,239	54,860	15,636	8,252	5,681
Total		**2,338,899**	**691,595**	**197,114**	**104,027**	**71,609**

[a] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing. Of the regulated housing, 75 percent are assumed to comply with the regulations.

See Table 4-4 for option descriptions.

Source: U.S. Census Bureau 2003; U.S. Census Bureau 2005b,d,f; EPA Calculations.

Estimating the Number of People Trained as Renovators and Workers

The RRP rule requires that a certified renovator be physically present when warning signs are being posted, the work site is being contained, and when the post-renovation cleaning is being done. The certified renovator must be available, either on-site or by telephone, at all other times when regulated renovation activities are being performed. In addition, only a certified renovator may perform the cleaning verification step required by the rule. This means that each establishment performing RRP work must employ at least one certified renovator per construction crew. To estimate the number of construction employees that will train to become certified renovators, EPA looked at the average number of construction employees in establishments performing residential RRP jobs. The average employment size was calculated by dividing the number of construction employees seeking training (Table 4-10) by the number of establishments certified (Table 4-9) in each industry.

This analysis also assumed that establishments will employ one certified renovator per every five construction employees. In other words, establishments that have one to five construction workers on staff will employ one renovator, establishments with six to ten construction workers on staff will employ two renovators, and those with 11 to 15 construction workers on staff will employ three renovators. The average number of construction workers per establishment was no higher than 15 in any affected sector.

To estimate the number of construction employees that would be trained as renovators, the estimated number of establishments seeking certification in each sector was multiplied by the expected number of renovators per establishment for that sector. Four of the affected sectors (Other Building Equipment Contractors, Other Building Finishing Contractors, Electrical Contractors and Drywall and Insulation Contractors) had, on average, between 10 and 15 construction employees per establishment and were assumed to have three renovators on staff each. The number of construction employees in each sector that will need to receive worker training was estimated by subtracting the number of people receiving renovator certification from the total number of people seeking training (see Table 4-10). The average establishment sizes, expected number of certified renovators per establishment, and the total first-year estimated numbers of certified renovators and workers in each industry are presented in Table 4-11.

Table 4-11: Estimated First-Year Number of Construction Employees Seeking Renovator and Worker Training							
Description	**Avg. number of construction workers / estab. (Expected Number of Renovators Trained)**	**Option A[a]**		**Options B & D[a]**		**Option C[a]**	
		Number of Certified Renovators Trained	**Number of Workers Trained**	**Number of Certified Renovators Trained**	**Number of Workers Trained**	**Number of Certified Renovators Trained**	**Number of Workers Trained**
Residential Remodelers	3 (1)	13,207	19,933	6,970	10,520	4,798	7,241
Siding Contractors	5 (1)	945	3,371	499	1,779	344	1,225
Finish carpentry Contractors	4 (1)	5,000	13,510	2,639	7,130	1,817	4,908
Other building equipment	15 (3)	1,718	6,794	907	3,586	624	2,468
Other building finishing	10 (3)[b]	957	2,237	505	1,181	347	813
Tile and terrazzo contractors	5 (1)	714	2,855	377	1,507	260	1,037
Plumbing and HVAC contractors	8 (2)	13,467	41,359	7,107	21,827	4,892	15,026
Glass and glazing contractors	6 (2)	785	1,742	414	919	285	633
Painting and wall covering contractors	5 (1)	2,775	10,359	1,465	5,467	1,008	3,764
Electrical contractors	10 (2)	8,206	31,547	4,331	16,649	2,981	11,460
Drywall and insulation contractors	13 (3)	3,519	12,116	1,857	6,395	1,279	4,402
Total	**5 (2)**	**51,292**	**145,822**	**27,069**	**76,957**	**18,634**	**52,976**

[a] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing. Of the regulated housing, 75 percent are assumed to comply with the regulations.

[b] The average Other Building Finishing contractor establishment has slightly more than 10 construction employees on staff.

See Table 4-4 for option descriptions.

Source: U.S. Census Bureau 2003; U.S. Census Bureau 2005b,d,f; EPA Calculations.

4.3.3 Estimating the Number of Self-Employed Contractors that will Seek Certified Renovator Training

Because all regulated RRP projects must be conducted under the direction of a certified renovator, all self-employed contractors performing regulated RRP work will be trained as renovators. Following training, these contractors will apply for firm certification. In this section, the number of non-employer establishments that will be trained as renovators and certified as firms is estimated.

The number of self-employed (non-employer) contractors in each of the eleven affected industry sectors was estimated and presented in Section 2.2.2 of Chapter 2. This analysis assumes that the percentage of self-employed contractors that perform regulated RRP work and will thus seek renovator training is equivalent to the percentage of establishments with employees that will seek certification under the

regulations. In other words, to estimate the number of self-employed contractors that will seek training, the estimated number of non-employer establishments in each industry was multiplied by that industry's ratio of residential RRP revenues to total construction revenues, and reduced by the percentage of U.S. households living in regulated housing. The resulting first-year estimates are presented in Table 4-12. Similarly to the number of employer firms, the total number of certified self-employed contractors in each industry in the second year will be the same under all options since all establishments performing work in pre-1978 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides will need to be certified.

Table 4-12: Estimated First-Year Number of Non-Employers (Self-Employed Contractors) Seeking Renovator Training and Firm Certification

NAICS	Description	Number of Non-Employer Estab. in Industry	Residential RRP Revenues as Percent of Total Value of Construction	Number of Non-Employers Trained as Renovators and Certified as Firms		
				Option A[a]	Options B &D[a]	Option C[a]
236118	Residential remodelers	82,747	56	30,993	16,356	11,259
238170	Siding contractors	6,632	50	2,272	1,199	825
238350	Finish carpentry contractors	35,087	50	26,381	13,922	9,584
238290	Other building equipment contractors	6,087	33	914	482	332
238390	Other building finishing contractors	3,729	30	1,682	888	611
238340	Tile and terrazzo contractors	8,950	28	3,769	1,989	1,369
238220	Plumbing and HVAC contractors	87,501	27	8,479	4,475	3,080
238150	Glass and glazing contractors	5,294	26	943	497	343
238320	Painting and wall covering contractors	38,943	25	14,640	7,727	5,318
238210	Electrical contractors	62,586	23	6,701	3,536	2,435
238310	Drywall and insulation contractors	19,598	21	6,189	3,266	2,249
Total		**357,154**	**31**	**102,961**	**54,337**	**37,403**

[a] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing. Of the regulated housing, 75 percent are assumed to comply with the regulations.

See Table 4-4 for option descriptions.

Source: U.S. Census Bureau 2003; U.S. Census Bureau 2005d,f; U.S. Small Business Administration 2005; EPA Calculations

This analysis makes several assumptions in order to estimate the number of non-employers who will be trained as certified renovators. First, as discussed in Chapter 2, the analysis assumes that the distribution of non-employer establishments among the six-digit industry codes within each 4-digit sector is identical to the distribution of establishments with employees within each 4-digit industry group. The analysis also assumes that the proportion of self-employed contractors involved in regulated RRP is equivalent to the proportion of establishments with employees involved in these activities. The uncertainties surrounding the latter assumption were discussed in Section 4.3.1 of this chapter. In the case of non-employers, the uncertainty is even greater since there are no data on revenues that self-employed contractors derive from residential RRP work – this data is only available from the U.S. Census for establishments with employees. It is possible that self-employed contractors are hired for RRP projects more often than larger establishments. It is also possible that they are hired less often for larger projects that disturb more than two square feet of paint. No current data is available from the U.S. Census or other sources in the public domain on the amount of RRP work performed by non-employer establishments.

4.3.4 Estimating the Number of Residential Property Management Establishments and Employees that will Seek Certification and Training

Instead of hiring an outside contractor for RRP work on properties under their management, Residential Property Managers (NAICS 531311) and Lessors of Residential Buildings and Dwellings (NAICS 531110) may choose to do the renovation work with their own staff. Since all firms performing RRP work in regulated housing must be certified, establishments that choose to perform their own RRP work will seek certifications under the regulations.

The U.S. Economic Census does not present any data on the amount of RRP work performed by Residential Property Managers on their own properties. Due to this lack of data, this analysis assumes that all Residential Property Management and Lessors of Residential Buildings and Dwellings establishments that have paid employees and manage housing regulated by the Renovation, Repair, and Painting rule will seek certification and train their employees as certified renovators or workers. Although this assumption is likely to overestimate the number of establishments and personnel seeking certification and training, it is not unreasonable since performing minor renovation or maintenance work in-house is often less expensive than hiring an outside contractor. The vast majority of establishments that manage regulated housing may thus find certification worthwhile. Note that only establishments with employees are expected to seek certification; non-employers are unlikely to have the time or manpower to perform renovations themselves and are more likely to hire an outside contractor.

To estimate the number of establishments that manage regulated units (and will thus seek certification), this analysis adjusted the total number of establishments in the Residential Property Manager and Lessors of Residential Buildings and Dwellings industries by the percentage of U.S. households residing in and the number of RRP events taking place in regulated housing. The total number of employees expected to seek training as certified renovators or workers was also estimated by adjusting the total number of personnel in the industry by the percentage of U.S. households residing in regulated and compliant housing units. Although based on 2002 U.S. Census Data, establishments in the Residential Property Manager industry employ about eleven people on average, it was estimated that each establishment will have only two (rather than three) certified renovators on staff; the remainder of the employees will be trained as workers. This estimate is based on the fact that Residential Property Manager establishments are involved in a variety of non-construction activities; it is thus highly unlikely that these businesses will have more than one ten-person construction crew on staff. Lessors of Residential Buildings and Dwellings establishments employ about five people on average, and will thus each have one certified

renovator on staff. The remaining employees involved in RRP projects will be trained as workers. Table 4-13 presents the estimated first-year number of NAICS 531311 and 531110 establishments and employees seeking certification and training, respectively. This is likely to overestimate the number of workers trained because only a portion of the establishment staff is likely to be involved in renovation work.

Table 4-13: Total Number of Residential Property Managers and Lessors of Real Estate Seeking Certification and Training			
	Option A[a]	**Options B &D[a]**	**Option C[a]**
NAICS 531310 - Residential Property Managers			
Total Number of Establishments	19,667	19,667	19,667
Total Number of Employees	217,403	217,403	217,403
Number of Establishments Seeking Certification	7,474	3,944	2,715
Total Number of Employees Seeking Training	82,617	43,601	30,014
Number of Employees Seeking Renovator Training	14,948	7,889	5,430
Number of Employees Seeking Worker Training	67,670	35,712	24,584
NAICS 531110 - Lessors of Residential Buildings and Dwellings			
Total Number of Establishments	46,340	46,340	46,340
Total Number of Employees	219,304	219,304	219,304
Number of Establishments Seeking Certification	17,610	9,294	6,398
Total Number of Employees Seeking Training	83,339	43,982	30,276
Number of Employees Seeking Renovator Training	17,610	9,294	6,398
Number of Employees Seeking Worker Training	65,729	34,688	23,879
Total: Residential Property Managers and Lessors of Residential Buildings and Dwellings			
Total Number of Establishments Seeking Certification	25,084	13,238	9,113
Total Number of Employees Seeking Training	165,956	87,582	60,290
Number of Employees Seeking Renovator Training	32,558	17,183	11,828
Number of Employees Seeking Worker Training	133,399	70,400	48,462

[a] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing. Of the regulated housing, 75 percent are assumed to comply with the regulations.

See Table 4-4 for option descriptions.

Source: U.S. Census Bureau 2003; U.S. Census Bureau 2004b; EPA Calculations.

4.3.5 Total Numbers of Establishments and Individuals that will Seek Certification and Training During the First Three Years

Table 4-14 presents a summary of the estimated number of establishments that will seek firm certification, as well as the estimated number of employees that will need to be trained as renovators and workers in Years 1-3. The number of renovators and firms that seek training and certification in the first three years is estimated slightly differently for the options without a phase-in period (Option A) and those that phase-in regulated housing in the second year (Options B, C, and D).

Options Without Phase-In (Option A):

In the first year, it is assumed that the number of renovators and firms that seek training and certification is equal to the number that is necessary to meet the demand for lead-safe RRP services in that first year. Thus, under Option A, the stock of renovators and firms required to meet the demand for lead-safe RRP services in all pre-1978 renter-occupied target housing units and owner-occupied target housing units

where a child under the age of six resides seeks training and certification. After the first year, it is assumed that one third of the necessary stock of individuals, and firms will obtain training and certification each year (since refresher-training and re-certification is required every three years).

Options With Phase-In (Options B, C, and D):

In the first year, it is assumed that the number of renovators and firms that seek training and certification is equal to the number that is necessary to meet the demand for lead-safe RRP services in that first year. Thus, under Options B and D, the stock of renovators and firms required to meet the demand for lead-safe RRP services in all pre-1960 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides seeks training and certification. Under Option C, the stock of renovators and firms required to meet the demand for lead-safe RRP services in all pre-1950 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides seeks training and certification.

In the second year, this analysis makes the simplifying assumption that one third of the number trained and certified in the first year seek initial- or re-certification.[14] In addition, the stock of individuals and firms required to meet the additional demand in the newly regulated housing stock obtain initial training and certification (1960-1978 and renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides for Options B and D, and 1950-1978 and renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides for Option C). In later years, it is assumed that one third of the necessary stock of individuals and firms will obtain training and certification each year (since refresher-training and re-certification is required every three years).

Training and Certification after the Initial Years

As indicated above, this analysis assumes a steady annual number of firm and individual certifications after the second year of regulation.[15] If all the individuals and firms needed to meet the demand for lead-safe RRP were trained and certified in the first and second years, one might expect a drop in the level of training and certification in the third year, followed by a spike in the next year. That is, one might expect a cyclical pattern of training and certification to emerge. However, it is difficult to predict how cyclical training and certification demand might be, or how this cyclicality might diminish over time. Therefore, this analysis assumes that a typical amount of training and certification occurs each year after the first two years because modeling a cyclical component would add little to the analysis without being able to estimate the extent of any cyclicality more precisely.

This analysis accounts for turnover in the regulated RRP industry by assuming a certain percentage of certifications each year are initial certifications. Specifically, after the first year, 52 percent of the renovators seeking training and certification are assumed to be seeking their initial certification; this is based on the relative number of Abatement Supervisors applying for certifications according to the Federal Lead-Based Paint Program (FLPP) database (EPA 2005). Similarly, 54 percent of firms seeking certification are assumed to be seeking their initial certification based on the relative frequency of initial certifications observed for abatement firms in the FLPP database.

[14] Adjusted for by 0.41 percent to reflect the decline in the pre-1978 housing stock.
[15] The number of certifications is assumed to decline by 0.41 percent to reflect the decline in the pre-1978 housing stock.

Table 4-14: Estimated Number of Establishments Seeking Certification and Workers and Renovators Seeking Training			
	Option A[a]	**Options B &D[a]**	**Option C[a]**
Year 1			
Total Number of Establishments (with Employees and without) Seeking Certification [c]	163,979	86,539	59,571
Total Number of Renovators Trained [b,c]	186,811	98,588	67,866
Total Number of Workers Trained [b,c]	279,221	147,357	101,437
Year 2			
Total Number of Establishments (with Employees and without) Seeking Certification [c]	54,436	105,851	123,756
Total Number of Renovators Trained [b,c]	62,015	120,589	140,987
Total Number of Workers Trained [b,c]	278,076	278,076	278,076
Year 3			
Total Number of Establishments (with Employees and without) Seeking Certification [c]	54,212	54,212	54,212
Total Number of Renovators Trained [b,c]	61,761	61,761	61,761
Total Number of Workers Trained [b,c]	276,935	276,935	276,935

[a] About 65 percent of U.S. households reside in buildings constructed before 1980, 34 percent reside in buildings constructed before 1960 and 22 percent reside in building constructed before 1950. Approximately 58 percent of all RRP events in pre-1978 and pre-1960 housing take place in renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides. This percentage is slightly higher (about 63 percent) for RRP events in pre-1950 housing. Of the regulated housing, 75 percent are assumed to comply with the regulations.

[b] Components may not add up to totals due to rounding.

[c] The number of firms and individuals certified and trained, respectively, are assumed to decline by 0.41 percent annually to account for the decline in the size of the regulated housing stock over time, and thus the demand for lead-safe renovation services.

See Table 4-4 for option descriptions.

Source: EPA calculations

4.3.6 Sampling Technicians

While the RRP rule creates the discipline of certified sampling technician, training and certification costs associated with this new discipline are not included in this analysis. It is expected that few individuals will seek sampling technician certification as a result of the RRP rule, and few RRP activities will use sampling technicians to conduct dust clearance tests following RRP activities because of the high cost of dust clearance testing relative to cleaning verification. A small number of individuals may seek certification as sampling technicians, however, primarily to perform dust clearance testing following interim control activities where clearance testing is required by HUD regulations. Interim controls are an activity where contractors reduce, but do not permanently eliminate, exposures to lead-based paint hazards. Rehanging windows in a manner that reduces friction-produced lead dust is one example of an interim control activity.

4.4 Training Costs

Training costs include the cost of the time spent on training activities as well as the associated travel and tuition costs. Note that tuition costs are assumed to include the costs associated with training provider accreditation. In other words, it is assumed that accredited training providers pass along their accreditation fees and other administrative costs through their tuition. These accreditation fees and other administrative costs are estimated in the paperwork burden analysis but are only implicitly accounted for (as part of tuition costs) in the estimates of the total cost of the rule.

4.4.1 Estimates of Wages

The wages of certified renovators and Workers are estimated for this analysis in order to estimate the costs of proposed changes to their training burdens. Wages are based on U.S. Bureau of Labor Statistics (2005a) data, from the occupational employment statistics series. All wages are fully loaded to account for fringe benefits with an average fringe rate for the construction industry of 23.5 percent. Certified renovators' fully loaded wages ($31.64/hour) are estimated from the wages earned by First-Line Supervisors/Managers of Construction Trades and Extraction Workers (Occupation 47-1011) who work in the residential building construction industry. Workers' loaded wages ($16.94/hour) are estimated from the wages of Construction Laborers who work in the residential building construction industry (Occupation 47-2061).

4.4.2 Tuition Rate Estimates

The estimated tuition cost for an accredited certified renovator course is based on data collected on the tuition rates of courses accredited under the 402/404 Abatement Rule. Tuition rates for an accredited certified renovator course are expected to be similar to tuition costs for lead evaluation and abatement courses since they have similar accreditation requirements and have a similar mix of classroom and hands-on training.

Tuition data were collected on the following accredited lead evaluation and abatement courses: Inspector, Risk Assessor, Abatement Supervisor, Abatement Worker, and Project Designer. Tuition rates were collected from a random sample of firms that offer one or more of the courses required for abatement certification. The National Lead Service Provider Listing System (Lead Listing), which was operated for HUD (2004),[16] lists 194 accredited training providers. These 194 providers form the universe on which the sample for this analysis is based. Many of these establishments are certified in multiple states and offer training in various locations.

The data sample consisted of 83 establishments selected from the Lead Listing directory of 194 training providers. The sample included all the establishments on the list that are certified to offer a Project Designer course (42 total), as well as a random sample of 41 establishments that are not certified to offer this class. Data were collected from company web sites (when available) and/or over the phone. Information was obtained from 68 training providers; a total of 15 providers could not be reached. Seven of the 68 contacted providers no longer offered lead hazard reduction training.

[16] The Lead Listing (HUD 2004) (www.leadlisting.org) website was run for the U.S. Department of Housing and Urban Development's Office of Healthy Homes and Lead Hazard Control that contained a directory of lead service providers. It is no longer in operation (as of late 2004).

To determine whether the 15 unreached firms created a non-response bias due to a lower response rate by a single type of provider, they were classified by type of establishment (private establishments, non-profits, unions). The fifteen non-response entities contained a very similar mix of provider types to those for which data was available; thus, there was no evidence of non-response bias.

Tuition Data Availability

Tuition data were collected from a total of 50 providers, including 35 establishments that were identified as private for-profit providers, 11 identified as educational institutions and 4 non-profit providers. Weighted averages of the tuition rates for each course were then calculated to account for the differences in the probability of selection between the providers that were certified to offer the Project Designer course (PD-certified) and those that were not.

Calculation of Tuition Rate Estimates

The following steps were taken to calculate the tuition rates for each course required by EPA based on the data collected.

a. Select tuition rates for courses that match EPA-mandated training hour requirements (listed in Table 4-15).

- All data were collected in 2004. Data include tuition rates for courses offered currently, previously, and in the future. Some of the tuition data are for courses that satisfy specific state requirements.[17] Since certification from authorized State and Tribal programs satisfies EPA certification requirements, all tuition data that meet EPA course-hour demands were included in the estimates. Several providers offer classes that are longer than those required by EPA (presumably in compliance with state regulations), while several others offer combined Lead Inspector/Risk Assessor courses. Tuition rates for these longer and combined classes were not included in the estimates. However, estimates are similar if these longer and combined classes are included in the sample with time-adjusted rates.

b. Assign a weight to each selected data element based on the probability of selection into the sample.

- Since all providers certified to offer the Project Designer course were selected, the probability of selection for these providers is one. The probability of selection for providers not certified to offer this class is as follows: (Number of providers in the sample)/ (Total Number of Providers - Number of PD-Certified Providers) = 0.27

- The weight assigned to each provider is equal to the inverse of the probability of selection. Thus each provider certified to offer the Project Designer course receives a weight of one while other providers receive a weight of 1/0.27, or approximately 3.71.

c. Calculate the weighted average tuition rates for each course.

Estimated Tuition Rates

Table 4-15 presents the estimated hourly tuition rates, based on the data obtained from the training providers, for each type of EPA-required course.

[17] In California, for example, lead professionals must take a general refresher course every two years.

Table 4-15: Average Hourly Tuition (2005$)	
Initial Course	
Inspector	$20.14
Risk Assessor	$21.24
Abatement Supervisor	$18.83
Project Designer	$27.52
Abatement Worker	$19.64
Refresher Course	
Inspector	$23.77
Risk Assessor	$24.54
Abatement Supervisor	$22.36
Project Designer	$35.17
Abatement Worker	$19.42
Average Hourly Tuition for All Courses	
$23.26	
Source: EPA Calculations.	

4.4.3 Aggregated Incremental Cost of Training

To estimate the incremental burden of training, several cost components are calculated, including tuition rates, wage rates, and travel and expense costs. Each certified renovator will participate in 8 hours of formal initial training. Refresher renovator certification training is required every three years; the refresher course is only four hours. Workers receive informal, on-the-job training; it is assumed that a certified renovator typically trains three Workers at a time and the training requires one hour.

Tuition for the initial certified renovator training class is estimated to be $186; the corresponding refresher course tuition is estimated to be $93. This estimate relies on the assumption that the average hourly tuition is equal to the observed rates for the accredited lead abatement and evaluation courses ($23.26).[18] Additional travel and meal costs associated with training are assumed to be $121.[19]

The time burden to certified renovators for formal initial training is $253 (8 hours at a loaded wage rate of $31.64/hour); the refresher training is half this amount, or $127. Certified renovators may be self-employed or might be employed by a larger company. Therefore, the incidence of the time burden is likely to represent a mix of lost wages and additional overhead to firms. Assuming one certified renovator trains three Workers at a time, and this informal training requires an hour, informal training is estimated to cost $27 per Worker trained. Thus, the aggregated incremental cost of training is $560 for initial certified renovator training, $341 for refresher certified renovator training and $27 for informal Worker training.

After the first year, 52 percent of the renovators seeking training and certification are assumed to be seeking their initial certification; this is based on the relative number of Abatement Supervisors applying for certifications according to the Federal Lead-Based Paint Program (FLPP) database (EPA 2005).

[18] The average of the hourly tuition rates are used rather than picking a single similar course because no single course is similar enough to the renovator course. For example, the initial courses are the only courses with hands-on training, but they are also longer than the renovator course. The refresher courses are more similar in length, but have no hands on requirements.

[19] Travel costs include 2 hours of travel time ($63), meals ($9), and mileage costs (50 miles, $49).

Table 4-16: Incremental Training Costs (2005$)				
	Tuition	**Time Burden**	**Travel and Meals**	**Total Burden**
Initial Training				
Certified Renovator	$186	$253	$121	$560
Worker	$0	$27	$0	$27
Refresher Training				
Certified Renovator	$93	$127	$121	$341
Source: EPA Calculations.				

4.5 Work Practice Compliance Costs

RRP projects generate varying amounts of leaded dust, paint chips, and other lead-contaminated materials depending on the type of work, area affected, and work methods used. For example, repairing a small area of damaged drywall is likely to generate less lead-contaminated dust and debris than sanding a large area in preparation for painting. Because of this variability, the size of the area that must be isolated and the containment methods used will vary from project to project. Large renovation projects could involve one or more rooms and potentially encompass an entire home or building, while small projects may involve a portion of a room or a building's exterior. The necessary work area preparations will depend on the size of the surface(s) being disturbed, the method used in disturbing the surface, and the building layout. The certified renovator assigned to a renovation would weigh all of these factors in determining the appropriate work area size and preparation level for that particular situation. For example, repairing a small area of damaged drywall would probably require a smaller work area and minimal preparation while demolition work would probably require a larger work area and extensive preparation in order to prevent the migration of dust and debris from the work area.

Since available data are not sufficient for estimating a distribution of work area sizes, this analysis used a simplified approach to estimating the per-event containment costs. First, for each type of event, the containment and cleaning cost was estimated for a typical large event and a typical small event. For the prescriptive option (Option D), the rule would define certain events as small and allow a smaller work area to be contained and cleaned for these events; the remaining events would be considered large and all rooms where work is performed would have to be contained and cleaned. It is assumed that 75 percent of events require the large event containment and cleaning practices and 25 percent require the small event containment and cleaning practices.

Under the flexible options (Options A, B, and C) the certified renovator may apply their training and experience to determine the size of the work area that must be contained and cleaned. This contrasts with Option D, which prescribes that the entire room or rooms where work is being performed must be contained and cleaned unless an event meets the small event criteria. For estimating the cleaning and containment costs under the flexible options, it is assumed that 25 percent of events require the small event cleaning and containment, 25 percent require the large event cleaning and containment, and the remaining 50 percent require something in between—with the containment and cleaning cost estimated as the average of the large event and the small event containment and cleaning costs.[20]

[20] This is equivalent to assuming that the average containment and cleaning cost per-event is the average of the small event and the large event cost.

4.5.1 LBP Test Kit Compliance Costs

It is assumed that tests kits are used to test for LBP before each RRP event; they are inexpensive to use and a negative result will allow the renovator to forgo the more costly containment, cleaning and verification requirements. Lead test kits currently can be purchased in bulk at a cost of approximately $0.50 per test; it is assumed that testing four samples will require about 15 minutes of a certified renovator's time. Thus, testing using the test kits is estimated to cost $10 per event.[21]

Alternatively, RRP purchasers may choose to have XRF testing conducted to detect the presence of LBP instead of using a test kit. XRF testing has the advantage of having lower false positive rates, but the testing cost per event is much higher than a test kit.

The purchase price of XRF machines ranges from $14,000 to $21,000. In addition, there are maintenance costs associated with replacing the source material or x-ray tube (about $2,000 to $4,000 every one to five years) and the time spent completing the manufacturer's training class for the XRF. For XRF devices using a radioactive source, the operator must apply for a state license, and may need to pay a fee and periodically reapply for the license. Because of these substantial costs, it is unlikely that renovation contractors will choose to buy and operate XRF machines. Instead, individuals who wish to have XRF testing conducted prior to a renovation will have to hire a certified inspector or risk assessor.

Hiring a certified inspector or risk assessor to test for the presence of LBP would typically cost $100 to $300 for a single room and $300 to $500 for an entire house. Factors such as travel time, size of the work area, accessibility of the work area, and administrative costs will determine the cost for any individual job. In addition to the direct costs of XRF testing, scheduling an inspection may impose delays on the RRP work. In contrast, a contractor can test for LBP with a test kit while visiting the site to provide an estimate.

The benefits of the lower false positive rates associated with XRF testing are likely to outweigh the higher testing costs only in a few cases.[22] Thus, the expected savings from avoiding the RRP rule's work practice costs are generally lower than the $100 to $500 cost of XRF testing. (If the XRF testing indicates that LBP is present, the purchaser would have to pay for the work practices in addition to the XRF testing costs.)

Another portable approach to lead paint testing is ultrasonic extraction/anodic stripping voltammetry (UE/ASV). However, UE/ASV instruments are unlikely to be selected for testing by renovators, repair persons, and painters. The steps involved in use of the equipment are complicated, requiring collecting a paint sample, placing the sample in dry ice to embrittle it, grinding the sample, adding nitric acid to the sample, adding water at approximately 50 degrees centigrade to bath the sample, conducting sample sonication for 30 minutes (up to 7 samples can be done at a time) to further dissolve the sample, adding distilled water to the sample, pouring the sample into a separate vial with a crushed electrolyte tablet, placing a portion of the sample onto an electrode, and operating and interpreting instrumentation to obtain a lead level. Hence, it is unlikely that renovation contractors will choose to buy and operate a UE/ASV instrument themselves. Given that much of the cost for hiring a certified inspector or risk assessor to test

[21] Alternatives for test kit costs and the development time-frame for the improved test kits are considered in sensitivity analyses presented in Chapter 7.

[22] The benefits of a lower false positive rate are increasing with the costs of using LSWP and decreasing with the likelihood of LBP (i.e., the larger the job and the newer the house, the more likely that a RRP purchaser can avoid paying extra for LSWP by having an XRF test).

for LBP is due to travel time, administrative costs, etc., the costs for scheduling an inspection using a UE/ASV are expected to be significantly higher than for a test kit. Since it is expected that few individuals will chose XRF or UE/ASV testing instead of the test kit prior to RRP events, this analysis assumes that all RRP purchasers use the test kit.

4.5.2 Containment, Cleaning, and Verification

The containment and cleaning practices covered in the cost estimates are:[23]

For large interior events:

- Remove or cover all objects in the room where the renovation will be performed, including furniture, rugs, and window coverings.
- Close and cover all ducts opening into the room with taped-down plastic sheeting or other impermeable material.
- Close windows and doors in the work area. Doors must be covered with plastic sheeting or other impermeable material. Doors used as an entrance to the work area must be covered with plastic sheeting or other impermeable material in a manner that allows workers to pass through while confining dust and debris to the work area.[24]
- Cover the floor with taped-down plastic sheeting or other impermeable material. Place a tack pad at the edge of the sheeting at the entrance to the room. Cover paths through the rest of the housing used by persons performing the renovation with plastic sheeting or other impermeable material.

For small interior events:

- Remove or cover all objects within five feet of the work area, including furniture, rugs, and window coverings.
- Close all windows, doors, and ducts within five feet of the work area. Cover ducts with plastic sheeting or other impermeable material.
- Cover the floor within five feet of the work area with taped-down plastic sheeting or other impermeable material.
- Wear disposable shoe covers and vacuum clothes.

For large and small exterior events:

- Cover the ground with plastic sheeting or other disposable impermeable material extending out from the edge of the structure a sufficient distance to collect falling paint debris.
- Ensure that doors within the work area that must be used while the job is being performed are covered with plastic sheeting or other impermeable material in a manner that allows workers to pass through while confining dust and debris to the work area.

For all events:

- Post signs warning occupants and other persons not involved in renovation activities to remain outside of the work area.
- Isolate the work area so that no visible dust or debris leaves the work area while the renovation is being performed.
- Contain waste from renovation activities to prevent releases of dust and debris before the waste is removed from the work area for storage or disposal.

[23] For the purposes of simplifying the modeling of the costs, some of the work practices described here are slightly different than those practices required by the rule. The costs of these practices are expected to be representative of the practices required by the rule.

[24] This analysis assumes that contractors will meet the entrance door requirement by creating an airlock using two sheets of plastic.

- At the conclusion of each work day, store waste from renovation activities under containment, in an enclosure, or behind a barrier that prevents release of dust and debris and prevents access to dust and debris.
- Pick up all paint chips and debris.
- Remove plastic sheeting from objects in the work area and the floor or ground. Mist the sheeting before folding it, fold the dirty side inward, and tape shut to seal. Dispose of the sheeting as waste.
- Clean all objects and surfaces in and around the work area in the following manner, cleaning from higher to lower:
    - Thoroughly vacuum all surfaces and objects in the work area, including furniture and fixtures, with a vacuum equipped with a high-efficiency particulate air (HEPA) filter. Where feasible, floor surfaces underneath a rug or carpeting must also be thoroughly vacuumed with a HEPA vacuum.
    - Wipe all surfaces and objects in the work area with a damp cloth (except for walls, ceilings, carpeted surfaces and upholstered surfaces).
    - Mop uncarpeted floors thoroughly, using a two-bucket mopping method that keeps the wash water separate from the rinse water, or using a wet mopping system.

Post-renovation cleaning verification for interior events:

- A certified renovator must perform a visual inspection to determine if visible amounts of dust, debris or residue are still present. If visible amounts of dust, debris or residue are present, these conditions must be eliminated by re-cleaning and another visual inspection must be performed.
- After a successful visual inspection, a certified renovator must:
    - Wipe uncarpeted floors within the work area with a disposable wet cleaning cloth. The cloth must remain damp at all times while it is being used to wipe the floor for post-cleaning verification. If the floor surface within the work area is greater than 40 square feet, the floor within the area must be divided into roughly equal sections that are less than 40 square feet. Wipe each such section separately with a new disposable cleaning cloth. If the cloths used to wipe each section of the floor within the work area match the cleaning verification card, that section of the floor has been adequately cleaned.
    - If the cloth used to wipe a particular section of floor does not match the cleaning verification card, re-clean that section of the floor using the two-bucket mopping method. Then wipe that section of the floor using a new wet cleaning cloth. If the cloth matches the cleaning verification card, that section of the floor has been adequately cleaned.
    - If the second cloth used to wipe a particular floor section does not match the cleaning verification card, re-clean that section of the floor using the two-bucket mopping method described above and allow the entire floor within the work area to dry completely. After the entire floor within the work area has completely dried, wipe the floor with electrostatic cleaning cloths until a cloth that has wiped the entire floor matches the cleaning verification card.[25]
    - Wipe the windowsills in the work area following the same protocol as used for floors, but with one wet-wipe per-windowsill.
    - When the area passes the post-renovation cleaning verification, remove the warning signs.

Post-renovation cleaning verification for exterior events:

- A certified renovator must perform a visual inspection to determine if visible amounts of dust, debris or residue are still present. If visible amounts of dust, debris or residue are present, these

[25] It is assumed that a second cleaning is required 30 percent of the time and a third cleaning is required 2 percent of the time.

conditions must be eliminated by re-cleaning and another visual inspection must be performed. When the area passes the visual inspection, remove the warning signs.

4.5.3 Cost of Each Containment and Cleaning Practice

The primary source of information on the cost of containment and cleaning practices, equipment and materials was the Means CostWorks Repair & Remodeling Cost Data (R.S. Means 2005). The data is designed to help contractors estimate the cost of a renovation project. The database provides the total labor and material costs of different renovation components on a unit basis. Most of the costs used from the R.S. Means database are for an asbestos abatement project, which requires much more elaborate containment and clean up than required under the analyzed options. The R.S. Means labor estimates have been adjusted downwards based on conversations with industry experts to reflect the less stringent requirements of this proposed rule. Depending on the type of activity, the unit may be a square foot, each item, or some other measure. Table 4-17 and Table 4-18 show the unit costs, labor requirements and total cost for the containment and cleaning practices for interior events and exterior events, respectively.

Table 4-17: Unit Costs of RRP Interior Activities (2005$)				
Cost Type	**Material Cost**	**Units**	**Labor Hours**	**Total Cost[a]**
Sign	$0.11[b]	Ea.	0	$0.11
Floors: Cover surfaces with polyethylene sheeting, each layer, 6 mil, incl. glue & tape	$0.08[c]	S.F.	0.006	$0.20
Walls[d]: Cover surfaces with polyethylene sheeting, each layer, 6 mil, incl. glue & tape	$0.08[c]	S.F.	0.008	$0.25
Tack pad	$0.51[e]	Per sheet	0	$0.51
Disposable shoe covers	$0.38[f]	Per pair	0	$0.38
Roll down polyethylene sheeting	$0.00	S.F.	0.002	$0.03
Bag polyethylene sheeting	$1.15	Ea.	0.05	$2.24
HEPA vacuum for work area	$0.63[g,h]	Ea.	0	$0.63
HEPA vacuum use	$0.01	S.F.	0.002	$0.05
Wet wipe, flat surfaces	$0.01	S.F.	0.002	$0.06
Electrostatic cloth sweeper	$0.01[g,i]	Ea.	0	$0.01
Disposable wet/dry cloth	$0.01[j]	S.F.	0.002[k]	$0.05

[a] Using a mean loaded wage rate of $20.62 (2005$) based on the wages of three construction laborers and one supervisor from the May, 2004 Occupational Employment Statistics data from the Bureau of Labor Statistics.

[b] The cost of a 9"x12" aluminum sign is $10.99; assumed to be used 100 times.

[c] Based on a web search which showed that duct tape costs $0.02 per square foot and 6 mil. polyethylene sheeting costs $0.06 per square foot.

[d] Estimate used for plastic on the doors, windows, and ducts.

[e] Based on a review of price lists on the web which showed that the average cost per disposable sheet is $0.51.

[f] Based on a review of price lists on the web which showed that the average cost per pair of shoe covers is $0.38.

[g] Assumes that it will be used for 1,000 events.

[h] Based on a review of price lists on the web which showed that the average cost for a HEPA vacuum is $626.

[i] Based on a review of price lists on the web which showed that the average cost of an electrostatic cloth sweeper is $13.60.

[j] Based on a review of price lists on the web which showed that the average cost of a electrostatic cloth wet cloth is $0.46. Also based on clearance requirements that the work area must be divided into roughly equal sections that are 40 square feet, therefore it costs $0.01 per square foot.

[k] Based on EPA's (2005b) "Disposable Cleaning Cloth (DCC) Lead Clearance Field Study" document that it would take 5 minutes per cleaning cloth and clearance requirements that the work area must be divided into roughly equal sections that are 40 square feet which is equivalent to 0.125 minutes per square foot or 0.002 hours per square foot.

Abbreviations: S.F. = Square Feet; Ea. = Each Item

Source: RS Means 2005; U.S. Bureau of Labor Statistics 2005b.

Table 4-18: Unit Costs of RRP Exterior Activities (2005$)				
Cost Type	**Material Cost**	**Units**	**Labor Hours**	**Total Cost[a]**
Sign	$0.11[b]	Ea.	0	$0.11
Floors: Cover surfaces with polyethylene sheeting, each layer, 6 mil, incl. glue & tape	$0.06[c]	S.F.	0.001	$0.08
Walls[d]: Cover surfaces with polyethylene sheeting, each layer, 6 mil, incl. glue & tape	$0.08[c]	S.F.	0.008	$0.25
Roll down polyethylene sheeting[e]	$0.00	S.F.	0.0005	$0.01

[a] Based on a mean loaded wage rate of $20.62 (2005$) based on the wages of three construction laborers and one supervisor from the May, 2004 Occupational Employment Statistics data from the Bureau of Labor Statistics.

[b] The cost of a 9"x12" aluminum sign is $10.99 and we assume that the sign will be used 100 times.

[c] Based on a web search which showed that duct tape costs $0.02 per square foot and 6 mil. polyethylene sheeting costs $0.06 per square foot. Based on the EPA 2000a Model Renovation Training Course, duct tape will be used to tape the plastic to the building and rocks will be used to weight down the edges therefore we assume only ¼ of the duct tape is needed for floors.

[d] Estimate used for plastic on the doors, windows, and ducts.

[e] Assume that for exterior events the contractor would tape the plastic up rather than bagging it.

Abbreviations: S.F. = Square Feet; Ea. = Each Item

Source: RS Means 2005; U.S. Bureau of Labor Statistics 2005a and 2005b.

4.5.4 Baseline Work Practices

Some of the containment and cleaning practice standards specified by EPA under the RRP rule are currently in use by some renovation contractors. The costs of work practices already in use are not incremental costs of the rule and are subtracted out of the cost estimates. In order to determine how often the proposed work practices are used without regulation, EPA work group members as well as other industry experts were contacted in 1999 to provide information on current industry practices. A series of questions were asked to determine if the listed work practices were currently in use and if they were, the frequency with which they occur. The questions were divided into four sections (1) Preparation, (2) Performing the Work, (3) Clean-Up, (4) Cleaning Verification. These industry experts were asked to check how frequently these work practices were used when performing work in units with known or suspected lead-based paint. The frequency categories and corresponding measures are listed in percentage terms as follows:

- Never = less than or equal to 2% of projects
- Rarely = 3%-29% of projects
- Often = 30%-69% of projects
- Usually = 70%-97% of projects
- Always = greater than or equal to 98% of projects

In order to use these data to revise the cost estimates, it was necessary to convert the ranges of frequencies into specific percentages. This percentage represents the percent of projects that already use a given work practice, and thus will not incur additional costs from the regulation. For example, if a response was "Rarely" for "Cover surfaces with polyethylene sheeting," then it was assumed that 16 percent (midpoint of 3-29 percent range) of the projects performed by that respondent already employ this work practice. The average of responses for each question was calculated to determine the percent of projects that already use that work practice. Table 4-19 presents the percentage of projects that are already using the

recommended work practices separately for remodeling and painting projects. Industry experts indicated that painting projects tended to employ greater containment than remodeling projects without painting. See section 5.5.3 for further details on the responses that were used to develop the percentages presented in Table 4-19.

Table 4-19: Current Work Practices

Work Practice Activity	Current Work Practices (percent of events where the work practice is already taking place)	
	Remodeling	Painting
Post warning signs – interior events	13.2%	13.2%
Post warning signs – exterior events	23.0%	23.0%
Cover surfaces with polyethylene sheeting	41.2%	51.2%
Use a tack pad	20.6%[a]	25.6%[a]
Wear disposable shoe covers	0.0%[c]	0.0%[c]
Roll down polyethylene sheeting	41.2%	51.2%
Bag polyethylene sheeting	23.0%	23.0%
HEPA vacuuming	41.2%[b]	51.2%[b]
Cleaning Verification with electrostatic cloth	0.0%[c]	0.0%[c]

[a] Not included in the 1999 survey. Set the frequency equal to half that of plastic sheeting.

[b] Industry experts were asked whether they HEPA vacuumed at the end of each day, but not whether they did so upon finishing a job. The analysis assumed that more jobs perform HEPA vacuuming at the end of a job than daily and estimated the frequency of end of the job HEPA vacuum use as equal to that of the use of plastic sheeting.

[c] Not included in the 1999 survey.

Source: Work group members and other industry experts (1999).

The analysis estimates incremental costs where work practices are not currently in use. In some cases, the work practices may be conducted in the baseline pursuant to other regulatory requirements. For example, OSHA's Lead in Construction Standard (29 CFR 1926.62) applies to a variety of construction activities by firms with employees, including repair and renovation work involving lead-based paint. The Lead in Construction Standard requires that floors and other surfaces where lead accumulates be cleaned wherever possible by vacuuming or other methods that minimize the likelihood of lead becoming airborne. Where vacuuming methods are selected, the vacuums shall be equipped with HEPA filters and used and emptied in a manner that minimizes the reentry of lead into the workplace. To the extent that firms are already using these practices, they are accounted for in the baseline work practice estimates, and the cost (and benefit) estimates are adjusted accordingly. Thus, firms complying with the OSHA standard would be among the 41% of firms assumed to use a HEPA vacuum upon finishing a remodeling job in the baseline.

4.5.5 Estimating the Size of Events

The costs for most of the containment, cleaning, and verification practices vary with the size of the room or housing unit involved. Based on the 2003 AHS, average unit sizes for housing units built before 1978 varied substantially across these categories of housing:

- Single-family owner (2,016 sq. feet),
- Single-family renter (1,471 sq. feet), and
- Multi-family owner & renter (1,135 sq. feet).

For interior events, the average square footage of particular rooms in a single-family owner-occupied home was determined by taking the average square footage of the whole unit from the 1997 AHS (approx. 1,750 sq. feet) and reviewing house plans for homes of similar square footage.[26] The average size of individual rooms was calculated as the average of all rooms of that type from a sample of five house plans. The average square footage of individual rooms in rental single-family units and multi-family units was scaled down from the single-family owner occupied values in proportion to their relative total square footage.

Costs were estimated for a small event (i.e., affecting only one side of the room or house) and a large event (i.e., affecting the entire area) for each event type. Both Whole and Contained Exterior events are assumed to be large events. It was assumed that some Exterior Paint Events could be small events that only affect one side of the house. The cost analysis also assumes that the removal of windows and doors can either be performed from the interior or the exterior of the house. When interior work is performed on windows and doors, the task is assumed to be a large event. Further, it assumes that on average a non-room-specific window and door removal event will require containment, cleaning, and verification methods for fifty percent of the housing unit. According to EPA's (1997) *Reducing Lead Hazards When Remodeling Your Home*, the alternative (small event) is to remove the windows and doors from the exterior, in which case plastic would cover the inside surface of the window or door and be laid on the interior and exterior floors extending five feet from the wall and one foot on each end of the window or door. The analysis assumes that an average of two doors connect the interior and exterior; fifty percent (one, in this case) of doors will be removed during exterior work. In both interior and exterior door and window removal, damaged paint on the removed door and window components will be wrapped with the plastic sheeting that is used to cover the floors.

For room-specific events, the analysis assumes that a small event would affect only one side of the room, so doors would not be covered. Based on the EPA Model Renovation Training Course (EPA 2000a) and work-practice recommendations described above, plastic sheeting would extend five feet on all sides of the work area. As mentioned above, a large event was assumed to involve the entire room. Based on the containment and cleaning practices described above, for a large event, the door opening used as the entrance will be air-locked with two layers of plastic sheeting, all other doors will be covered with one layer of plastic sheeting, ducts will be covered with plastic sheeting, all windows will be closed, all movable objects will be removed and all floor space will be covered. It was assumed that on average an extra 10 percent of plastic would be needed to cover any unmovable furniture. It was necessary to estimate the size of an average door, window, and air duct to calculate how much plastic sheeting would be needed to cover them. Based on information in R.S. Means, an average door is 20 square feet (3'×6'8"), an average window is 6.8 square feet (2'×3'5") and an average air duct is one square foot (0.5'×2'). For large events, a tack pad (sticky pad that removes dust from the soles of shoes) would be needed. A path through the rest of the house would be created which is assumed to be 60 square feet (2'×30').

To estimate the affected square footage of non-room-specific events and interior paint events, EPA assumed that a non-room-specific event and interior paint event would affect 50 percent and 25 percent, respectively, of the total square footage in the housing unit. The 2003 AHS data was used to estimate the number of rooms in each type of housing unit and therefore the number of affected doors, windows, and ducts.

[26] Reviewed house plans at http://www.store.homestyles.com/homestyles/plans/search (Homestyles.com 2002).

Addition events include the events in which rooms are created through the demolition of an existing wall for a new addition or by structural changes in an existing room, such as the creation of a wall. For a large Addition event, it is assumed that the workers would have to lay plastic sheeting over and clean an area of floor equal to the average size of the room from which the work is being performed (i.e., kitchen, bathroom, bedroom, "other" room). Since kitchens, bedrooms, and "other" rooms are similar in size and bathrooms are much smaller, the average size of a room was estimated as the smallest average room size between kitchens, bedrooms, and "other" rooms. For a small Addition event, it is assumed that the workers would be required to prepare and clean along the affected wall of the room using the guidelines for a small event. Again, work is assumed to affect a portion of a wall equal to an average sized wall of the room being added.

The square foot costs of an external event are estimated for both an event involving the whole of the exterior (e.g. replacing siding) and for one where just a contained section of the unit (e.g., replacing a deck) is involved. The structures in a Contained Exterior event are outside the main body of the house and the structural work and contamination is primarily outdoors. The perimeter of a contained exterior structure is estimated to be 60 feet (10'×20'). Containment is necessary along the entire perimeter of a detached structure. However, it is assumed that less containment is required for attached contained exterior structures, which are assumed to be attached to the main structure of the house along a 20 foot side of the detached contained exterior structure. The analysis averages the cost of an attached and detached structure to estimate the cost of a Contained Exterior Event.

To calculate the relevant square footage of a Whole Exterior or Exterior Painting event, the perimeters of the typical single-family and multi-family housing unit were estimated. The perimeter estimate for a single-family unit was calculated following the procedure used in EPA's Economic Analysis for the TSCA Section 403 rule (EPA 2000b). It was assumed that the home is rectangular with a front to side ratio of 2:3 and an average first floor area of 1,390 sq. feet.[27] This assumption leads to a perimeter of 152 feet for a single-family owner occupied home. The perimeter of a single-family renter unit was estimated to be 130 feet, which assumes that the proportion of a single-family renter unit has the same proportion of total square footage to square footage of the first floor of a single-family owner unit. The perimeter of a multi-family housing structure (which contains several multi-family units) was calculated assuming the first-floor area was three times as large as a single-family unit. This perimeter estimate is 264 feet.

For an exterior event, based on the training manual instructions, plastic would be placed stretching out 10 feet from the structure including rounded corners. Based on the containment and cleaning practices described above, for a large event, the door opening used as the entrance to the building during the work will be air-locked with two layers of plastic sheeting, all other doors will be covered with one layer of plastic sheeting, and all windows on the same floor and floors below will be closed. Based on the EPA Model Renovation Training Course, duct tape will be used to tape the plastic to the building and rocks will be used to weight down the edges. Therefore, only one-fourth of the duct tape that would be needed for an interior event is necessary.

[27] Estimated based on information from http://www.dreamhomesource.com (2005) on the average size of the first floor of nine 2,000 square foot two stories homes (1,280 sq. feet). The weighted average of a first floor was calculated using 2003 AHS data which shows that 85% of single-family housing units are two stories high and the remaining 15% of homes are one story (i.e., first floor is 2,016 sq. feet).

4.5.6 Estimating Total Per Event Containment and Cleaning Costs

For each event, containment and cleaning costs are estimated by multiplying the containment and cleaning unit costs listed in Table 4-17 and Table 4-18 by the square footage and units of material and labor required for each event. The number of units required for each event was estimated using the containment and cleaning standards and size assumptions detailed in Section 4.5.2 and Section 4.5.5, respectively. Table 4-20 shows the estimated per event containment and cleaning costs combined with the cleaning verification costs described in Section 4.5.7. These costs are not adjusted for noncompliance or baseline work practices.

4.5.7 Cleaning Verification Costs

The interior cleaning verification costs for all of the proposed options includes the cost of wiping the windowsills and uncarpeted floors with a disposable wet cleaning cloth until it matches the cleaning verification card as described in Section 4.5.2. It was assumed that 30 percent of windowsills and uncarpeted floors would fail the cleaning verification card test the first time and 6 percent of those failures would fail a second time. According to the requirements described above, after the first failure the uncarpeted floors would have to be cleaned again using the two-bucket mopping method. For both the windowsills and uncarpeted floor, a new disposable wet cleaning cloth would be needed to check against the cleaning verification card. If the second cloth used to wipe a particular floor section does not match the cleaning verification card, that section of the floor would have to be re-cleaned using the two-bucket mopping method described above and the entire floor within the work area would need to dry completely. After the entire floor within the work area has completely dried, the floor would be wiped with a dry electrostatic cleaning cloth that would need to be checked against the cleaning verification card again. It is assumed that there would be no further failures. For all events it is assumed that visual clearance is attained as part of the cleaning activities.

The cleaning verification costs are estimated by multiplying the unit compliance costs of the wet wipe, electrostatic cloth sweeper, and disposable wet/dry cloths from Table 4-17 by the square footage and units of material and labor required for an event. The costs are combined with the containment and cleaning costs of Section 4.5.6 and are listed in Table 4-20. These costs are not adjusted for noncompliance or baseline work practices.

Note that households may choose to have a sampling technician perform dust clearance testing following a renovation instead of performing cleaning verification. Because dust clearance testing is substantially more expensive than the cleaning verification, EPA expects few households to have dust clearance testing performed. Since the frequency of dust clearance testing is expected to be low, and therefore not to have a significant impact on the total cost of the rule, this analysis assumes that cleaning verification is always performed.

4.5.8 Summary of Containment, Cleaning, and Verification Costs

The costs presented in Table 4-20 combine the total containment and cleaning costs with the cleaning verification costs based on the methods outlined in Sections 4.5.6 and 4.5.7, respectively. These are the total compliance costs associated with using the containment, cleaning, and verification procedures, without any adjustment for baseline work practices. Event costs primarily vary with the size of the area that requires containment and cleaning. That is, small events or events confined to smaller areas have lower costs because they require less containment and cleaning.

Table 4-20: Summary of Housing Unit Containment, Cleaning, and Verification Compliance Costs: Not Adjusted for Compliance with the Rule or Baseline Work Practices[a] (2005$)						
Event Type	**Single-Family Owner Occupied Housing Unit**		**Single-Family Rental Housing Unit**		**Multi-Family Housing Unit**	
	Small Event Cost	**Large Event Cost**	**Small Event Cost**	**Large Event Cost**	**Small Event Cost**	**Large Event Cost**
Kitchen Remodel	$37.18	$132.23	$32.88	$110.26	$27.77	$87.77
Bathroom Remodel	$22.71	$63.28	$22.69	$63.20	$22.68	$63.17
Additions	$33.26	$117.13	$30.17	$101.77	$25.50	$65.04
Non-Room-Specific Interior Wall	$75.31	$527.97	$63.81	$396.52	$57.17	$317.25
Non-Room-Specific Window/Door	$117.60	$527.89	$97.54	$396.52	$57.90	$317.25
Interior Paint	$54.58	$284.92	$46.99	$218.68	$42.01	$176.73
Whole Exterior Remodel[b]	na[b]	$180.85	na[b]	$160.86	na[b]	$281.15
Exterior Remodel in Contained Area[b]	na[b]	$76.66	na[b]	$76.66	na[b]	$76.66
Exterior Paint	$46.66	$180.85	$41.66	$160.86	$71.73	$281.15

[a] Assumes 100% compliance with the rule and 0% of work practices already in use in the baseline.

[b] All whole exterior remodel events and exterior remodels in a contained area were assumed to be large events.

Source: RS Means 2005; U.S. Census Bureau 2003.

Table 4-20 presents the full per-event costs that a contractor will incur if they use the required work practices. These costs presented in Table 4-20 indicate how much more a contractor could charge for using all the required LSWP compared to a contractor who was not going to use any of the required work practices—assuming a contractor can pass on the full cost of using LSWP. The costs presented in Table 4-20 are not, however, the per-event work practice burden attributable to the rule, because some contractors are incurring the costs presented in Table 4-20 in the baseline. Table 4-21 subtracts the work practice costs that are incurred in the baseline from the costs in Table 4-20 to arrive at the incremental impact of the rule on work practice costs. [28] Therefore, the costs presented in Table 4-21 are the costs that are multiplied by the number of events where LSWP are used to arrive at the total costs of using LSWP that are attributable to the RRP rule.

[28] It is estimated that about 47 percent of the post-rule containment, cleaning, and verification costs would be incurred in the baseline scenario (assuming 75 percent compliance).

This analysis assumes that 75 percent of establishments and events will be in compliance with the rule. It is assumed that the contractors and events that are not in compliance with the rule are contractors that are not using any of the required work practices in the baseline. For example, 13 percent of contractors post signs in the baseline and 75 percent will post signs under the rule—it is assumed that the 13 percent of contractors posting signs in the baseline will all comply with the rule. In other words, 17.3 percent (13 divided by 0.75) of compliant contractors do not incur any new costs due to the sign posting requirement, while 82.7 percent (62 divided by 0.75) incur new costs associated with posting a sign under the rule. Thus, the expected regulatory impact per compliant event associated with posting signs is estimated as follows: A sign costs 11 cents, and in 82.7 percent of the compliant events the costs of posting a sign would not have been incurred in the baseline. However, in 17.3 percent of the compliant events the costs of posting a sign would have been incurred both under the baseline and after the rule. Therefore, the expected cost of the requirement to post a sign averages 9 cents per compliant event—since 82.7 percent of 11 is 9.

Table 4-21 shows the average expected per-compliant event costs, accounting for the relative number of small and large events, and for flexible options, the reduced per-event costs. Under the prescriptive requirements (Option D), it is assumed that 25 percent of events are small and 75 percent are large. Under the flexible options (Options A, B, and C), it is assumed that 25 percent of events are small, 25 percent are large, and 50 percent will have expected compliance costs at the midpoint of the small and large event expected compliance costs. These are average expected costs so some individual events will be above the average and some will be below it.

Table 4-21: Summary of Per-Event Containment, Cleaning, and Verification Costs (Adjusted for Baseline Work Practices, Assumes 75 Percent Compliance)

Event Type	Flexible Options (A, B, and C)			Prescriptive Option (D)		
	Single-Family Owner-Occupied	Single-Family Renter-Occupied	Multi-Family	Single-Family Owner-Occupied	Single-Family Renter-Occupied	Multi-Family
Kitchen	$45	$38	$30	$56	$47	$37
Bathroom	$23	$23	$23	$27	$27	$27
Additions	$39	na[a]	$24	$49	na[a]	$28
Non-Room-Specific Wall/Ceiling	$155	$117	$96	$212	$159	$128
Non-Room-Specific Window/Door	$163	$124	$95	$216	$162	$128
Interior Painting	$69	$54	$44	$90	$69	$56
Whole Exterior	$82	$73	$127	$82	$73	$127
Contained Exterior	$35	$35	$35	$35	$35	$35
Exterior Painting	$36	$32	$56	$47	$42	$73

[a] For rental housing units, it was not possible to estimate the number of Additions. Renovation activities in these rooms are likely to be accounted for as Non-Room-Specific events.

See Table 4-4 for option descriptions.

Source: RS Means 2005; U.S. Census Bureau 2003; EPA Calculations.

4.6 Certification Costs: Firm Paperwork Burden and EPA Administrative and Enforcement Costs

Under the RRP Rule, states are given the option of administering the regulations as long as the state implementation plan is approved by EPA. EPA will directly administer programs in states that do not have an approved implementation plan. This section of the analysis estimates costs that EPA expects to incur while administrating and enforcing the RRP program under the assumption that EPA administers the program everywhere. States that choose to implement the rule themselves are expected to incur similar costs.

EPA will perform three tasks as part of administering the RRP program: accrediting training providers, certifying firms, and processing training provider notifications. In addition to administrative costs, EPA will also incur costs to enforce the RRP rule. To reduce the burden on the regulated community, EPA has decided not to require formal certification for renovators and workers.

Accreditation/certification cost estimates are based on responses from nine states to a phone survey conducted in support of the TSCA §402(a)(3) "Fees Rule." Data were collected from California, Illinois, Maine, Massachusetts, New Hampshire, Ohio, Rhode Island, Vermont, and Virginia. States were asked to provide the number of hours per applicant required to perform a variety of administrative tasks under the broader §402(a) lead abatement training and certification regulation. While §402(a) defines training and certification requirements for five different categories of lead abatement professionals, the type of administrative activities associated with the §402(a) rule are similar to those expected for the Renovation, Repair, and Painting Rule. As a result of these similarities, the state-provided data were not adjusted unless specifically noted.

The nine states provided information on the hours required to perform the following administrative activities:

- Application Processing and Recordkeeping;
- Fee Transactions and Waivers;
- Issuance of Accreditation/Certification Papers;
- Public Assistance/Outreach;
- Reporting;
- Management; and
- Auditing Training Courses for Training Provider Accreditation Only.

These data were used to estimate the costs of accrediting training providers and certifying firms. In each case, the amount of time necessary to implement the rule was calculated as the simple average of the hours reported by the nine states surveyed for the §402(a) rule. Hours are reported for three categories of workers: clerical, technical, and managerial. These hourly burden estimates were multiplied by wage rates for each job category to determine the per-entity cost of administering the rule.

Wage rates for administrative staff vary from region to region. EPA used the Office of Personnel Management's (2005a-c) General Salary Table 2005-GS to estimate government employee wage rates. The labor rates used were: $49.44 per hour for managerial staff (GS-13, Step 1), $34.69 per hour for technical staff (GS 11, Step 1), and $21.09 per hour for clerical staff (GS-6, Step 1)[29]. These wage rates were multiplied by the hourly time estimates to derive total unit costs for accreditation/certification.

4.6.1 Costs for Accrediting Renovator Training Providers and Processing Training Notifications

The task of accrediting training providers includes approving curricula and quality assurance/quality control (QA/QC) programs for instructors, and maintaining a database of accredited training providers. The Renovation, Repair, and Painting Rule requires that renovators receive formal training in lead-safe work practices from an accredited training provider. In addition, renovators are required to take a refresher course once every three years. EPA, in turn, must accredit training courses by reviewing the curriculum and ensuring that training providers have acceptable quality assurance/quality control (QA/QC) procedures in place to ensure quality instruction by every instructor. EPA will review and document all applications for accreditation, audit training courses, process fees and fee waivers, issue accreditation papers, perform public outreach/assistance, report to overseeing organizations or legislative bodies, and perform other general program management activities (i.e., budgeting). In addition, EPA will process notifications submitted by training providers prior to and following each course session.

Data on the time required to perform training accreditation activities were available from eight of nine states. The time required to administer the §402(a) program varies widely by state. In particular, the amount of time spent auditing training courses differs substantially among respondents. EPA used the simple average of time estimates for all eight responding states to determine the time required to process a single application in a typical state. EPA then adjusted the number of hours spent on auditing training courses to account for the fact that the renovator course is shorter than the majority of initial abatement training courses. EPA estimates an average of 12 FTE hours will be spent on auditing each training course.

The average time spent performing each of the seven administrative activities associated with accrediting training courses is shown in Table 4-22. Notification processing time is assumed to be included in the Reporting hours estimate. The total unit cost of accrediting a training course is $1,796 based on these estimates and the above labor rates. Note that the cost of accrediting training courses are not used to calculate the certification cost impact of the rule. This is because this analysis assumes that training providers will recover their accreditation fees (which in turn cover the administrative and enforcement costs of training provider accreditation) through the tuition they charge. Thus, the cost of accrediting training courses is accounted for in the tuition estimates.

[29] These wage rates are fully loaded, and were calculated using the standard government multiplier of 1.6 to cover overhead and fringe benefits.

Table 4-22: Per-Unit Cost of Accrediting Training Providers				
	Clerical Hours (GS-6, Step 1) ($21.09/hr)	**Technical Hours (GS-11, Step 1) ($34.69/hr)**	**Managerial Hours (GS-13, Step 1) ($49.44/hr)**	**Unit Cost**
Application Processing and Recordkeeping	1.94	17.3	0	$641
Auditing Training Courses	0	12	0	$416
Fee Transactions and Waivers	0.24	0	0	$5
Issuance of Accreditation Documents	0.79	0	0	$17
Public Assistance/Outreach	0	5.79	0	$201
Reporting	0	2.16	0	$75
Other Management	0	0	8.93	$441
Total	**2.97**	**37.25**	**8.93**	**$1,796**
Source: U.S. EPA 1999, U.S. OPM 2005a-c.				

Based on the U.S. Department of Housing and Urban Development's Lead Listing and on contacts with a randomly selected group of training providers, EPA estimates that there are approximately 168 firms/organization currently accredited to offer lead abatement training. It is assumed that each training provider can teach 10 classes a month with an average class size of 25 students. As such, 168 providers can train 42,000 renovators each month, or 504,000 a year. EPA estimates that under Option A, only 186,811 renovators will seek training in the first year; this number is lower for the other Options. Thus, this analysis estimates that under Option A, all 168 training providers will seek accreditation prior to the first year that renovators will need to be certified. For the remaining Options, the number of training providers accredited by or in the first year will be proportional to the number of renovators trained (and, as such, to the regulated housing stock). At the same time, EPA believes that there will be at least two accredited training providers per state, thus at least 100 providers will seek accreditation under each option. The estimated numbers of training providers accredited by or in the first year (by option) are presented in Table 4-23. In the long run, all 168 training providers will seek accreditation regardless of the option.

Table 4-23: Estimated Number of Training Providers Accredited in the First Year, by Regulatory Option				
	A	**B**	**C**	**D**
Number of training providers accredited	168	100	100	100

[a] In the first year, the number of renovators seeking training under Option B (Option C, D) is equal to 54 percent (40 percent, 54 percent) of renovators seeking training under Option A.

See Table 4-4 for option descriptions.

Source: U.S. HUD 2004; EPA Calculations.

To estimate the total administrative cost associated with training provider accreditation and notification processing, EPA multiplied the accreditation cost per-provider by the number of providers accredited under each Option. The resulting first-year administrative costs range from $180 thousand (Options B, C and D) to $302 thousand (Option A).

4.6.2 Costs of Certifying Renovation Firms

The Renovation, Repair and Painting Rule will require renovation establishments to submit a completed application and fee. For the purpose of estimating costs, it is assumed that EPA will review the certification statement for completeness, review the firm's environmental compliance history, record the establishment's information in a database, and mail a certification form to the establishment.

Data on the time required to perform establishment certification activities were available from six of nine states. The states of California, New Hampshire, and Ohio did not provide any information on the cost of certifying establishments under §402(a). The time required to administer the §402(a) program is reasonably consistent among states. The simple average of the six states' data was used to determine the time required to certify an establishment in a typical state.

Table 4-24 provides the average time spent performing six administrative activities associated with certifying establishments. The total unit cost of certifying establishments is $318 based on these estimates and the above labor rates.

Table 4-24: Per-Unit Costs of Certifying Renovation Establishments				
	Clerical Hours (GS-6, Step 1) ($21.09/hr)	**Technical Hours (GS-11, Step 1) ($34.69/hr)**	**Managerial Hours (GS-13, Step 1) ($49.44/hr)**	**Unit Cost**
Application Processing and Recordkeeping	0.21	1.49	0	$56
Fee Transactions and Waivers	0.16	0	0	$3
Issuance of Accreditation Documents	0.12	0	0	$3
Public Assistance/Outreach	0	1.66	0	$58
Reporting	0	1.58	0	$55
Other Management	0	0	2.9	$143
Total	**0.49**	**4.73**	**2.9**	**$318**
Source: U.S. EPA 1999, U.S. OPM 2005a-c.				

Table 4-25 presents the estimated first-year numbers of renovation establishments (employers and self-employed contractors) expected to seek certification under each regulatory option and the associated administrative costs.[30]

Table 4-25: First-Year Total Costs of Certifying Renovation Establishments by Regulatory Option		
	Number of Establishments Certified	**Total Certification Costs**
Option A	163,979	$52,145,322
Option B	86,539	$27,519,402
Option C	59,571	$18,943,578
Option D	86,539	$27,519,323
See Table 4-4 for option descriptions. *Source: EPA Calculations.*		

4.6.3 Costs of Enforcement

In addition to administering the accreditation and certification requirements, EPA will perform a variety of enforcement activities to ensure that the training and performance (including containment, cleaning, and verification) requirements of the rule are met. Based on previous experience with similar programs, EPA estimates that it will need 2 Headquarters and 10 Regional FTEs for enforcement activities under each regulatory Option. Headquarters enforcement costs were calculated by loading the 2005 Washington/Baltimore area annual salary rates for a GS-12, Step 1 employee ($100,618). Regional enforcement costs were estimated using the GS-12, Step 1 employee salary listed in the 2005 General Schedule ($86,754).[31] Based on these salaries and the indicated numbers of FTEs, total annual enforcement costs are estimated at $1,068,776. EPA assumed that enforcement costs associated with training providers is equal to 0.4 percent of the total enforcement costs, or $4,275 per year. Thus, costs of

[30] Firms already certified to perform lead-based paint activities would be deemed certified to perform renovations and are not included in this calculation.

[31] These salaries are fully loaded, and were calculated using the standard government multiplier of 1.6 to cover overhead and fringe benefits.

ensuring certified firm compliance account for 99.6 percent of the enforcement burden, or $1,064,501 per year.

4.6.4 Administrative and Enforcement Costs: Contribution to Total Costs

Similar to the regulations governing abatement, EPA is likely to recover its administrative and enforcement costs from certified firms and Accredited Training Providers through their certification and accreditation fees, respectively. However, these fees will be set by a separate rulemaking and may be apportioned differently than assumed in this analysis. Thus, while the estimation of these fees is outside the scope of this analysis, EPA's administrative and enforcement costs are considered a part of the regulatory impact estimated here. Simply adding these costs to the other cost components, however, will result in some double counting. Specifically, this analysis assumes that training providers will recover their accreditation fees (which in turn cover the administrative and enforcement costs of training provider accreditation) through the tuition they charge. Thus, only costs associated with certified firms are used to calculate the certification cost impact of the rule; EPA's burden of administering and enforcing the RRP Rule will be higher. The EPA costs that will be recovered from RRP firms in a given year are thus calculated as follows:[32]

$$\text{EPA Administrative and Enforcement Costs that will be recovered from Firms}_{\text{Year X}} = \$318 * \#\text{ of Firms Certified}_{\text{Year X}} + \$1{,}064{,}501$$

4.6.5 Firm Paperwork Burden

In addition to EPA's administrative and enforcement costs, annual firm certification costs also include the paperwork burden incurred by certified firms. Note that there is also a paperwork burden borne by Accredited Training Providers, but like the fees, these costs are also assumed to be recovered through tuition charges. The training provider paperwork burden is estimated in Chapter 8, however, where it is considered separately from the total costs of the rule.

It is estimated that firms will spend a total of three hours to familiarize themselves with the RRP rule's requirements and a half an hour to fill out and mail the one-page Application for renovator certification. In addition, firms will spend 5 minutes per-event keeping records that demonstrate compliance with the Renovation, Repair and Painting Rule training and work-practice requirements. At a loaded wage rate of $31.64, the time burden in the first year will be $276 per firm (see Table 4-26). Additional costs are minor; these costs include: one application printout, one photocopy for personal records, an envelope, and a stamp. The total first year information collection burden is estimated be $276 per firm. Firms applying for re-certification will incur all the costs of initial certification, less the time burden associated with learning about the rule, or $181 per firm. In years where firms will not need to apply for re-certification their information collection burden will only include the recordkeeping burden of $165.

[32] The administrative costs associated with firm certification are estimated to be $318 per firm seeking certification; the annual costs of ensuring certified firm compliance is estimated to be $1.06 million.

Table 4-26: Costs to Firms Associated with Information Collection			
	First Year/Initial Certification Year	**Re- Certification Year**	**Other Years**
Rule familiarization (3 hours)[b]	$94.93	$0	$0
Certification form (half hour)[b]	$15.82	$15.82	$0
Recordkeeping (5 hours per firm)[b]	$164.85	$164.85	$164.85
2 photocopies	$0.16	$0.16	$0
1 envelope	$0.02	$0.02	$0
1 stamp	$0.37	$0.37	$0
Total[a]	**$276**	**$181**	**$165**

[a] Rounded to nearest dollar.

Source: EPA Calculations and (b) U.S. Bureau of Labor Statistics 2005a.

4.6.6 Total Certification Costs: Firm Paperwork Burden and EPA Administrative and Enforcement Costs

Table 4-27 shows the total certification costs for the RRP rule in the first, second, and third years. Total per-firm costs are the sum of EPA's administrative costs per firm and the firm paperwork burden. This per-firm cost is multiplied by the number of establishments estimated to provide lead-safe RRP services (See Section 4.3.5).

In the first year, all the firms listed in the number of establishments column are presumed to seek initial certification, paying their share of EPA's administrative costs ($318 per firm, see Section 4.6.4) and their share of the enforcement costs ($1.06 million in total, see Section 4.6.3). In addition, they are subject to a paperwork burden of $276 (see Table 4-26). In the second year, EPA administrative costs per-firm and the firm paperwork burden are estimated based on the costs presented in Table 4-26 and the relative number of firms seeking initial-certification, re-certification, and not seeking certification. Section 4.3.5 describes and presents these estimates. The number of establishments includes all firms, even those not seeking certification or recertification that year. Since one-third of the firms under Option A will seek recertification in the second year, the average cost over all firms is one-third of $318. Under Option B, over 100,000 firms are seeking initial certification in year two. In addition, one-third of the firms certified in the first year are seeking recertification. Thus, the average cost over all firms is $206. Finally, in the third year, the average firm's share of the administrative costs is $106 ($318/3, since one third of firms are paying a certification fee), and the average firm's paperwork burden is $187.[33]

[33] After the first year, 54 percent of firms seeking certification are assumed to be seeking their initial certification based on the relative frequency of initial certifications observed for abatement firms in the FLPP database (EPA 2005).

Table 4-27: Average Firm Annual Certification Costs: Firm Paperwork Burden and Fees in the First, Second, and Third Years of Regulation (including EPA Administrative and Enforcement Costs)						
	EPA Administrative Costs, Average per Firm	**Average Firm Paperwork Burden**	**Total Average Cost per Firm**	**Number of Establishments**	**Annual Enforcement Costs, Total (millions 2005$)**	**Total Certification Costs (millions 2005$)**
First Year of Regulation						
Option A	$318	$276	$594	163,979	$1.06	$98
Option B	$318	$276	$594	86,539	$1.06	$52
Option C	$318	$276	$594	59,571	$1.06	$36
Option D	$318	$276	$594	86,539	$1.06	$52
Second Year of Regulation						
Option A	$106	$187	$293	163,307	$1.06	$49
Option B	$206	$229	$435	163,307	$1.06	$72
Option C	$241	$244	$485	163,307	$1.06	$80
Option D	$206	$229	$435	163,307	$1.06	$72
Third Year of Regulation						
All Options	**$106**	**$187**	**$293**	**162,637**	**$1.06**	**$49**
See Table 4-4 for option descriptions.						
Source: EPA Calculations.						

4.7 Total Costs

This section presents the total costs of the regulation. Total costs are estimated for the first, second and third years of regulation and also calculated as total 50-year costs and 50-year annualized costs. Estimates are calculated using discount rates of 3 and 7 percent.

4.7.1 Total Costs in the First Year of Regulation

Table 4-28 presents the total first year costs of the Renovation, Repair, and Painting Rule. Total containment, cleaning, and verification costs are calculated by adding the cost of testing using the LBP test kits to the costs of containment, cleaning, and verification. The total costs of containment, cleaning, and verification are calculated by multiplying the number of events presented in Table 4-7 by the corresponding incremental costs in Table 4-21. The total cost of conducting LBP tests using test kits is estimated as the number of events presented in Table 4-4 by the cost of conducting the test, $10 (see Section 4.5.1). Total training costs are calculated by multiplying the number of workers presented in Table 4-14 by the corresponding incremental costs in Table 4-16. Total certification costs are calculated by multiplying the number of firms presented in Table 4-14 by the corresponding incremental costs in Table 4-27.

The total costs in the first year of regulation are highest under Option A, the only option that requires all pre-1978 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides to follow the rule's requirements. Both Options B and D regulate the same universe of housing units in the first year, all pre-1960 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides, but Option D has higher first year costs because of its more prescriptive containment requirements. Option C has the lowest first year costs

because the regulated universe is limited to all pre-1950 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides.

Table 4-28: Total First Year Costs of the Renovation, Repair, and Painting Rule (millions 2005$)				
	Option A	**Option B**	**Option C**	**Option D**
First Year				
Total Work Practice Costs	$713	$419	$315	$533
Total Training Costs	$112	$59	$41	$59
Total Certification Costs	$98	$52	$36	$52
Total Costs	**$924**	**$531**	**$393**	**$645**
See Table 4-4 for option descriptions.				
Source: EPA Calculations.				

4.7.2 Total Costs in the Second and Third Years of Regulation

From the second year forward, the universe of regulated housing units is the same under all four options; all pre-1978 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides are subject to the rule. Thus, Table 4-29 shows that the work practice costs are the same for the flexible options (A, B, and C). Despite the second year expansion of the number of regulated events under Options B and D, the total work practice costs are lower than in the first year. This decline results from the improved effectiveness of the test kit, from a false positive rate of 63 percent to a 10 percent rate, which yields a larger savings than the cost increase associated with the larger universe of regulated events. Under Option C, however, the cost increase from the regulated universe expansion in the second year is large enough to overshadow the cost savings associated with the improved test kit.

In the second year, the training and certification costs are highest under Option C, and are relatively higher under Options B and D. This reflects the delayed start-up costs associated with training and certifying the additional individuals and firms needed to meet the demand increase that corresponds with the expansion in the regulated universe (to include all pre-1978 renter-occupied target housing units and owner-occupied target housing units where a child under the age of six resides). From the third year forward, the training and certification costs are the same under all four options.

Table 4-29: Total Second and Third Year Net Present Value Costs of the Renovation, Repair, and Painting Rule (millions 2005$)								
	3 Percent Discount Rate				7 Percent Discount Rate			
	Option A	Option B	Option C	Option D	Option A	Option B	Option C	Option D
Second Year								
Total Work Practice Costs	$413	$413	$413	$510	$397	$397	$397	$490
Total Training Costs	$35	$70	$82	$70	$33	$67	$79	$67
Total Certification Costs	$47	$70	$78	$70	$46	$67	$75	$67
Total Costs	**$495**	**$552**	**$572**	**$649**	**$476**	**$532**	**$551**	**$625**
Third Year								
Total Work Practice Costs	$399	$399	$399	$493	$370	$370	$370	$457
Total Training Costs	$34	$34	$34	$34	$31	$31	$31	$31
Total Certification Costs	$46	$46	$46	$46	$43	$43	$43	$43
Total Costs	**$479**	**$479**	**$479**	**$572**	**$443**	**$443**	**$443**	**$530**

See Table 4-4 for option descriptions.

Source: EPA Calculations.

4.7.3 Total 50-Year and 50-Year Annualized Costs

The total costs are also calculated discounted over a 50-year period. Discounting refers to the economic conversion of future costs (and benefits) to their present values, accounting for the fact that society tends to value future costs or benefits less than comparable near-term costs or benefits. Discounting is important when the values of costs or benefits occur over a multiple year period and may vary from year to year. Discounting enables the accumulation of the cost and benefit values from multiple years at a single point in time, accounting for the difference in how society values those costs and benefits depending on the year in which the values are estimated to occur.

To estimate the 50-year costs of options considered, EPA first developed a profile, over the period of analysis, of the compliance costs associated with each option. EPA defined the period of analysis as a period of 50 years based on the economic analysis done for the TSCA Section 403 Lead-Based Paint Hazard Standards.

EPA developed a profile of costs over time by estimating the decline in pre-1978 housing stock, 0.41 percent per-year, and assumed that the regulated universe would decrease by that rate every year. To estimate that rate, EPA calculated the average annual compound rate of change in the pre-1980 housing stock using data from the 1990 and 2000 Decennial Census (U.S. Census Bureau 1990 and 2000c). This rate affects costs because it decreases the number of events and number of workers trained every year.

As discussed above in Section 4.7.1 (Total Costs in the First Year of Regulation), the first year training and certification costs account for the training and certification of all certified renovators and the certification of all certified firms to meet the demand for lead-safe RRP services in the first year. Similarly for the phase-in options (Options B, C, D) in the second year, it is assumed that the additional individuals and firms needed to meet the demand increase associated with the larger regulated universe will obtain training and certification. In subsequent years, it is assumed that one third of the necessary

stock of individuals and firms will obtain training and certification each year (since refresher-training and re-certification is required every three years).

In fact, if all the individuals and firms needed to meet the demand for lead-safe RRP are trained and certified in the first and second years, one might expect a drop in the level of training and certification in the third year, followed by a spike in the next year. That is, one might expect a cyclical pattern of training and certification to emerge. Thus, this analysis assumes a typical amount of training and certification occurs each year because modeling such a trend would add little to the analysis without being able to precisely estimate the extent of any cyclicality.

The total 50-year costs and the 50-year annualized costs are discounted using rates of 3 and 7 percent. These discount rate values reflect guidance from the Office of Management and Budget regulatory analysis guidance document, Circular A-4 (OMB, 2003).

EPA used the following formula to calculate the present value (PV) of the time stream of costs:

$$PV = \frac{Cost_{x,t}}{(1+r)^{(t-1)}}$$

where:

$Cost_t$	=	Costs in year t;
r	=	Discount rate (3 percent and 7 percent); and
t	=	Year in which cost is incurred.

This analysis also presents the 50-year annualized costs of the rule. Conceptually, the 50-year annualized cost is the level annual payment that one would have to make to pay off a debt equal to the present value total 50-year cost for a given interest rate (the discount rate).

The following formula is used to calculate the 50-year annualized cost.

$$AC = PV_r \times \frac{r \times (1+r)^{50}}{(1+r)^{(50)} - 1}$$

where:

AC	=	Annualized 50-Year Costs;
PV_r	=	Present Value Total 50-Year Costs assuming a discount rate of r; and
r	=	Discount rate (3 percent and 7 percent)

Table 4-30 shows the present value of the total 50-year costs and Table 4- 31 shows the annualized 50-year costs for the options considered. The differences among the flexible options (A, B, and C) are driven by the differences in the regulated universe during the first year the rule is in effect. Because the test kits available for the first year have a high false positive rate, including the newer units in the regulated universe is relatively costly. This is because the high rate of false positives will require many units without LBP to use the more costly work practices. The difference between Option D's total 50-year and 50-year annualized costs compared with the other options' costs is primarily due to the higher costs of Option D's prescriptive containment and cleaning requirements.

Table 4-30: Total Present Value 50 Year Costs of the Renovation, Repair, and Painting Rule (millions 2005$)								
	3 Percent Discount Rate				7 Percent Discount Rate			
	Option A	Option B	Option C	Option D	Option A	Option B	Option C	Option D
Total Work Practice Costs	$10,785	$10,491	$10,388	$12,967	$6,280	$5,986	$5,882	$7,405
Total Training Costs	$959	$940	$934	$940	$580	$561	$554	$561
Total Certification Costs	$1,257	$1,234	$1,226	$1,234	$739	$715	$706	$715
Total Costs	**$13,001**	**$12,666**	**$12,548**	**$15,141**	**$7,599**	**$7,261**	**$7,142**	**$8,680**

See Table 4-4 for option descriptions. Assumes 75 percent rate of Compliance.
Source: EPA Calculations.

Table 4- 31: Annualized 50 Year Costs of the Renovation, Repair, and Painting Rule (millions 2005$)								
	3 Percent Discount Rate				7 Percent Discount Rate			
	Option A	Option B	Option C	Option D	Option A	Option B	Option C	Option D
Total Work Practice Costs	$419	$408	$404	$504	$455	$434	$426	$537
Total Training Costs	$37	$37	$36	$37	$42	$41	$40	$41
Total Certification Costs	$49	$48	$48	$48	$54	$52	$51	$52
Total Costs	**$505**	**$492**	**$488**	**$588**	**$551**	**$526**	**$518**	**$629**

See Table 4-4 for option descriptions. Assumes 75 percent rate of Compliance.
Source: EPA Calculations.

Appendix 4A. Lead Abatement

The analysis does not adjust for the decrease over time in the stock of housing regulated by the RRP rule due to lead paint abatements. The number of abatements is small compared to the universe of housing covered by the RRP rule. Furthermore, an abatement does not necessarily eliminate all the lead-based paint in a home. Not all lead-based paint is in hazardous condition. A home that has been abated may still contain intact lead-based paint. This intact lead-based paint could be disturbed during subsequent RRP events.

This appendix reviews the annual rate of lead abatement in target housing using data on notifications from contractors conducting the abatements. The information is submitted by contractors directly to EPA in states where EPA administers the lead abatement program. In states that administer their own programs, the information is sent to the state, and EPA collected data from several of these states. Results for the two groups of states are discussed separately below.

4A.1 Abatements in EPA Administered States

At the time the information for this analysis was completed, EPA administered the lead abatement program in twelve states. The Agency promulgated a notification rule in April 2004 requiring contractors in states where EPA administers the lead abatement program to notify the Agency at least 10 days before performing an abatement.[1] EPA records this data in its Federal Lead Based Paint Program (FLPP) database. At the time the information was collected for this analysis, the FLPP database contained notification data from May 2004 to February 2005. The annual number of abatements was estimated by doubling the reported number of abatements for the six months between September 2004 and February 2005. The results are shown in Table 4A-1. Only five of the twelve EPA administered states reported any abatement activity between May 2004 and February 2005.[2]

[1] 69 FR 18489, found at 40 CFR 745.227(e)(4).

[2] The states of Alaska, Idaho, Montana, Nevada, South Carolina, South Dakota, and Wyoming did not report any activity. According to the Department of Housing and Urban Development (HUD), all of these states except for South Carolina have a relatively small stock of housing with lead hazards.

Table 4A-1: Target Housing Abatements in EPA Administered States[a]			
State	**Target Housing Abatements May 2004 - February 2005**	**Target Housing Abatements September 2004 - February 2005**	**Estimated Annual Target Housing Abatements**
Arizona	79	32	64
Florida	4	2	4
Hawaii	1	0	1
New Mexico	16	15	30
New York	1,145[b]	979[b]	1,958[b]
Other EPA States[c]	0	0	0

[a] Notifications reported for the six months between September 2004 and February 2005 were doubled to yield an annual estimate, except for Hawaii. All available months were included for Hawaii, which had one reported abatement during the time period.

[b] The absolute number of abatements in New York is large relative to the number in other EPA administered states. However, as demonstrated later in the report, the percent of the housing stock abated in New York is comparable to other states.

[c] Alaska, Idaho, Montana, Nevada, South Carolina, South Dakota, and Wyoming did not report any activity.

Source: EPA FLPP database.

4A.2 Abatements in States Administering their Own Lead Programs

EPA requested data from nine states that administer their own lead abatement programs; the data from seven of those states was incorporated into the analysis.[3] Table 4A-2 presents the abatement data collected from seven states that administer their own lead programs.

Data on abatements was available online for Massachusetts. When the information was collected for this analysis, the data for 2002 and beyond were incomplete. Therefore, the analysis averaged the number of abatements in 2000 and 2001 (2,267 and 2,711), yielding an estimate of 2,489 target housing abatements per year in Massachusetts. The portion of the housing stock abated in Massachusetts is much higher than in any other state with available data, due to specific state requirements in Massachusetts for housing with lead-based paint.

[3] Data collected from Minnesota was not comparable with data from other states since HUD funded abatements are not reported in Minnesota, so the reported data does not represent the total number of abatements in the state. One other state that was contacted did not provide any results.

Table 4A-2: Target Housing Abatements in Seven States Administering their Own Lead Programs					
State	**2002**	**2003**	**2004**	**Average for 2002 to 2004**	**Estimated Annual Target Housing Abatements**
Connecticut[a]	365			365	365
Illinois	1,086	1,134	1,091	1,104	856[b]
Maine	132	123	131	129	129
New Jersey	255	313	237	268	268
Ohio	892	729	789	803	803
Pennsylvania	770	637	518	642	642
Texas[c]	457	277	498	411	411

[a] Connecticut data was only available for 2002.

[b] Illinois data included interim controls as well as abatements. The average for the reported data was multiplied by 77.55%, since HUD data indicates that abatement accounts for 77.55% of all lead hazard reductions that utilized either interim control or abatement strategies.

[c] Texas data included abatements in child occupied facilities (COFs) as well as target housing. COFs are thought to represent a small fraction of abatements; in EPA-administered states, COFs account for 1.34% of total abatements.

4A.3 Percent of Housing Abated

Table 4A-3 compares the estimated annual number of abatements for each state to the pre-1980 housing stock (some fraction of which contain lead-based paint) and the stock of housing with lead hazards. Not all lead-based paint is in hazardous condition. Therefore, housing with lead hazards is a subset of housing with lead-based paint, which is in turn a subset of all pre-1980 housing. The stock of housing with lead hazards was estimated by combining HUD data on the prevalence of lead hazards by the age of dwelling with data on the distribution of the housing stock by age and state. The percent of the pre-1980 housing stock abated annually for the total sample is 0.02%, and the percent of the hazardous housing stock abated annually is 0.06%. The percent of target housing with lead-based paint that is abated annually is somewhere between these two values.

Table 4A-3: Estimated Lead Abatements Compared to the Housing Stock					
(1) State	(2) Estimated Number of Abatements Annually	(3) Pre-1980 Housing Stock	(4) Stock of Housing with Lead Hazards	(5) Percent of Pre-1980 Housing Stock Abated Annually	(6) Percent of Hazardous Housing Abated Annually
EPA Administered States					
Arizona	64	977,504	170,813	0.01%	0.04%
Florida	4	3,736,874	715,105	0.00%	0.00%
Hawaii	1	309,754	61,453	0.00%	0.00%
New Mexico	30	461,377	116,249	0.01%	0.03%
New York	1,958	6,552,424	2,765,456	0.03%	0.07%
Other EPA States	0	2,360,698	596,611	0.00%	0.00%
States Administering their own Programs					
Connecticut	365	1,074,747	406,726	0.03%	0.09%
Illinois	856	3,761,546	1,399,151	0.02%	0.06%
Maine	129	461,431	194,431	0.03%	0.07%
New Jersey	268	2,538,919	935,743	0.01%	0.03%
Ohio	803	3,680,341	1,348,072	0.02%	0.06%
Pennsylvania	642	4,222,021	1,794,770	0.02%	0.04%
Texas	411	4,639,948	1,074,401	0.01%	0.04%
Massachusetts	2,489	2,113,926	909,932	0.11%	0.27%
Total Sample	8,020	36,891,510	12,488,913	0.02%	0.06%

REFERENCES

Dreamhomesource.com. 2005. Available at: www.dreamhomesource.com. (Accessed 2005).

Gilkeya, David; Jacob Hautaluomaa, Taslim Ahmeda, Thomas Keefea, Robert Herrona, Philip Bigelowb. 2003. Construction Work Practices and Conditions Improved After 2-Years' Participation in the HomeSafe Pilot Program. American Industrial Hygiene Association Journal, May/June 2003.

Harrington, David, et. al. 2004. "Can Half-Day Training Motivate Small Contractors to Address Lead Safety?" *Health Promotion Practice*. 5(3), 297-305.

Homestyles.com. 2002. Available at: http://www.store.homestyles.com/homestyles/plans/search. (Accessed 2002).

Morbidity and Mortality Weekly Report (MMWR). 1997. Update: Blood Lead Levels – United States, 1991-1994. Center for Disease Control and Prevention. 46(07); 141-146.

Morbidity and Mortality Weekly Report (MMWR). 2003. Surveillance for Elevated Blood Lead Levels Among Children – United States, 1997-2001. Center for Disease Control and Prevention. Sep 12. .

Personal Communication with Kermit Baker, Joint Center for Housing Studies (JCHS) at Harvard University, August 2005.

Personal communication with work group members and other industry experts. 1999.

Personal communication with the Painting and Decorating Council.

RS Means, 2005, *Means CostWorks Repair & Remodeling Cost Data 2005 CD-ROM*, 7th Edition http://www.rsmeans.com/bookstore/detail.asp?sku=65045

U.S. Bureau of Labor Statistics. 2005a. Occupational Employment Statistics Series.

U.S. Bureau of Labor Statistics. 2005b. Consumer Price Index: All urban consumers; other goods and services. Bureau of Labor Statistics, Washington, DC.

U.S. Census Bureau. 1990. "H025. Year Structure Built - Universe: Housing units." American Fact Finder. Available at: http://factfinder.census.gov/ (Downloaded 10/26/2005)

U.S. Census Bureau. 2000c. "H34. Year Structure Built [10] - Universe: Housing Units." American Fact Finder. Available at: http://factfinder.census.gov/ (Downloaded 10/26/2005)

U.S. Census Bureau. 1997 and 2003. *American Housing Survey (AHS)*.

U.S. Census Bureau. 2003b. *American Community Survey Profile.*

U.S. Census Bureau. 1995. Property Owners and Managers Survey (POMS)

U.S. Census Bureau. 2004a. *2002 Economic Census: Industry Series* (For NAICS 61, 54, 56 and 53). Available at: http://www.census.gov/econ/census02/guide/INDSUMM.HTM. (January 12, 2004).

U.S. Census Bureau. 2004b. "Sector 53: Industry Series: Summary Statistics for the US: 2002." *American Fact Finder*. Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=53&ds_name=EC0200A1&_lang=en&_ts=141736463723 (Downloaded 8/3/2005)

U.S. Census Bureau. 2005b. "Sector 23: Industry Series: Detailed Statistics for Establishments: 2002." *American Fact Finder*. Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005d. "Sector 23: Industry Series: Value of Construction for Establishments by Type of Construction: 2002." *American Fact Finder*. Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005g. *American Housing Survey –Overview*. Available at: http://www.census.gov/hhes/www/housing/ahs/overview.html.

U.S. Census Bureau. 2005h. *Property Owners and Managers Survey (POMS) – Overview*. Available at: http://www.census.gov/hhes/www/housing/poms/overview.html

U.S. Department of Housing and Urban Development. 2000. *National Survey of Lead and Allergens in Housing.*

U.S. Department of Housing and Urban Development. 2004. *The National Lead Service Provider Listing System (The Lead Listing).*

U.S. EPA. 1997. *Reducing Lead Hazards When Remodeling Your Home.* EPA 747-K-97-001, September.

U.S. EPA. 1999. *Economic Analysis of the Final TSCA Section 402(a)(3) Lead-Based Paint Aaccreditation and Certification Fee Rule.* Available at: http://www.epa.gov/lead/lead2-26-99.pdf.

U.S. EPA. 2000a. *Model Renovation Training Course*. EPA 747-B-00-005/6. Available at: http://www.epa.gov/lead/rrmodel.htm.

U.S. EPA. 2000b. *Economic Analysis of Toxic Substances Control Act Section 403: Lead-Based Paint Hazard Standards*. December 21.

U.S. EPA. 2005. *Federal Lead Based Paint Program (FLPP) Database.*

U.S. EPA, 2005b. *Disposable Cleaning Cloth (DCC) Lead Clearance Field Study*. July.

U.S. EPA, 2005c. *Estimates of Concentration of Lead in Paint by Age of Housing.* October.

U.S. Office of Management and Budget. 2003. *Circular A-4.*

U.S. Office of Personnel Management. 2005a. *2005 General Schedule (Base, Annual).* Available at: http://www.opm.gov/oca/05tables/pdf/gs.pdf (Annual) and

U.S. Office of Personnel Management. 2005b. *2005 General Schedule (Base, Hourly).* Available at: http://www.opm.gov/oca/05tables/pdf/gs_h.pdf (Hourly).

U.S. Office of Personnel Management. 2005c. *Salary Table 2005-DCB.* Available at: http://www.opm.gov/oca/05tables/pdf/DCB.pdf.

U.S. Small Business Administration. 2005. "Non-Employer Statistics." *Firm Size Data*. Available at: http://www.sba.gov/advo/research/data.html. (Downloaded 8/3/2005).

Weil, David. 1999. Assessing OSHA Performance: Evidence from the Construction Industry. Boston University, October 1999.

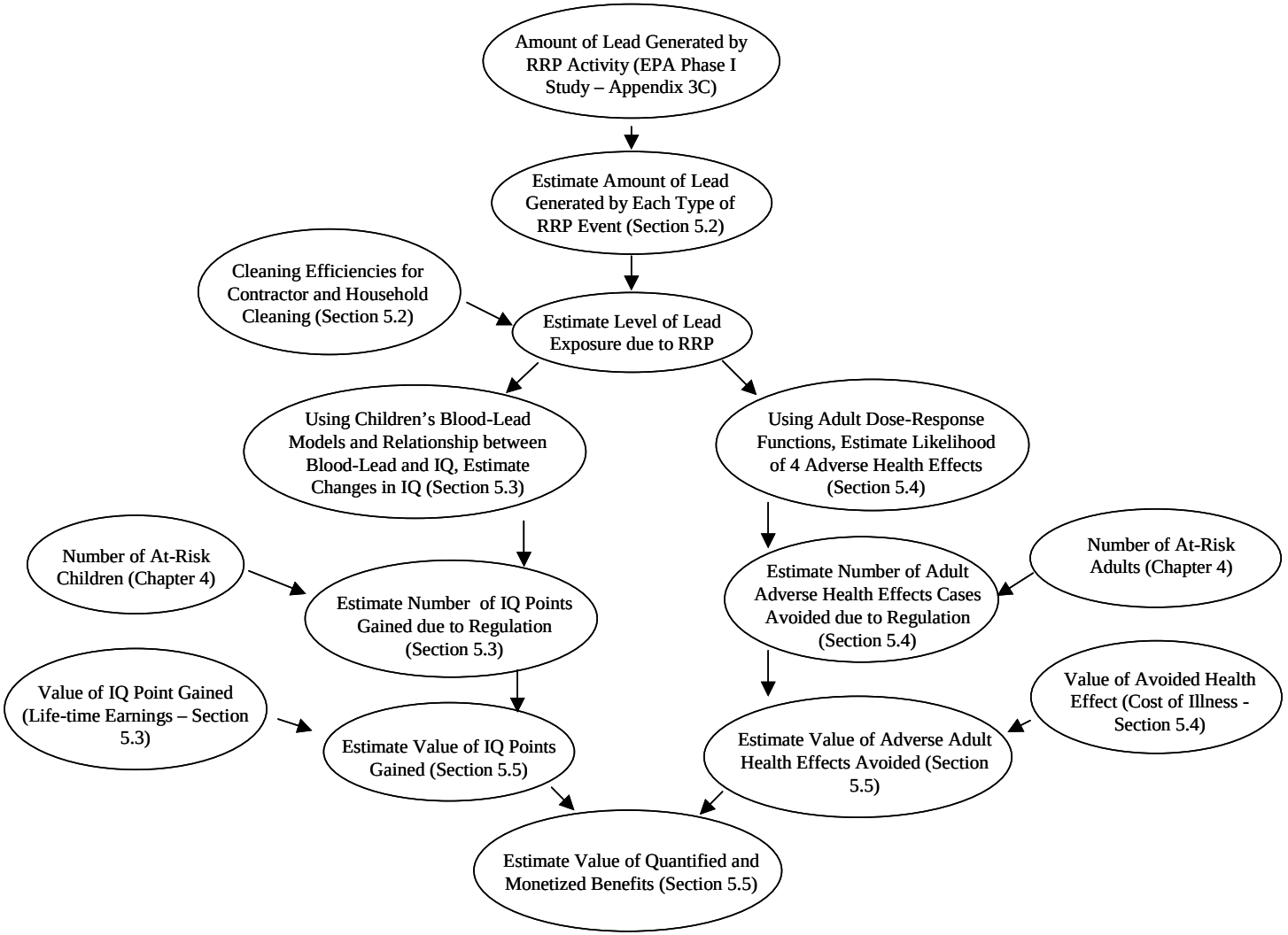
5. Benefits

This chapter contains an analysis of the benefits associated with the proposed regulations under TSCA Section 402(c)(3). The proposed work practices, training and certification requirements will reduce lead exposure by increasing the containment and cleanup of dust generated by renovation, repair, and painting (RRP) activities. These reductions in exposure will in turn reduce the risks of adverse health and ecological effects in the vicinity of these activities.

Given the uncertainty associated with many of the inputs underlying the estimate of benefits, a Monte Carlo approach was used to model the expected benefits. Conceptually, each uncertain parameter in the benefits model could be treated as a random variable and the functional form and moments of the distribution of expected benefits could be mathematically derived. In practice however, given the large number of uncertain parameters, this derivation is impossible. The Monte Carlo approach, however, approximates the true underlying statistical distribution of expected benefits.

The chapter is organized around the analytical steps involved in estimating the benefits. These steps are outlined in Figure 5-1. Section 5.1 of this chapter presents an overview of these steps, including: (1) estimating the amount of lead contamination due to RRP events, (2) estimating the resultant changes in blood lead levels, (3) estimating the resultant adverse health effects, including reduction in IQ, and (4) estimating the dollar value of the reductions in adverse effects. Steps one through three are conducted for both the "without rule" situation (i.e. the baseline) and for the with rule situations. The difference between the number of cases of adverse health effects and loss of children's IQ points avoided under the rule as compared to the baseline are the quantified benefits of the rule, and are assigned dollar values in Step four. Section 5.2 provides details on step one, the estimation of lead levels generated by RRP events and the effectiveness of cleaning. Section 5.3 presents the analytical details of steps two, three, and four as they relate to children. Section 5.4 presents analytical details on steps two, three, and four as they relate to adults. The final section (Section 5.5) describes the derivation of the underlying estimates of the number of RRP events and the number of children affected, as well as the parameters used in the Monte Carlo analysis and their assumed values or distributions. The final part of Section 5.5 presents the numerical estimates of the value of the benefits for both children and adult. Four appendices supplement this chapter. They are Appendix 5A: Lead-Related Health Effects and Ecological Effects, Appendix 5B: Adult Benefit Calculations, Appendix 5C: Identifying and Characterizing Lead Loadings for Interior RRP Tasks, and Appendix 5D: Distributions of Inputs and Results. Appendix 5A contains Chapters 5 and 6 of the Air Quality Criteria Document for Lead, First External Review Draft (EPA 2005).

Figure 5-1: Overview of Analytical Steps



5.1 Overview of Approach

Lead exposure causes many adverse health effects; a great deal of information on the health effects of lead is available from decades of medical observation and scientific research. Because inhaled or ingested lead is initially distributed throughout the body and is toxic to many organ systems, it damages a wide range of systems and its toxicity manifests itself in the form of many different types of adverse health effects. A reduction in lead exposure resulting from the rule would lead to a reduction in these adverse health effects and the costs of treating them. Young children are particularly sensitive to lead, which impairs a child's neuropsychological development (most commonly measured as reduced IQ). Increased blood-lead levels have also been associated with aberrant behavior in school-age children and a decrease in their growth rate and stature. These cognitive and behavioral effects are strongly related to their future productivity and expected earnings. Adverse health effects also include hypertension, coronary heart disease (CHD), stroke, blood disorders, kidney damage, thyroid hormone abnormalities, immune system damage, many types of neurological abnormalities, increased incidence of stillbirths and miscarriage, low sperm rates, abnormal sperm, and infertility (ATSDR 1999). It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development, may occur at blood-lead levels so low as to be essentially without a threshold (IRIS 2004). Appendix 5A presents an assessment of the animal toxicology and human epidemiology data available for a range of health effects associated with lead.

There are an assortment of health effects associated with exposure to lead (see ATSDR 1999 and Appendix 5A). This analysis is able to include only a subset of adverse health effects, due to limitations in understanding and quantifying the dose response relationships for some of the health effects. Even where the dose-response relationships are known, many cases are not included in the estimates because exposure levels cannot be estimated for all potentially affected individuals. Consequently, this benefits assessment focuses on two major categories of health effects: effects on cognitive function in young children (under the age of six) and cardiovascular disease (hypertension, coronary heart disease and stroke) and premature mortality in adults. There are additional uncertainties in the quantification of adult effects, which are addressed in Section 5.5.5.

It should be noted that even for these two categories of effects, some potential cases of these health effects are not included in the benefits estimates. This is because exposures of some potentially affected individuals (for example, neighbors of households performing renovations) have not been estimated in this assessment.

To estimate the benefits of the proposed rulemaking, the quantified adverse health effects associated with exposures to lead from RRP tasks in the baseline (i.e., without RRP regulation) are first calculated; then, health effects associated with exposures are calculated assuming the RRP regulations are in place. Since the rule requires actions intended to reduce contamination, fewer adverse health effects are expected with the rule. This reduction in adverse health effects is the rule's major benefit. The most commonly used measure of the amount of lead in the body is blood-lead level (PbB), although lead also bioaccumulates in bone, hair, teeth, and other tissues. Published studies relate one or more of these measures to adverse health effects. Some studies have examined the question of whether the neurological effects of exposures in early childhood are ameliorated when blood-lead levels decline. The data are mixed on this issue. In a study that treated lead-exposed children with a chelating agent, Ruff (1993) found that children whose blood-lead levels had the greatest decline showed the most improvement in IQ. In contrast, Rogan (2001)

found that treatment with a chelation agent lowered blood-lead levels in children but did not appear to improve neurological function. Liu (2002) also found that chelation therapy, while lowering blood-lead levels, did not improve neurological function in children at 5 years of age. While the study did detect a relationship between declining blood-lead and improved neurological function, this association was observed only in the untreated group, leading the authors to speculate that some other factor besides declining lead levels from chelation therapy (such as greater parental involvement), led to the neurological gains. Dietrich (2004) had similar findings in the same cohort of children at 7 years of age. One study cited in ATSDR (1999) showed impaired motor and cognitive function at a current mean level of 2.9 µg/dL, about 20 years after exposure when blood-lead levels were 40-50 µg/dL (Stokes 1998). These studies suggest that *medical interventions aimed at* lowering blood-lead levels may not lead to dramatic improvements in neurological function, further supporting the concern that early exposures to lead (Pb) lead to irreversible damage, and supporting the benefits of regulatory interventions to prevent or reduce lead exposure.

The estimation of the adverse health effects associated with renovation, repair, and painting projects involves four steps:

1. Estimate the amount of lead contamination due to the renovation project under various assumptions about cleaning;
2. Estimate the blood-lead levels resulting from this contamination;
3. Estimate the adverse health effects (e.g., loss in IQ points, increased incidence of hypertension) due to increased blood-lead levels using dose-response functions; and
4. Assign medical costs, reduced income, or another proxy for willingness-to-pay to avoid the adverse health effects.

Each of these steps is briefly discussed below; methods for implementing these steps are described in detail in Sections 5.2 and 5.4.

Step 1: Estimate the amount of lead contamination due to the renovation project

Most of the events covered by this rule are expected to generate lead dust levels that exceed the EPA floor hazard standard of 40 μg/ft^2 promulgated in 2001.[1] As described in detail in Appendix 5C, all RRP events undertaken where lead-based paint is present have the potential to exceed the 40 μg/ft^2 hazard standard if precautions are not taken. In some cases contractors are already taking precautions even without the rule, and the number of RRP events where this is the case is estimated in Section 4.2 of this document. (Also see Section 5.5 of this chapter.) In addition, not all homes contain lead-based paint; the likelihood that lead-based paint occurs in a house is estimated in Section 4.2.5 of this document, and summarized in Table 4-6. In the majority of RRP events, however, contractors do not take these precautions. RRP events with precautions already in place are not included in the benefits calculations; only those RRP events performed without appropriate precautions are included in the calculations. Unless the appropriate safe work practices, containment, and cleanup are used, lead dust from the renovation activities can migrate throughout the residence and residents living in these units could be exposed to lead levels that are high enough to cause adverse health effects, even when accounting for normal household cleaning.

Step 2: Estimate blood-lead levels from this contamination

Several studies establish a strong correlation between lead dust levels and blood-lead concentrations in children. Dust caught in carpets that is later released due to vacuuming, as well as dust in window wells and on uncarpeted floors, can contribute to increased blood-lead levels among children. In a study of lead exposure among urban children, Lanphear (1998a) showed a dramatically rising probability of blood-lead levels exceeding 10 μg/dL,[2] with a probability of over 50 percent for lead dust greater than 100 μg/ft^2. Another analysis that measured lead dust on multiple surfaces (carpeted and non-carpeted floors as well as window sills and window wells) found that lead dust was significantly correlated with the probability of increased blood-lead levels for every surface tested (Lanphear 1996). When compared against several other factors, window trough lead dust highly correlated with blood-lead levels in the Lead-Safe Cambridge program (Potula 2001).

The studies discussed above evaluated the correlation between lead dust and blood-lead levels without specifying the activities that generated the leaded dust. Further, the studies either do not specify the duration of the exposure to the lead dust, since the dust and blood-lead measurements are concurrent, or in one case, specifically examined chronic lead dust exposure and excluded cases where there had been spikes of exposure such as renovation (Lanphear 1996). However, two other recent studies focused specifically on the impact of home renovation on lead exposure among children. In New York City, authors conducted a case-control study comparing children living in homes that had undergone renovation and/or repair (cases) to those children living in homes without these activities (controls). One criterion for including children in the study was that they had no prior history of increased blood-lead measurements; thus it is very unlikely that the renovations were carried out as abatements to reduce lead

[1] The final lead hazard standards were established under the authority of Section 403 of the Toxic Substances Control Act. These standards were based in part on a benefit-cost analysis comparing clean-up costs to the value of IQ points lost in children without the cleanup. The objective of the Section 403 benefit-cost analysis was to identify a standard at which net benefits are maximized, assuming that all households with children under the age of seven undertake appropriate lead clean-up activities if their home exceeds the hazard standard.

[2] This is the CDC level of concern, which is intended to trigger community-wide prevention activities. It is not a threshold of effect.

exposure to children living in the house (which could have biased the study). The study found that children with increased blood-lead levels were more likely to live in a house that had undergone renovations (1.2 times more likely), had interior surfaces prepared for painting (3.5 times more likely), or had work-related dust dispersed throughout the house (6.3 times more likely), as compared to control children (Reissman 2002). In a Department of Health study also from New York (but which excluded New York City), half of the families with a child with increased blood-lead levels reported more than one type of paint removal activity in their house (CDC 1997). Thus, the studies concluded that increased blood-lead levels are correlated with renovation activities.

Decreases in lead dust have been shown to decrease blood-lead levels among children. Several studies have investigated the effectiveness of lead dust controls in conjunction with or in the absence of other lead-control activities. One intervention study, which trained families in home dust-control measures, found a reduction of up to 4.0 µg/dL after one year of the program (Hilts 1998). Thus, control of dust is an important element of any renovation and clean-up event.

Step 3: Estimate the adverse health effects (e.g., loss in IQ points, increased incidence of hypertension) due to increased blood-lead levels

As described above, this assessment estimates the adverse health impact of increased blood-lead levels on cognitive function and, more specifically, IQ function in young children as well as cardiovascular effects in adults. Appendix 5A provides a review of the recent literature related to the cognitive effects of lead in children. Young children are particularly sensitive to lead, which impairs a child's neuropsychological development (most commonly measured as reduced IQ). Increased blood-lead levels have also been associated with aberrant behavior in school-age children and a decrease in their growth rate and stature. These cognitive and behavioral effects are strongly related to their future productivity and expected earnings. EPA believes there is essentially no threshold for adverse health effects of lead in children. Indeed dose-effect curves for lead effects on children's IQs show a non-linear, inverse relationship with the greatest effects occurring at the lowest detectable blood-lead levels. In an effort to determine what a blood-lead level of concern should be, the Workgroup of the Advisory Committee on Childhood Lead Poisoning Prevention to the Centers for Disease Control and Prevention (CDC 2005a) found that the overall weight of available evidence supports an inverse association between blood-lead levels and the cognitive function of children in the low range of exposure (less than 10 µg/dL blood). The evidence for such an association is bolstered by the consistency across both cross sectional and longitudinal studies in varied settings. Further, the association is not weaker in studies where the populations' mean blood-lead levels are relatively lower (CDC 2005a). Thus, this analysis assumes that there is no evidence of a threshold below which the adverse health effects of lead are not experienced.

Similarly, U.S. EPA's Integrated Risk Information System (IRIS 2004) concluded: "by comparison to most other environmental toxicants, the degree of uncertainty about the health effects of lead is quite low. It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development, may occur at blood-lead levels so low as to be essentially without a threshold."

This assessment also considers the cardiovascular effects of lead on adults. In 1986, US EPA published an addendum to the Air Quality Criteria Document for Lead (EPA 1986); this addendum reviewed in detail the existing evidence for the relationship between blood lead and blood pressure. Based on the review of the evidence, the 1986 Addendum to the Air Quality Criteria document concluded that overall, two large-scale population studies, the British Regional Heart Study and the NHANES II, provide "highly

convincing evidence demonstrating small but statistically significant" relationships between blood lead and blood pressure in adult men. Another addendum was published in 1989 (EPA 1989). Much of the discussion in the new Addendum was based on an extensive peer review of the literature (the International Symposium on Lead-Blood Pressure Relationships; for more detail see http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?PrintVersion=True&deid=38444). That document concluded that the data since the 1986 Addendum further supported the conclusions of that document, i.e. that there is strong evidence for a relationship between blood lead and blood pressure, based on data from four large scale population studies and several smaller scale studies.

In 2005, EPA released an external review draft of another addendum to the Air Quality Criteria Document for Lead (EPA 2005c). This document, portions of which are included as Appendix 5A, provides a detailed weight of evidence review of all the animal toxicology and epidemiology studies on the relationship of lead exposure to blood pressure. The conclusions of the epidemiology studies can be found in section 6.5.6 (page 6-207), and are as follows:

> "The combined blood lead studies using blood pressure/hypertension as an outcome continue to support the conclusions of the 1990 Supplement that there is a positive association between blood lead and increased blood pressure. The occasional finding of significant negative associations of blood lead with blood pressure (e.g., the Cadmibel study, one NHANES III study, the postpartum phase of the Los Angeles pregnancy study) have not been adequately explained and require further confirmation and study. The reported meta-analysis succinctly characterizes the blood pressure findings with blood lead: 1.0 mm Hg systolic pressure increase with each doubling of blood lead; 0.6 mm Hg diastolic pressure increase with each doubling of blood lead. Although females often show lower lead coefficients than males, and blacks higher lead coefficients than whites, where these differences have been formally tested, they are usually not statistically significant. The tendencies may well arise in the differential lead exposure in these strata, lower in women than in men, higher in blacks than in whites. The same sex and race differential is found with blood pressure.
>
> The most promising developments in this field since the 1990 Supplement have been the use of bone lead as a long-term cumulative lead exposure index and the introduction of genetic analysis into the studies as potential lead effect modifiers. With one exception, all studies using bone lead have found a consistently positive and significant effect on blood pressure and/or hypertension. The ability to estimate past exposure in cross-sectional studies is a significant advance. The results of the bone lead studies to date highlight the important role of accumulated lead exposure in the development of cardiovascular problems.
>
> Though the study of genetic polymorphisms is still in its infancy in this field, it too holds great promise in accounting for individual variability in development of cardiovascular disease and individual response to lead exposure."

The draft Air Quality Criteria Document (AQCD) for Lead has not yet been peer reviewed by the Clean Air Act Scientific Advisory Committee (CASAC). The report may be revised in response to the CASAC review. EPA intends to reflect revisions to the AQCD in the economic analysis for the final lead RRP rule. For more information on the AQCD, see Appendix 5A and Section 5.5.5.

Understanding the underlying biological mechanisms by which lead can induce hypertension strengthens the case for causation. A number of studies describe animal experiments designed to elucidate the mechanism of action by which lead exposure could cause hypertension (Goch and Goch, 2005; Durnsun et al 2005; Bagchi and Preuss, 2005; Zysko et al, 2004; Farmand et al 2005; Vaziri and Sica 2004; Apostoli et al 2004; Lustberg et al 2004)). A plausible mechanism proposed by several authors is that exposure to lead causes oxidative stress. As further evidence for this mechanism of action, Ni et al (2004) found that human endothelial and vascular smooth muscle cells exposed to lead had increased production of superoxide and hydrogen peroxide. Changes in angiotensin converting enzyme (ACE) (an enzyme involved in regulating blood pressure through the kidneys) may also be involved in the hypertensive effects of lead (Sharifi et al 2004). A detailed discussion of these studies can be found in section 5.5 of the 2005 external review draft of the addendum to the Air Quality Criteria Document for Lead.

Changes in blood pressure has been related to changes in risk for hypertension, coronary heart disease, stroke, and premature mortality in adults, as discussed in Appendix 5B. This assessment first estimates the change in blood pressure to due lead exposure and then estimates the number of cardiovascular disease cases and premature mortality associated with the predicted change in blood pressure.

Step 4: Assign medical costs, reduced income or other proxy for willingness to pay to avoid the adverse health effects

In the following analysis, standard values from the economic literature are used for the benefits valuation. In lieu of willingness to pay, medical costs and reduced income are used as an estimate of the cost of chronic conditions. For potentially lethal outcomes, the statistical value of life used by EPA is included.

5.2 Estimating Lead Dust Contamination Levels from RRP Activities

The benefit estimates provided in this report reflect the following sequence of events. In the baseline, an RRP event occurs, generating lead dust in both the area where the work occurs and the adjacent area (e.g., the adjacent room). In the baseline (without rule), the contractor cleans the work area before he/she leaves by sweeping or vacuuming. While this contractor cleaning substantially reduces the lead dust in the work area, it rarely brings the lead levels down to the EPA hazard levels of 40 μg/sq.ft (Dixon 1999, Ettinger 2002). In most cases, this cleaning also does not address the lead dust that may have migrated into the rest of the house during the RRP event. Following the end of the RRP event, the household cleans the work area and the rest of the house on a regular basis. Periodic cleaning continues to reduce the lead dust levels over time. Under the rule, the same sequence of events occurs, but it is assumed that the containment, cleaning, and cleaning verification practices required by the rule reduce lead dust loadings to 40 $\mu g/ft^2$ or less after contractor cleaning. For the benefits analysis, exposures to both indoor dust and to soil contaminated from exterior painting are evaluated.

5.2.1 Initial Dust Loadings from Interior RRP Activities

EPA estimated the lead dust loadings associated with an interior RRP event using the U.S. Census Bureau's 1997 and 2003 American Housing Survey (AHS), the 1995 Property Owners and Manager Survey (POMS), and EPA's 1997 "Lead Exposure Associated with Renovation and Remodeling Activities: Environmental Field Sampling Study" (EFSS). The AHS and POMS provide information on the number of households in which renovation and repair tasks of various types are carried out during the

prior two years.[3] EPA used this information to estimate the number of renovation and remodeling activities that could potentially generate lead dust. The AHS and POMS do not detail the amount of lead dust a particular RRP event could generate. As a result, EPA used data provided in the EFSS to estimate the lead dust loadings associated with each RRP task identified in the 1997 AHS. For a more detailed description of the approach and methods used to estimate the lead dust loadings for interior RRP tasks, see Appendix 5C.

5.2.2 Effect of Cleaning on Interior Dust Loadings

Cleaning by the contractor immediately after the RRP work is completed decreases the amount of residual lead dust on household surfaces. Following the contractor cleaning, the household is expected to undertake routine cleaning, further decreasing lead levels generated by the RRP event. This section describes the development of cleaning effectiveness estimates for various specific cleaning methods. Section 5.5 presents the modeling assumptions about the types of cleaning and the frequency of cleaning undertaken by contractors and households in the baseline and under the rule.

The amount of lead present at any particular time is a function of the initial lead levels, the effectiveness of the cleaning and the number of times that cleaning has occurred in the intervening period, as represented by the formula:

$$Pb\ Concentration\ at\ time\ t = [Pb\ concentration\ at\ time\ 0] * (1\text{-}Efficiency)^{Frequency}$$

where:

Efficiency = the percent of lead dust removal associated with each cleaning activity; and
Frequency = the number of times the cleaning technique is employed between time 0 and time t.

As described in more detail below, cleaning efficiency rates vary with the type of surfaced cleaned, the type of cleaning done and the amount of dust present. While cleaning efficiencies typically decline as the amount of dust declines (Yiin 2002, Rich 2004), this analysis assumes a constant rate for any particular situation, and thus overestimates the effectiveness of multiple cleanings. This in turn results in an underestimate of the benefits of the regulation. The model further assumes that successive cleaning by the householder will continue to reduce floor lead levels until the floor lead dust loading reaches a minimum of 1.1 $\mu g/ft^2$. At this point, lead levels will no longer decline. The 1.1 $\mu g/ft^2$ level is the U.S. household geometric mean for floor lead dust (Jacobs 2002).[4] The length of time to reduce floor lead dust loadings from a particular RRP event is a function of the amount of lead generated by the RRP event, the type of cleaning method used, the frequency of cleaning, and whether the work practices specified in the proposed rule are used.

EPA assumes that the contractor will initially clean the workspace and that the householder will perform subsequent cleanings using a normal household vacuum or broom. To estimate the efficiency of clean-up activities performed by the householder (i.e. non-HEPA portable or central vacuum and/or broom sweeping), EPA conducted a literature review of studies that performed clean-up activities after RRP events. Of the studies reviewed by EPA, the majority described clean-up activities consisting of

[3] Details are provided in Section 5.5 and Chapter 4 of this report.

[4] This value is used to represent the lowest lead level that cleaning can feasibly achieve over time. It is used in the analysis to indicate the background lead level before an RRP event was commenced, hence the lowest level one could expect to achieve after an event if all lead from the RRP event was eventually removed by cleaning.

vacuuming, mopping, sweeping and/or using a wet clean-up method (i.e., phosphate detergent or water) on either a carpeted or non-carpeted surface. Of the studies selected, EPA only considered studies that described the effectiveness of clean-up activities associated with RRP events.

The studies identified by EPA used a variety of clean-up methods and reported a wide range of cleaning efficiencies. To determine the most representative cleaning efficiency value, EPA analyzed each study and selected the studies with the most robust study design to establish a householder clean-up efficiency for both carpeted and non-carpeted surfaces. None of the studies, however, looked at cleanup of dust from the full range of activities that could occur during RRP activities.

Rich 2002, Yiin 2004, Dixon 1999, and Ettinger 2002 each use a clean-up method consisting of a HEPA vacuum alone or a HEPA or non-HEPA vacuum in conjunction with either a tri-sodium phosphate (TSP) or non-TSP detergent. The HEPA studies were excluded from the analysis because normal householder clean-up activities do not employ a HEPA vacuum. Studies reporting efficiencies from the use of non-HEPA vacuuming combined with wet cleaning were eliminated because wet cleaning was not included as an initial cleaning method in the analysis. [5]

Yiin 2002, Clemson Environmental Technologies Laboratory (CETL) 2001, and Figley and Makohon (Canadian Mortgage and Housing Corporation (CMCH)) 1992 and EFSS 1997 describe clean-up efficiencies on both carpeted and/or non-carpeted surfaces. The Yiin, CETL, and CMCH studies used similar non-HEPA vacuums with an agitator head while the CMCH also used a non-HEPA vacuum with a plain tool head. It would be expected that each type of vacuum would remove a similar amount of lead dust from a carpeted surface, but Yiin 2002 reported that non-HEPA vacuums remove 14.0%-36.6% of lead dust deposited after a RRP event, the CMCH 1992 study reported a non-HEPA clean-up efficiency of 23.7%-65.3%, and the CETL 2001 study reported a non-HEPA clean-up efficiency of 66%-84%. The large discrepancy between the clean-up efficiencies reported in each of these studies could be attributed to three factors: (1) the lead dust level applied to the carpet prior to clean-up, (2) whether the study accounted for the size of the dust particles, and (3) whether and how the study accounted for the redistribution/deposition of lead dust after clean-up.

Yiin 2002 had both a lead dust level similar to those found in RRP events and accounted for redistribution/deposition of lead dust after cleanup. The study measured the efficiency of removing lead dust from carpet using a non-HEPA vacuum in two different experiments. The first experiment observed the clean-up efficiency of non-HEPA vacuums on carpets with low levels of lead dust (geometric mean: 54.4 µg/ft2), while the second experiment measured the clean-up efficiency of non-HEPA vacuums on "soiled" or high levels of lead dust (geometric mean: 113 µg/ft2). After vacuuming the carpeted surface Yiin et al. waited at least 1 hour to allow for the redistribution/deposition of lead dust prior to measuring the amount of lead dust remaining in the carpet. This practice was intended to account for the remaining lead dust levels because under normal vacuuming conditions airborne lead dust will be generated as a result of the agitator action of the vacuum head. Using the clean-up efficiencies (as measured by vacuum) from both the low dust level and high dust level experiments, EPA calculated a cleaning efficiency range for Yiin 2002 of 14.0%-36.6% for non-HEPA vacuums on carpets. This is applied to both contractor and householder non-HEPA cleaning of carpets.

[5] While contractors can use wet cleaning methods under the rule, such methods are not appropriate for carpeted and upholstered surface. To simplify the benefits estimation, dry methods were assumed to always be used.

The CETL 2001 study measured the clean-up efficiency on carpeted and non-carpeted surfaces of a variety of non-HEPA vacuums by applying a defined amount of lead dust to either a carpeted or non-carpeted surface. Unlike the Yiin 2002 study in which the lead dust level applied to the carpeted surface is more indicative of what would be found in a "real world" situation, CETL applied extremely high levels of lead dust, 1,000,000 µg/ft^2, to both carpeted and non-carpeted surfaces. As a result, the clean-up efficiencies detailed within the study may be an overestimation because it is easier to reduce the percentage of lead dust found on a surface if there is more lead dust initially. Further, the CETL study does not take into account the redistribution/deposition of lead dust after clean-up.

The CMCH 1992 study measured the clean-up efficiency of a variety of non-HEPA vacuums on carpeted and non-carpeted surfaces. Although the CMCH study used an extremely high level of dust to determine these clean-up efficiencies, 3,700,000 µg/ft2, the study did not use lead dust generated from RRP events. Instead the study used "a representative dust sample… produced by gathering floor debris including wallboard/plaster scraps, dust and paint chips from an existing building renovation." To produce a dust sample containing lead, lead stearate was added to the sample, but it represents only a "very small mass component of the test dust… [and artificially skewed] the lead content analysis… towards the fine particle sizes." EPA excluded the non-HEPA vacuum clean-up efficiencies detailed within the CMCH study for carpeted and non-carpeted surfaces because the study does not use lead dust generated from a RRP event and, therefore, it is unclear if the efficiencies detailed are consistent with what would be found if the experiment used lead dust generated from a RRP event. EPA did include the broom clean-up efficiencies in this analysis although the study did not use lead dust generated from a RRP event because the broom clean-up efficiencies are consistent with those reported in the EFSS.

The EFSS 1997 study measured the clean-up efficiency of brooms on non-carpeted surfaces, i.e. linoleum. Unlike the other studies considered by EPA, the EFSS study performed the clean-up operations on lead dust generated from drilling and sanding activities on wood door surfaces covered with lead-based paint. After the generation of lead dust the lead loadings in the workroom were measured at 0 ft and 6 ft from the activity.[6] The study found that at distances from 0-1 ft from the activity the broom had clean-up efficiencies similar to non-HEPA vacuums for lead dust generated from work activities, 98.8 percent for drilling and 99.5 percent for sanding. The study did wait one hour after each clean-up activity to allow for redistribution/deposition of lead dust prior to determining the clean-up efficiency. The broom clean-up efficiencies obtained in the EFSS are similar to those found in CMCH 1992 for the lead dust levels generated at 0-1 ft, which supports the clean-up efficiencies in Table 5-1. The main discrepancy with broom clean-up efficiencies reported in EFSS compared to those reported in CMCH exists at 5-6 ft from the work activity. EFSS found at 5-6 ft from the work activity broom clean-up efficiencies decreased to 25.1 percent - 38.3 percent. In using the higher clean-up efficiencies, the analysis produces lower benefit estimates than would be the case if the lower efficiency numbers had been used

The values used in the benefits estimate are shown in Table 5-1.

[6] At 0 ft from the activity the geometric mean lead loading was 26,700 µg/ft2 for drilling and 653,000 µg/ft2 for sanding, while the geometric mean lead loadings at 6 ft from the activity were 65 µg/ft2 for drilling and 1,380 µg/ft2 for sanding.

Table 5-1: Efficacy of Clean-up Activities for Contractor and Household Cleaning			
Clean-up Option	**Surface**	**Reduction in Lead Dust Loadings**	**Citation**
Portable and Central Vacuum. No HEPA, no washing	Carpet	14% - 36.6%	Yiin 2002
Portable and Central Vacuum or Sweeping. No HEPA, no washing	Non-carpeted surface	94.8% - 98.5%	Clemson Environmental Technologies Laboratory (CETL) 2001; Figley and Makohon 1992.

Because the cleaning efficiencies vary depending on whether floors are carpeted or not, it was also necessary to estimate the percentage of floors covered by carpet. The percent of single family and multi-family homes with any carpet is presented in HUD (2000). For homes with carpet, these data also provide the percentage of area of flooring (in square feet) that is covered in carpet. Using these two values, the analysis calculated the total percentage of the area of flooring covered in carpet among all single family homes and multi-family homes covered by the proposed regulation. This value ranges from 33 to 38 percent. As described in detail in Chapter 4 of this document, the American Housing Survey (AHS) provides information on the number of RRP homes that are single family and multi-family. Using these values, a weighted average percent of area of flooring that is carpeting across all types of homes covered by the regulation was created. This weighted average is 36 percent.

With the rule, EPA requires more containment, cleaning and cleaning verification than would be undertaken without the rule. EPA assumes that these activities taken together will result in lead dust levels at or below the clearance level of 40 $\mu g/ft^2$. The data in the literature do not support a quantitative assessment of the independent efficiency of containment, cleaning and cleaning verification. However, the NCHH review (Staes and Rinehart 1995) details two abatement studies by Farfel that follow most of the "HUD interim guidelines."[7] These studies report a reduction in post-abatement floor lead dust levels when compared with pre-abatement levels. While these studies do not include dust from "prohibited practices", they do support the conclusion that the barriers, work practices and clean-up activities, taken together, are effective in reducing post-abatement lead levels. Further, in the preliminary study of six dwellings, Farfel (1991) showed that the geometric mean floor lead dust level at 6-9 months post abatement was 56 $\mu g/ft^2$; in the follow-up study of thirteen homes, Farfel (1994) showed that the geometric mean floor lead dust level was 37 $\mu g/ft^2$ one and a half to three and a half years post-abatement. The results of the study are consistent with the assumption that the proposed regulatory controls will result in a floor lead dust level below the EPA clearance level of 40 $\mu g/ft^2$. Lange (1997) reported on the abatement of a single building where barriers such as one layer of polyethylene plastic were established for all openings to the outside environment and for applicable internal openings. All critical barriers were sealed using duct tape and spray glue. In addition, safe work practices such as a three-stage decontamination chamber to prevent release of lead dust and debris from personnel and materials and negative air pressure inside the regulated area were used. The study measured airborne lead concentrations and determined that they were below both the U.S. Department of Labor's Occupational Safety and Health Administration (OSHA) action limit and the permissible exposure limit (PEL) for

[7] Lead abatement activities differ from renovation activities in that they are conducted with the intent to remove lead-based paint or otherwise permanently eliminate a lead-based paint hazard. Unlike abatement activities, renovation projects do not intend to remove lead-based paint, but may disturb it in the process of the renovation.

airborne lead. The study supports the efficacy of barriers and safe work practices in reducing airborne lead dust, which would be the source of dust loading in homes.

In order to model the effect of household cleaning on the levels of residual dust over time, it was necessary to estimate a frequency of cleaning. Simcox (1995) conducted a study of pesticide exposures from household dust. As part of this study, the authors surveyed families about the frequency of cleaning activities. The study reported 40 percent of survey respondents vacuumed more than once per week, 45 percent vacuumed once per week and 16 percent vacuumed less often than once per week. For this analysis, 40 percent of households were assumed to vacuum twice per week; 45 percent were assumed to vacuum once per week and 15 percent were assumed to vacuum once every two weeks.[8]

5.2.3 Soil Loadings from Exterior RRP events

According to the AHS survey, slightly over one-half of households who performed RRP conducted an exterior event; of these approximately 88 percent are exterior painting. However, estimates of lead loadings from exterior activities were not included as part of EPA's 1997 Lead Exposure Associated with Renovation and Remodeling Activities: Environmental Field Sampling Study (EFSS). A more recent study done by the University of Illinois (2002) investigated five different methods used to remove lead paint from exterior surfaces of homes in preparation of painting these surfaces. This study contains data that can be used to estimate lead loadings from exterior painting. For the analysis of exterior events, only lead exposures resulting from exterior painting were evaluated. Other exterior events were not modeled. As a result, benefits of avoiding exposure to lead from these events may be underestimated. However, given that these un-modeled events constitute a relatively small proportion of the number of exterior events, and given that the area of lead paint disturbed in these events (e.g., replacing a deck) are relatively small compared to the amount disturbed by exterior painting, it is unlikely the benefits are significantly underestimated by this omission.

To estimate exposures to lead resulting from exterior paint, the analysis first estimated the increase in lead concentrations in soil that could result from exterior RRP activities involving lead-based paint. In the University of Illinois study, lead loadings from the five paint removal methods were measured on six, 12-inch by 12-inch collection plates evenly placed at designated intervals within a 6.5 foot by 11 foot area on the ground directly under, and centered on, the work area. Lead deposited to surface soils is mostly immobilized and is retained within the top 2 inches if left undisturbed. EPA (1986) documents that lead deposited from air is basically retained within 2-5 cm of topsoil. Therefore, in this analysis, the lead deposits are assumed to be distributed within the top 2 inches of soil. Transport of lead contaminated soil can occur through soil erosion, however, it is assumed that this erosion is negligible in residential areas due to appropriate land grading and good vegetative cover commonly found in these areas. Estimation of the concentration of lead in soils for a mass loading is a function of the dry density of the soil. Dry densities can vary from 1.1 g/cm^3 for clays to 1.6 g/cm^3 for sands. This analysis assumes an average density of 1.36 g/cm^3 corresponding to a loam soil (EPA 1986).

[8] Note that the analysis modeled each cleaning as having the same level of efficiency. In fact, several studies have shown that cleaning efficiency is dependent on the lead concentration. Initial cleanings can be more efficient than later cleanings after much of the lead dust has been removed. Further, at least one study (Ewers 1994) showed that vacuuming could actually increase the surface lead dust level on carpets by bringing lead trapped in carpets to the surface. To the extent that this analysis overestimates baseline cleaning efficiencies, the benefits are underestimated.

By dividing the lead loading on the collection plates by the mass of soil, the analysis obtained the additional concentration of lead in soil that could be contributed by exterior paint from each of the five methods. In the analysis, the five values were used to represent a distribution (each value with equal probability) of possible soil lead concentrations from exterior paint removal. This additional lead was added to background levels of lead assumed to be present in soil around houses painted with lead based paint. This value, 490 µg/g, was derived from the National Survey of Lead and Allergens in Housing (HUD 2000) for all pre-1980 houses.

The study data found that almost all (94.0 percent to 99.8 percent) of the lead fell on the front center plate, located directly beneath, and centered on, the work area. This 12-inch by 12-inch plate was placed so that its nearest edge was 6 inches from the base of the house. Therefore, the analysis assumed that the observed lead loading in this plate would fall over an area 18 inches around the perimeter of the house and calculated the resulting soil concentrations in this area.

When adults or children are exposed to soil during outdoor play, yard work, gardening or other outdoor activities, they can be exposed to soil anywhere in the yard surrounding their homes. Therefore, the analysis averaged the concentration in the contaminated area with the background soil concentrations assumed to be present in the remainder of the yard. The perimeter and total yard areas of single and multi-family homes were calculated in the EPA Section 403 Economic Analysis (U.S. EPA 2001).

The inputs used to calculate the soil concentrations from exterior paint activities are summarized in Table 5-2.

Table 5-2: Soil Concentrations from Exterior Paint Activities			
Parameter		**Value**	**Reference**
Lead loadings in front center plate	Alkaline Chemical Paste	10,242 mg/ft^2	University of Illinois 2002
	Heat Gun	58,218 mg/ft^2	
	Paint Shaver	10,071 mg/ft^2	
	Safe Stripper	46,556 mg/ft^2	
	Wet Scrape	43,328 mg/ft^2	
Density of soil		1.36 g/cm^3	U.S. EPA 1986
Size of yard – single family home		2,988 ft^2	U.S. EPA 2001
Size of yard – multi-family home		6,417 ft^2	U.S. EPA 2001
Area within 18 inches of perimeter – single family home		235.37 ft^2 - owner 201.92 ft^2 - renter	See Chapter 4.5.5
Area within 18 inches of perimeter – multi-family home		402.47 ft^2	See Chapter 4.5.5

The analysis assumes that one-quarter of exterior paint jobs involve all sides of the building, one-quarter involve only one side of the building, and the other one-half involve areas in between one side and all sides. In calculating soil lead concentrations due to RRP events that involve all four sides of the building, the contaminated area is calculated as the entire area within 18 inches of the structure. These are the perimeter values presented in the table above. For exterior painting events that involve only one side of the structure, the soil concentration is calculated assuming that only one-quarter of the perimeter is contaminated, and the rest of the yard (including the other three sides of the structure) have background lead levels. The average of these two contamination levels are used to characterize contamination levels for the exterior painting events that are "in between."

For exterior renovations without the rule, it is assumed no cleaning or soil replacement occurs. Furthermore, no degradation of lead is assumed to occur over time. Under the rule, contractors place plastic sheeting on the ground 10 feet out around the perimeter of the house to catch the dust and debris, and they remove it prior to possible exposure.

5.3 Benefits Assessment -- Children

Research suggests that exposure to lead in children can have immediate and long term impacts on health including cognitive and other neurobehavioral deficits. Data suggests that the risk for lead effects in children is due both to a greater likelihood of exposure in young children who have a greater frequency of hand-to-mouth behaviors than older children and adults, and an increased sensitivity of the developing nervous system. Previous data supported adverse effects of lead on the nervous system in children from 0-3 years of age. (Bellinger et al., 1991, 1992) based on a correlation of blood lead levels at 2 years of age with cognitive impairment at 57 months and 10 years of age. Recent data (Canfield et al., 2003, 2004, Chen et al., 2005; Dietrich et al., 1993; Lanphear et al., 2000, 2005; Tong et al., 1996; Wasserman et al., 2000) demonstrate that the adverse effects of lead on the nervous system extend to school-age children and into adolescence and adulthood. Further data by Rice and Barone (2000) also demonstrate the long-term effects of childhood lead exposure in adults as a magnification of earlier exposure with aging. Furthermore, for exposures to dust and soil, young children are also at risk because of their behaviors (i.e., higher levels of dust and soil ingestion).

5.3.1 Estimation of the change in blood-lead levels resulting from lead contamination

To estimate the change in blood-lead levels in children per change in lead dust loadings or soil lead concentrations, the analysis used two alternative approaches. In the first approach, the analysis used EPA's Integrated Exposure Uptake Biokinetic (IEUBK) model (U.S. EPA 2005). The IEUBK model estimates age-specific lead intake from environmental media (air, water, soil, dust, diet) and then models absorption and excretion in a child's body to estimate the level of lead in blood. The model can be used to predict age-specific blood-lead levels for children ages 6 months to 84 months. For dust exposures from interior RRP activities, exposures occur from the time that RRP activity is completed (including contractor clean-up) until the time that the dust falls to background levels due to routine household cleaning (background is around 1.1 µg/ft2, the typical background level of floor dust cited in Jacobs et al., 2002). In the modeling exercise performed for this assessment, where contractor and household cleaning are assumed to reduce dust levels over time, the dust levels generally fall to background levels in less than one year. However, because IEUBK predicts blood-lead for children in one-year age brackets, the analysis calculated the average lead dust during the entire year when RRP activities take place and used this value to represent the average dust exposure during the year that a child is exposed. At all other times during early childhood (from ages 6 months to 6 years), children are assumed to be exposed to background levels of household lead dust, equal to 1.1 µg/ft^2. For soil exposures from exterior painting, the analysis assumes that lead loadings remain in the soil and are not cleaned up or abated after exterior painting work is completed. Therefore, children are assumed to be exposed to contaminated soil from the year when exposure begins until the age of 6 years.

The IEUBK requires an estimate of dust concentration rather than loadings. To estimate the relationship between floor dust loadings and hand lead dust concentrations, this analysis used a regression equation to describe hand dust-lead measures (PbH, µg) as a function of floor dust-lead loading (PbF, µg/ft^2), estimated using geometric mean floor dust-lead loadings and mean hand dust loadings from Clark (1985, as cited in Battelle 2005).

An alternative approach to the use of the IEUBK is to estimate the blood-lead level directly as a function of floor lead dust loadings. In fact, the Rochester Lead-in-Dust study (URSM and NCLSH, 1995) concluded that lead dust loading is a better predictor of children's blood-lead levels than is lead dust concentration. This analysis used a regression equation that directly links dust loadings and blood-lead levels, previously presented in U.S. EPA (2000a), which was based on data from the Rochester Lead-in-Dust Study. The regression model used (Model C) was:

$$log(PbB) = 1.337 + 0.140 * log(PbF) + 0.004 * (PbP) + error$$

where:

PbB = the blood-lead concentration, µg/dL;
PbF = the floor lead dust loading, µg/ft2; and
PbP = the percent of painted surfaces containing deteriorated lead-based paint, assumed to be 0% in this analysis.
Error = 0.580

This model applies only to lead dust and is not used to describe blood-lead concentrations from soil lead exposures. Although the Rochester data were collected for young children (ages 1-22 months), the model is used in this analysis for both young children (2 years old) and for children up to 6 years old.

5.3.2 Estimation of the adverse health effects (e.g., loss in IQ points) due to increased blood-lead

Numerous cross-sectional and longitudinal studies have estimated the decrement in IQ points associated with an increase in blood-lead levels. In cross-sectional studies, blood-lead levels are measured only once; usually in very early childhood between 6 and 24 months, when children's mouthing behavior leads to relatively high rates of ingestion of dust and soil, and when children are believed to be particularly vulnerable to neurological effects from exposure to lead. In longitudinal studies, blood-lead levels are typically measured several times during the course of young childhood (around 6 months to around 6 years) and may be presented in several ways: as the peak blood-lead concentration (typically occurring around 24 months of age), as the average "lifetime" blood-lead concentration (where lifetime is equal to the time of first measurement until the time of the administration of the IQ testing); and blood-lead levels concurrent to the time of testing. These metrics are, of course, closely correlated. The studies reviewed for this analysis are listed on Table 5-3.

Table 5-3: Association between Blood-lead Levels and IQ			
Study	**Metric**	**Initial Blood-lead Levels of Study Participants**	**Study Results**
Dietrich 1993, 1995	Peak and concurrent blood-lead levels	20 ug/dL or greater	Concurrent blood-lead levels were more strongly associated with IQ than peak-blood levels
Tong 1996	Peak and child lifetime average blood-lead levels	20 ug/dL or greater	Child lifetime average blood-lead levels were more strongly associated with IQ than peak-blood levels
Chen 2005	Peak, average, concurrent blood-lead levels	20 ug/dL or greater	Concurrent blood-lead levels always had the strongest association with IQ, and this association grew stronger with age
Canfield 2003	Child lifetime average, concurrent, average during infancy (6-24 months) and peak concentrations of blood-lead levels	Child lifetime average of 7.4 µg/dL; Peak value of 11.1 µg/dL	All four measures were significantly related to IQ declines, but the child lifetime average and concurrent blood-lead levels were more highly significant than average infancy and peak blood-lead concentrations
Lanphear 2005	Child lifetime average, concurrent, peak, and very early childhood blood-lead levels	Meta-analysis	Concurrent or child lifetime average blood-lead levels more strongly associated with IQ declines than peak or very early childhood blood-lead concentrations; IQ decline was significantly greater among children whose peak blood-lead was below 7.5 µg/dL
Schwartz 1994	**Peak Exposure**: Cross sectional studies: Blood-lead level measured once Longitudinal studies: integrated blood-lead up to age three and the 24-month blood-lead level	Meta-analysis	Overall decline in IQ points: 0.257 IQ points per 1 µg Pb/dL increase in blood-lead; higher IQ point losses among children with blood-lead levels below 15 µg/dL
Canfield 2003	**Average Exposure**: Child lifetime average, concurrent, average during infancy (6-24 months) and peak concentrations of blood-lead levels	7.4 µg/dL child lifetime average among all participants	**Overall**: IQ points decreased by 0.46 per 1 µg/dL change in child lifetime average blood-lead **Sub-analysis**: Children with peak blood-lead level <10 µg/dL had greater IQ points loss per 1 µg/dL change in blood-lead than those with blood-lead levels >10 µg/dL **Linear model**: estimated a 1.37 reduction in IQ points for an increase of 1 µg/dL in child lifetime average blood-lead concentrations **Non-linear model**: estimated a 7.4 reduction in IQ points for an increase of 10 µg/dL in child lifetime average blood-lead. Children with peak blood-lead levels above 10 µg/dL have an estimated reduction of 2.5 IQ points as blood-lead levels increase from 10 µg/dL to 30 µg/dL

Peak blood-lead levels typically occur when children are young (around 2 years of age), but neurological function is difficult to measure until children are older (at around age 4 years or more). The question remains whether peak levels of exposures early in life are the cause of neurological effects reflected later in life or if the effects are the result of cumulative effects of exposures during early childhood.

Because of the difficulty in answering this question, different theories have emerged. Some researchers have argued that peak lead exposures occurring around the ages of 1 to 2 years will affect neurological development more critically than exposures at other ages. Before the age of 2 years, the neural network in the brain is still undergoing substantial development, and many basic cognitive functions form during this period (ATDSR 1999). In a longitudinal study of lead-exposed children in Boston, Bellinger (1992) found a significant relationship between IQ and blood-lead levels at 2 years of age, but not with blood-lead levels at 57 months or 10 years of age.

Several more recent studies have found a stronger association with child lifetime average or with concurrent, rather than peak exposure, and have found an attenuation of association between peak blood-lead levels and IQ over time. Note that in this circumstance, "lifetime average" is defined as the mean blood lead from the first blood lead test (usually around 6 months) to concurrent blood lead tests. For clarity, this assessment will henceforth refer to this measure as "child lifetime average." The "concurrent blood lead" test is the blood lead measurement made closest in time to the IQ tests, which are typically administered between 5 and 7 years of age.
Dietrich (1995) and Dietrich (1993) found that concurrent blood-lead levels were more strongly associated with IQ than peak blood-lead levels, while Tong (1996) found that child lifetime average blood-lead levels were more strongly associated with IQ than peak blood-lead levels. Chen (2005) examined the question by following children from about 2 years until 7 years of age, and comparing peak, average and concurrent blood-lead levels to IQ at different ages. Chen found that concurrent blood-lead levels always had the strongest association with IQ, and this association grew stronger with age. This result suggests that peak exposures at the age of 2 did not fully account for the neurological effects seen in older children, and that lower level, concurrent exposures are also influential.

All of the studies were generally conducted on children with higher blood-lead concentrations (around 20 µg/dL or more). Other recent studies have examined the question whether these results applied to children with lower blood-lead levels. Canfield (2003) studied the relationship of blood-lead measurements throughout early childhood to IQ measured at 3 and 5 years of age, using a variety of regression models. Among children included in the Canfield (2003) data analysis, the average blood-lead level was relatively low (child lifetime average of 7.4 µg/dL and a peak value of 11.1 µg/dL). The authors evaluated child lifetime average, concurrent, average during infancy (6-24 months) and peak concentrations of blood-lead levels. Although all four measures were significantly related to IQ declines, even after adjustment for covariates, the authors found that the child lifetime average and concurrent blood-lead levels were more highly significant (as measured by the P-value) than average in infancy and peak blood-lead concentrations. In a recent meta-analysis, Lanphear et al. (2005) also found the concurrent or child lifetime average blood-lead levels to be more strongly associated with IQ decrements than peak or very early childhood blood-lead concentrations.

It should be noted again that EPA currently assumes that any exposure of young children to lead may result in IQ reductions. EPA believes that some effects, particularly changes in aspects of children's neurobehavioral development, may occur at blood-lead levels so low as to be essentially without a threshold (IRIS 2004).

The appropriate blood-lead metric is an important consideration for this proposed rulemaking, because the exposure associated with RRP activities is not expected to be a chronic exposure. If, in fact, this short-term lead exposure occurs during a critical window of development, where lead can cause permanent cognitive and neurobehavioral deficits, then the full IQ decrement can be attributed to this period of exposure, and the appropriate metric of exposure is the blood-lead concentration measured during this developmental period. If in contrast, the IQ decrement is associated with the cumulative exposure of the child, then the more appropriate blood-lead exposure metric is the child lifetime average blood-lead concentration, where the blood-lead levels resulting from exposures to RRP generated dust are averaged with blood-lead levels during the rest of early childhood.

This analysis presents two different approaches to estimate the reduction in IQ associated with increased blood-lead levels. In the first case, peak exposures are assumed to be the most relevant exposures for predicting IQ point loss. In this case, the blood-lead levels associated with floor lead dust exposures from RRP activities are averaged over one year, and are assumed to represent a peak of exposure between the ages of 0 and 6 years old. The change in IQ from a 1 µg/dL increase in peak blood-lead concentration is predicted using the results from Schwartz (1994). This meta-analysis was based on the results of seven studies (three longitudinal and four cross-sectional). Blood-lead was only measured once in the cross-sectional studies, and these point-in-time measures were used in the meta-analysis as the exposure metric. For two of the longitudinal studies, the integrated blood-lead up to age 3 was used, while for one of the longitudinal studies, the 24-month blood-lead was used. For the purposes of this analysis, the results of this meta-analysis are interpreted as the IQ loss associated with peak blood-lead. The overall estimated decrement in IQ was estimated to be 0.257 IQ points per 1µg Pb/dL increase in blood-lead.

In the second approach, the analysis assumed that the IQ decrement is associated with the average exposure over the lifetime of the child between the ages of 6 months and 6 years old (that is, over the course of 5 and one-half years). The analysis then uses the results of Canfield (2003) to predict the loss of IQ associated with a change in child lifetime average blood-lead. Canfield measured blood-lead concentrations in 172 children at six-month intervals from the age of 6 months until the age of 2 years, and then at one-year intervals until the age of 5 years. They related blood-lead measurements to IQ measured at 3 and 5 years of age, using a variety of regression models. The authors evaluated child lifetime average, concurrent, average during infancy (6-24 months) and peak concentrations of blood-lead levels. The researchers estimated a change of -0.46 IQ points per 1 µg/dL change in child lifetime average blood-lead, based on analyses across the entire range of blood-lead levels found in the study. However, in a separate analysis, they found that children whose peak blood-lead remained below 10 µg/dL exhibited greater IQ loss than those with peak blood-lead levels greater than 10 µg/dL. Using linear models, they estimated a loss of 1.37 IQ points for each increase of 1 µg/dL of child lifetime average blood-lead concentration among this subset of children. Using a nonlinear model, they estimated a loss of 7.4 points per 10 µg/dL increase in child lifetime average blood-lead. (Among children with peak blood-lead above 10 µg/dL, the estimated decrease was 2.5 IQ points as blood-lead increased from 10 µg/dL to 30 µg/dL.) Note that this finding is consistent with Schwartz (1994) who found higher IQ losses among children with blood-lead levels less than 15 µg/dL. This finding was also consistent with Lanphear (2005) who used data from seven longitudinal studies and found that the IQ decrement per deciliter of change was significantly greater among children whose peak blood-lead was below 7.5 µg/dL.

Because the blood-lead levels among children estimated in this analysis may range from below 10 µg/dL to above 10 µg/dL depending on the dust exposure level, this analysis used the Canfield (2003) overall

estimate of -0.46 IQ point per 1 µg/dL, derived using data across all blood-lead ranges observed in that study, rather than the greater IQ loss estimated for children with blood-lead levels below 10 µg/dL.

5.3.3 Populations at risk

Based on the epidemiological evidence discussed above and elsewhere in the extensive literature on the topic, children 0 to 6 years old are considered to be the population at highest risk from lead contaminated dust and soil. However, because the levels of lead dust generated from a single RRP event are expected to remain at increased levels for only a short period of time (generally less than a year), the exposure occurs only during a fraction of a child's life between the ages of 0 and 6 years. Furthermore, due to the particular vulnerability of the nervous systems of very young children (around the age of 2 years old), the timing of the short-term exposure may also influence the magnitude of adverse health effects associated with the exposure.

This analysis examines two possible scenarios: in the first scenario, the analysis evaluates risks to children 1 to 2 years old only. At this age, behaviors such as mouthing and crawling lead to relatively high levels of dust and soil exposure, and, as discussed earlier, nervous system structures are considered particularly vulnerable to adverse effects from lead exposures at this age. In this case the analysis calculates peak blood-lead and child lifetime average blood-lead concentrations, assuming that the child is exposed to RRP-contaminated dust between the ages of 1 and 2 years old, and to RRP-contaminated soil beginning at age 1 year. When calculating benefits, the size of the population of children ages 1 to 2 years estimated to be living in regulated housing with RRP events was used.

Children of other ages are assumed to be exposed to lead from RRP activities, and may have health effects associated with these exposures; however, it is not known if exposures of the duration associated with RRP events occurring *only* at these other ages will have the same influence on IQ as exposures that occur at around the age of 2 years. Therefore, in this first scenario, risks to other age groups are not assessed quantitatively. Thus, IQ benefits may be underestimated.

In the second scenario, the analysis assumes that short-term lead exposures that occur at any age under 6 years have the same magnitude of effect on neurological decrement as exposures that occur when children are around the age of 2 years. In this case, risks to all children under the age of 6 were assessed. Because exposures to lead in dust or soil for young children could occur at any age under 6 years old, the analysis calculated the effect on blood-lead for exposures occurring at different times during young childhood. To do so, the analysis first calculated the effect of a single year of exposure to lead-contaminated dust for each age group separately. That is, the analysis first calculated the peak and child lifetime average blood-lead for a child, assuming exposure to RRP dust occurred when the child was 6 months to 1 year old; then assuming the exposure occurred when the child was 1 to 2 years old; then assuming exposure occurred when the child was 2 to 3 years old, and so on, for each one-year age group until the age of 5 to 6 years. The peak and child lifetime average blood-lead values for each age group were then weighted by the proportion of children in each age group in the U.S. population, according to the 2000 Census to derive "population-weighted average" peak and child lifetime average blood-lead values associated with exposures to dust. Similar calculations were made for exposures to lead-contaminated soil for each one-year age range, assuming exposures start at the beginning of the age range and continue until the age of 6 years. All children under the age of 6 years within the populations for each regulatory option were then used to calculate benefits. Using a population-weighted average for benefits assessment assumes that

using a population average will yield equivalent results to calculating lost IQ points based on the blood-lead metrics derived for each age group separately.

5.3.4 Assignment of a medical cost, reduced income or other proxy for willingness to pay to avoid the adverse health effects

The estimated value of an IQ point is $12,953 (2005 dollars), which is derived from coefficients provided by Salkever (1995). The IQ value is modeled as the present value of a loss in expected lifetime earnings due to a one point IQ drop.[9] The present value is calculated assuming that while most people start working at age 18, average income in the early adult years is reduced because some are still in school. In addition, the present value assumes a retirement age of 67 years old, due to the revisions of the Social Security law that are incrementally increasing the retirement age so that it will be at age 67 by the time today's children are retiring. Further, the analysis assumed that children would be affected by lead at 3 years of age, the median of the range when children are most susceptible to lead hazards. As a result, the value of an IQ point is only discounted back to age 3. Limiting the valuation estimation to reduced income underestimates the value of children's neurological benefits. Additional measures of the impact on IQ are: additional education costs for special and remedial education, and medical costs to treat very high levels of lead. This analysis does not generate the information needed to estimate the number of such cases, so these measures are not included in the valuation of children's benefits.

5.4 Benefits Assessment - Adults

In this section, the analysis estimates the exposure of adults to lead-contaminated dust and soil from RRP activities and uses existing dose response relationships to calculate increased risks of hypertension, coronary heart disease (CHD), stroke and premature mortality. (The uncertainties in the quantification of adult effects are addressed in Section 5.5.5.) Costs for treatment of each disease were then applied and a total cost of health effects for each option was calculated. The following describes the process and results of this analysis.

5.4.1 Estimation of lead contamination levels and estimation of the change in blood-lead levels resulting from lead contamination

The methods used to evaluate exposure and resultant changes in blood-lead levels differ for adults and children. For adults, the total daily lead exposure from incidental ingestion of soil and dust was calculated using an adaptation of Equation 1 from the U.S. EPA Adult Lead Methodology (U.S. EPA 2003):

$$PbBadult,\ central = PbBadult,\ 0 + PbD * IRD * BKSF * AFs$$

where:

PbBadult, central	=	Central estimate of blood-lead concentrations (µg/dL) in adults that have exposures to lead dust (PbD) from RRP activities;
PbBadult, 0	=	Typical blood-lead concentration (µg/dL) in adults in the absence of exposures to lead dust from RRP activities;
PbD	=	lead dust concentration (µg/g);
IRD	=	Intake rate of dust, including both outdoor soil and indoor soil-derived dust (g/day);

[9] Present value of earnings calculated at a 3 percent discount rate.

BKSF = Biokinetic slope factor relating (quasi-steady state) increase in typical adult blood-lead concentration to average daily lead uptake (µg/dL blood lead increase per µg/day lead uptake); and

AFS = Absolute gastrointestinal absorption fraction for ingested lead in soil and lead in dust derived from soil (dimensionless).

The data sources and derivation of each of the parameters in this model are discussed below.

PbBadult, 0

For blood-lead values, the geometric mean blood-lead values for adult men and women ages 20-59 and ages 60 and greater were obtained from National Health and Nutrition Evaluation Study (NHANES) III data. These data are summarized in Table 5-4.

Table 5-4: Summary of Geometric Means of Blood-lead (measured in µg/dL) for Adults, from NHANES 1999-2002

Age group (years)	Geometric mean (µg/dL) all racial groups	95% confidence interval
Men 20-59	2.0	1.9-2.0
Men >=60	2.7	2.6-2.8
Women 20-59	1.2	1.2-1.2
Women >=60	1.9	1.8-2.0
Source: CDC 2005b		

PbD

For children, empirically derived relationships are available to estimate the concentration of lead in dust (in µg/g) based on floor lead dust loadings (in µg/ft^2). For adults, such empirical relationships are not available; therefore, the lead dust concentration must be calculated from the assumptions regarding the floor lead dust loadings and the amount of dust on surfaces in a household. The lead dust concentration is calculated using the following equation:

$$PbD = (Dlead / Dtotal) * 1{,}000{,}000$$

where:

PbD = Concentration of lead in dust (µg/g);

Dlead = Lead dust loading (µg/m^2);

Dtotal = Total household dust loading from all sources (µg/m^2); and

1,000,000 = Conversion from µg to g.

The interior dust loadings for adults, Dlead, are calculated in the same fashion as the dust loadings for children, as described in Section 5.2. For total dust loadings in a household from all sources, Dtotal, this analysis used the value given in Hawley (1985), which was estimated to be 560 mg/m^2. Hawley derived this value from studies of residential dustfall (Hunter and Howe 1969 and Corn 1968, as discussed in detail in Hawley (1985, p 290)). This value was consistent with overall floor dust loading estimates derived data reported in another study, which measured floor dust levels of cadmium and lead in homes (Solomon and Hartford, as discussed in Hawley, 1985, p. 290). Soil lead concentrations for adults are calculated in the same manner as for children, as described in Section 5.2 above.

IRD

The Exposure Factors Handbook (U.S. EPA 1997b) recommends the use of a value of 50 mg/day to represent adult daily incidental ingestion rate of soil (which includes outdoor soil and indoor dust). However, as this value includes exposures from both indoor dust and outdoor soil, its relevance to exposures that are only related to lead-contaminated indoor dust is not certain. Hawley (1985) estimates the daily consumption of incidental consumption of dust from living spaces to be approximately 0.56 mg/day. For exposures to indoor dust alone, the analysis uses this value. For exposures to soil contaminated by exterior painting, this analysis uses the 50 mg/day value. These represent the total amount of dust and soil ingested; lead represents a fraction of these amounts.

BKSF

The Adult Lead Methodology (EPA 2003) recommends using, as a default value, 0.4 µg/dL blood per µg lead absorbed per day for the BKSF parameter. This value is based on data reported by Pocock (1983) on the relationship between tap water lead concentrations and blood-lead concentrations for a sample of males and on estimates of the bioavailability of lead in tap water.

AFS

The Adult Lead Methodology (EPA 2003) recommends a value of 0.12 for the fraction of lead in soil ingested daily that is absorbed from the gastrointestinal tract. This value is based on the assumption that the absorption factor for soluble lead is 0.2, and the relative bioavailability of lead in soil compared to soluble lead is 0.6.

5.4.2 Estimation of adverse health effects from changes in blood-lead levels

Cases of hypertension are assumed to be related directly to an estimated change in blood-lead levels for adults. For CHD, stroke and premature mortality, the cases are calculated based upon the expected increase in blood pressure due to an increase in blood-lead levels, which leads to a change in the risk of each disease. (Dose-response equations for these diseases are summarized in Table 5-5 and described in detail in Appendix 5B. The uncertainties in the quantification of adult effects are addressed in Section 5.5.5.)

Table 5-5: Health Functions Used in the Renovation, Remodeling, and Painting (RRP) Analysis					
Health Endpoint	**Gender**	**Study**	**Age Group**	**Notes**	**Function**
PbB Levels and Hypertension	Men	Schwartz 1988	20-74	Hypertension defined as diastolic blood pressure above 90 mm Hg	$\Delta \Pr(Hyp) = \frac{1}{1+e^{2.744-0.793*(\ln PbB_1)}} - \frac{1}{1+e^{2.744-0.793*(\ln PbB_2)}}$
PbB Levels and Blood Pressure	Men	Schwartz 1992	Variable	Change in blood pressure associated with a decrease in blood-lead from 10 µg/dL to 5 µg/dL	$\Delta DBP_{men} = 1.4 \times \ln(\frac{PbB_1}{PbB_2})$
Blood Pressure and Coronary Heart Disease (CHD)	Men	Pooling Project Research Group (PPRG) 1978	40-59	10-year probability of occurrence of CHD event	$\Delta \Pr(CHD_{40-59}) = \frac{1}{1+e^{4.996-0.030365*(DBP_1)}} - \frac{1}{1+e^{4.996-0.030365*(DBP_2)}}$
Blood Pressure and Coronary Heart Disease (CHD)	Men	Shurtleff 1974	60-64	2-year probability of occurrence of CHD event	$\Delta \Pr(CHD_{60-64}) = \frac{1}{1+e^{5.19676-0.02351*(DBP_1)}} - \frac{1}{1+e^{5.19676-0.02351*(DBP_2)}}$
Blood Pressure and Coronary Heart Disease (CHD)	Men	Shurtleff 1974	65-74	2-year probability of occurrence of CHD event	$\Delta \Pr(CHD_{65-74}) = \frac{1}{1+e^{4.90723-0.02031*(DBP_1)}} - \frac{1}{1+e^{4.90723-0.02031*(DBP_2)}}$

Table 5-5: Health Functions Used in the Renovation, Remodeling, and Painting (RRP) Analysis					
Health Endpoint	**Gender**	**Study**	**Age Group**	**Notes**	**Function**
Blood Pressure and First-Time Stroke (Initial Cerebrovascular Accidents (CA))	Men	Shurtleff 1974[2]	45-74	2-year probability of CA	$\Delta \Pr(CA_{men}) = \frac{1}{1+e^{8.58889-0.04066*(DBP_1)}} - \frac{1}{1+e^{8.58889-0.04066*(DBP_2)}}$
Blood Pressure and First-Time Stroke (Initial Atherothrombotic Brain Infarctions (BI))	Men	Shurtleff 1974[2]	45-74	2-year probability of BI	$\Delta \Pr(BI_{men}) = \frac{1}{1+e^{9.9516-0.04840*(DBP_1)}} - \frac{1}{1+e^{9.9516-0.04840*(DBP_2)}}$
Blood Pressure and Premature Mortality	Men	Framingham Study (McGee and Gordon 1976)	40-54	12-year probability of death	$\Delta \Pr(MORT_{40-54}) = \frac{1}{1+e^{5.3158-0.03516*(DBP_1)}} - \frac{1}{1+e^{5.3158-0.03516*(DBP_2)}}$
Blood Pressure and Premature Mortality	Men	Shurtleff 1974	55-64	2-year probability of death	$\Delta \Pr(MORT_{55-64}) = \frac{1}{1+e^{4.89528-0.01866*(DBP_1)}} - \frac{1}{1+e^{4.89528-0.01866*(DBP_2)}}$
Blood Pressure and Premature Mortality	Men	Shurtleff 1974	65-74	2-year probability of death	$\Delta \Pr(MORT_{65-74}) = \frac{1}{1+e^{3.05723-0.00547*(DBP_1)}} - \frac{1}{1+e^{3.05723-0.00547*(DBP_2)}}$
PbB Levels and Hypertension	Women	Schwartz 1992	Variable	Hypertension defined as diastolic blood pressure above 90 mm Hg	$\Delta DBP_{women} = (1.4) \times \ln(\frac{PbB_1}{PbB_2})$
Blood Pressure and Coronary Heart Disease (CHD)	Women	Shurtleff 1974	45-74	2-year probability of occurrence of CHD event	$\Delta \Pr(CHD_{women}) = \frac{1}{1+e^{6.9401-0.03072*(DBP_1)}} - \frac{1}{1+e^{6.9401-0.03072*(DBP_2)}}$

Table 5-5: Health Functions Used in the Renovation, Remodeling, and Painting (RRP) Analysis					
Health Endpoint	**Gender**	**Study**	**Age Group**	**Notes**	**Function**
Blood Pressure and First-Time Stroke (Initial Cerebrovascular Accidents (CA))	Women	Shurtleff 1974[2]	45-74	2-year probability of CA	$\Delta \Pr(CA_{women}) = \frac{1}{1+e^{9.07737-0.04287*(DBP_1)}} - \frac{1}{1+e^{9.07737-0.04287*(DBP_2)}}$
Blood Pressure and First-Time Stroke (Initial Atherothrombotic Brain Infarctions (BI))	Women	Shurtleff 1974[2]	45-74	2-year probability of BI	$\Delta \Pr(BI_{women}) = \frac{1}{1+e^{10.6716-0.0544*(DBP_1)}} - \frac{1}{1+e^{10.6716-0.0544*(DBP_2)}}$
Blood Pressure and Premature Mortality	Women	Shurtleff 1974	45-74	2-year probability of death	$\Delta \Pr(MORT_{women}) = \frac{1}{1+e^{5.40374-0.01511*(DBP_1)}} - \frac{1}{1+e^{5.40374-0.01511*(DBP_2)}}$

[1] For coronary heart disease (CHD) and stroke this analysis estimates the probability of only non-fatal CHD and stroke events.
[2] Shurtleff (1974) estimates that 70% of strokes are non-fatal.
[3] Non-fatal CHD events estimated by assuming two-thirds of estimated events were not fatal (Shurtleff 1974).

5.4.3 Blood pressure data

Data on diastolic blood pressure (DBP) have not been reported recently in NHANES summaries; this analysis uses the values from NHANES, 1976-1980.[10] Table 5-6 shows the values for age ranges relevant to this study.

Table 5-6: Summary of Mean Diastolic Blood Pressure (measured in mm Hg) 1976-1980 for Adults, from NHANES 1976-1980

	Age		
Sex	***45-54***	***55-64***	***65-74***
Men	85	85	83
Women	82	82	82
Source: HHS 1986			

Calculation of annual cases

As indicated in the dose-response equations, some of the dose-response functions reflect probabilities of cases of disease and death occurring over multiple years. To estimate the number of cases occurring each year, the total number of cases was divided by the number of years over which the probability is estimated. The costs associated with the cases were discounted back to 2005 using a 3 percent discount rate.

5.4.4 Assignment of medical cost or other proxy for willingness to pay to avoid the adverse health effects

The benefits of preventing chronic cases of adverse health effects are estimated using the avoided cost of these effects. This approach is described in the U.S. EPA Cost of Illness Handbook (U.S. EPA 1999) and Appendix G of "The Benefits and Costs of the Clean Air Act: 1970 to 1990," prepared for U.S. Congress by U.S. EPA, Office of Air and Radiation in 1997 (U.S. EPA 1997c). The costs cited by these two sources came from published economic and medical studies and are presented in Table 5-7 along with a brief description of their origin.

[10] EPA plans to investigate the use of more recent NHANES data in an expanded risk assessment it intends to perform for this rulemaking.

Table 5-7: Per-Case Direct Medical Costs of Lead-Related Adverse Health Effects			
Adverse Effect	**Gender**	**Cost per Case (2005$)**	**Cost Description**
Hypertension	Male	$14,613	The cost estimates were derived by taking Cropper and Krupnick's (1990) average annual per-person costs of hypertension and applying Hartunian's (1981) methods for calculating lifetime costs of treating hypertension using a 3% discount rate. The costs include physician charges, medication costs, hospitalization costs and lost work time.
	Female	$12,524	
Coronary Heart Disease	Male	$79,161	The costs were estimated (Wittels 1990) for 3 CHDs (acute myocardial infarction, uncomplicated angina pectoris, and unstable angina pectoris) for 5 years post-diagnosis using a 3% discount rate. The probability of a medical service was multiplied by the estimated price of the service and the average cost for the three CHD types was determined. Since the effect of increased blood-lead levels on CHD incidence rates is beyond the scope of this analysis, weighting factors were not used to account for the different probabilities of contracting the three types of CHD.
	Female		
Stroke	Male	$295,704	The cost estimates (Taylor 1996) represent the expected lifetime cost of a stroke for males and females age 45-74, including the present discounted value of the stream of medical expenditures and the stream of lost earnings, using a 5% discount rate.
	Female	$221,777	
Death – Any Effect	Male	$6.98 Million	A range of values taken from hedonic wage studies and/or contingent valuation studies of primarily middle aged adults was used (U.S. EPA 200b), and converted to 2005$.
	Female		

In addition to providing cost estimates for the medical treatment of each adverse effect, the benefit estimates include the number of deaths resulting from each disease, in terms of the value of a statistical life (VSL). The dollar value of VSL was taken from EPA's 2000 Guidelines for Preparing Economic Analyses, which presents a VSL of $5.8 million (1997 dollars) (U.S. EPA 2000b).

5.5 Results

To summarize, the benefit estimates provided in this section reflect the following sequence of events. In the baseline an RRP event occurs, generating lead dust in both the area where the work occurs and the adjacent area (e.g., the adjacent room). In the baseline (without rule), the contractor cleans the work area before he/she leaves by sweeping and vacuuming. While this contractor cleaning substantially reduces the lead dust in the work area, it rarely brings the lead levels down to the EPA hazard levels of 40 µg/sq.ft. In most cases, this cleaning also does not address the lead dust that may have migrated into the rest of the house during the RRP event. Following the end of the RRP event, the household cleans the work area and the rest of the house on a regular basis. Periodic cleaning continues to reduce the lead dust levels over time. Under the rule, the same sequence of events occurs, but it is assumed that the containment, cleaning, and cleaning verification practices required by the rule reduce lead dust loadings to 40 $\mu g/ft^2$ or less after contractor cleaning.

The blood-lead models used in the analysis require an estimate of the annual lead exposure to occupants of homes where RRP occurs. To obtain that value, the models perform the following calculations:

1. Lead dust levels in the **work area** due to the RRP event are estimated as described in Section 5.2 and Appendix 5C.
2. Lead dust levels due to the RRP event in the room(s) **adjacent** to the work area are estimated to be 16 percent of the lead levels in the work area (i.e., before contractor cleaning). See Appendix 5C for the derivation of this factor.
3. Lead dust levels in the rest of the house are assumed to be zero.[11]
4. Average work area lead levels when the contractor leaves are estimated by applying normal contractor cleaning efficiencies to the lead levels estimated in step 1. See Section 5.2 and Appendix 5C and further discussions below in Section 5.5.3.
5. **Average household lead dust levels** when the contractor leaves are estimated as the weighted average of the lead dust levels due to the RRP event in the work room after contractor cleaning, the adjacent room, and the rest of the house. Each of these three values is weighted by the relative square feet of the area involved. The average work area size is estimated for each type of RRP event in Chapter 4 and then expressed as a percentage of the total size of the housing unit[12]. The size of any household's work area is the sum of percentages shown in Table 5-8 for the events that are performed. The maximum work area size for a household is calculated as the average size of the largest event (a Non-Room-Specific event), which is 30 percent of the unit.[13] The adjacent area is assumed to equal the work area in size

Table 5-8: Work Area Size by Event Type (Percent of Housing Unit)

Event Type	**Work Area Size**
Kitchen	6%
Bathroom	3%
Addition	5%
Non-Room-Specific	30%
Interior Painting	16%
Average Household Work Area	**24%**

Source: Calculated from the American Housing Survey, see Chapter 4 for details.

[11] It is likely that in some circumstances the lead dust from RRP events can contaminate other areas of the house beyond the work room and the adjacent room. Because no data were located specifically addressing lead dust levels in the rest of the house from RRP events, the level was assumed to be zero. However, this assumption is likely to understate the extent of lead dust contamination from RRP events, and to underestimate the benefits of the rule.

[12] For large events, the work area size is estimated as the size of the room where the RRP work is performed (or 50 percent and 25 percent of the housing unit for non-room specific and interior painting events, respectively); for small events the work area is estimated as an area the size of one wall by five feet (to reflect the spreading of plastic out 5 feet from the work). To maintain consistency with the assumptions regarding the mix of large and small events estimated for the cost analysis, the typical work area size is estimated as the midpoint between these two estimates.

[13] Note that 30 percent of the unit is the *average* work area of the *largest* event, a non-room-specific event. While some non-room-specific events are larger, and others are smaller; the average size is used in the benefits calculations.

5. Periodic household cleaning is applied to this weighted average and the decline in lead levels is tracked over time so that the yearly average can be calculated.
6. The benefits are estimated based on exposure that starts when the contractor leaves, having performed his/her cleaning. Thus the exposure estimates used in the benefits estimation do not include any exposure to household occupants or neighbors (or the RRP workers) that might occur during the RRP event itself. While many RRP events only last for one day, some last for many days but information on the distribution of event lengths are not available at this time.

5.5.1 The Monte Carlo Model

A Monte Carlo modeling approach was used to estimate blood-lead (and thus health effect) levels in both the baseline and with the regulations in place. A Monte Carlo approach was used because it provides a means of incorporating the uncertainty around each input parameter, as long as the uncertainty can be described in terms of a statistical distribution. For each run of the Monte Carlo model, a single value for each uncertain parameter is drawn from the distributions describing the uncertain parameters.

This analysis treats each input as a statistically independent parameter. The expected benefits are calculated given this set of values for the uncertain input parameters. This is done multiple times, keeping track of the expected benefits calculated at each model run. The result of the Monte Carlo approach is a distribution of values for expected benefits that is described by its mean, standard deviation and percentile values.

Uncertainty distributions are incorporated into the benefits model for a number of key inputs. For example, the initial lead loadings used in estimating exposures are drawn from distributions developed based on the frequency of different RRP activities and associated lead dust and soil concentration estimates.

Further, for indoor exposure, the frequency of household cleaning and the cleaning efficiency of vacuums on carpet and vacuuming/sweeping on non-carpeted floors are uncertain. Using values from the literature the analysis characterizes the uncertainty of these important inputs.

Several inputs that are known to be uncertain are treated as point estimates in the benefits model because the data that are necessary to statistically describe the uncertainty are not available. Therefore, although the benefits model incorporates as much input uncertainty as feasible, the outputs described below underestimate the level of uncertainty in the estimation of the benefits associated with the rule options.

5.5.2 Alternative Blood-lead Modeling Assumptions

While the causal relationship between lead exposure and IQ reduction in children is well established (see section 5.3.2), there remains some uncertainty about the exact form of the dose-response functions and whether exposure should be measured in terms of peak exposure or average exposure over the first six years of life. This uncertainty is handled by using six alternative sets of assumptions that reflect alternative combinations of: blood-lead models, age of children exposed and exposure metrics. These differences are discussed in detail in Section 5.3.1 and Section 5.3.2 of this chapter. The six alternative sets of assumptions are presented in Table 5-9. Age Group refers to the age at which exposure has an

effect, and Lead Exposure Metric refers to whether exposure level is measured in terms of peak or six-year average lead exposure.

Table 5-9: Alternative Blood-Lead Assumptions			
Blood-lead Assumptions	Age Group	Blood-Lead Model	Lead Exposure Metric
Set 1a	1-2 years old	IEUBK	Peak (age 1-2 year old)
Set 1b	1-2 years old	IEUBK	Average (age 0 thru 5 years old)
Set 1c	1-2 years old	Empirical Model	Peak (age 1-2 year old)
Set 1e	1-2 years old	Empirical Model	Average (age 0 thru 5 years old)
Set 2a	0 thru 5 years old	IEUBK	Peak (at any age 0 thru 5 years)
Set 2b	0 thru 5 years old	IEUBK	Average (age 0 thru 5 years old)

The Empirical Model was not used for Assumption Sets 2a or 2b because these sets assume that the relevant age group is children from 0 through 5 years of age. The Empirical Model, however, was derived from observations of very young children (around 2 years old) and automatically incorporates the behaviors of these young children when estimating how floor dust relates to blood lead. Because older children have different behaviors than very young children, the Empirical Model does not represent the relationship between blood lead and floor dust lead in older children.

5.5.3 Size of Population that Avoids Exposure After the Rule

The size of the population that has a reduced exposure to lead because of the rule is estimated using the 1997 and 2003 American Housing Surveys (AHS) and the 1995 Property Owners and Managers Survey (POMS). Four major steps are taken to estimate this population: (1) estimate the number of individuals living in housing where there is a regulated RRP event; (2) estimate the proportion of regulated RRP events where lead-based paint (LBP) is present; (3) adjust for the baseline use of containment and clean-up practices to account for individuals who would avoid exposure in the absence of regulation; and (4) adjust for compliance rates. The basic analysis presented in this chapter assumes a 75 percent compliance rate, based on analyses of compliance rates with OSHA construction regulations. Alternative compliance rates are presented in the Sensitivity Analyses shown in Chapter 7.
The first three steps are described in more detail below.

Number of Individuals Living in Housing Units with Regulated RRP

The number of individuals living in owner-occupied households with regulated RRP is estimated directly from the 2003 AHS, which reports renovation data together with information on the occupants of owner-occupied housing. For rental-units, the percentage of units estimated to have had at least one regulated RRP event is estimated using the POMS. This percentage is applied to the total number of individuals living in regulated rental units, according to the 2003 AHS, to estimate the number of individuals living in units where there was a regulated RRP event.

Proportion of Regulated RRP Events where LBP is Present

The likelihood that a housing unit has LBP is estimated from HUD's 2000 National Survey of Dust Lead Hazards and Allergens in Housing (HUD 2000). In this survey, samples were collected from a nationally representative sample of 750 housing units; lead samples include dust wipes, vacuum samples (carpets), soil, and in-situ XRF testing. Various components of each housing unit were sampled and these

component-specific lead probabilities are used to estimate event-specific lead likelihood values. This is described in more detail in Chapter 4. These probabilities are applied to the number of individuals living in housing units with regulated RRP to estimate the number who are at risk for lead exposure.

Adjustment for Baseline Lead Safe Work Practices

Even without the proposed regulation, contractors already perform some containment and clean-up. In order to determine how often various work practices are used in the baseline, nine industry experts were questioned. (The data collection effort is described in Section 4.5.4). The questions and responses on work site preparation (containment) and clean-up are summarized in Table 5-10. As shown in Table 5-10, the baseline frequency varies widely across different work practices. For example, respondents indicated that floors, outdoor areas, and doorways were covered with impermeable material (e.g., polyethylene plastic) in approximately 40 percent of events, work areas were vacuumed daily with a HEPA-filtered vacuum on a daily basis in less than 20 percent of events, and that exterior debris was wet misted and the impermeable material was rolled and sealed with duct tape in less than 5 percent of events. While the survey did not ask about cleaning verification, there are probably few renovation contractors performing the cleaning verification required by the rule.

Care must be taken in interpreting these data. First, there were only 9 respondents the survey. Second, the questions only asked how frequently each of the various activities or practices was used (e.g. rarely, often, usually), not how often they are used when needed. Thus it is not clear whether the relatively low value for some activities reflects situations where the activity is not needed, or situations where they should be but were not undertaken. Third, some of the activities might be considered substitutes (e.g. turning off HVAC system versus sealing HVAC vents). Fourth, the survey asked about individual practices, but a combination of practices is needed to provide adequate protection. Finally, the survey did not address whether the activities were being performed properly to protect occupants. For example, contractors using containment may not do so effectively unless they have been trained in how to properly lay, affix, and dispose of plastic sheeting. Improper containment can release lead dust and contaminate the housing unit.

Table 5-10 and 4-19 differ, Table 5-10 presents the actual survey questions while Table 4-19 relates to the work practices required by the rule. Because the survey was completed before the current proposed rule was developed, some of the survey questions do not match the rule's requirements. In these cases the survey results in Table 5-10 were used to develop an assumption about the percentage of events where some form of a work practice required by the rule is already in use. For example, the survey asked how often a HEPA vacuum was used on a daily basis (shown in Table 5-10 to be estimated at 18.8 percent of events), but the rule only requires the use of a HEPA vacuum when the renovation is completed. It was assumed that some events that are not cleaned with a HEPA vacuum on a daily basis are cleaned with a HEPA vacuum when the renovation is completed. It was further assumed that a HEPA vacuum was used at the end of the renovation with the same frequency that polyethylene sheeting was used, or in approximately 40 percent of renovation jobs (as shown in Table 4-19).

Table 5-10: Summary of Current Practice Survey Results	
Activity	**Percentage of time the activity is already taking place**
Preparation	
Restrict access to the work area by placing impermeable material (e.g. polyethylene plastic) over doorways	39.3%
Turn off the HVAC systems and close vents	16.9%
Seal off HVAC vents with impermeable material	29.6%
Cover floor of work area with impermeable material	41.2%
Create a runner of impermeable material between work area and outside door	29.1%
Cover occupants belongings with impermeable material	61.9%
Cover surrounding ground/soil with impermeable material during outdoor renovation projects	37.6%
Place warning signs outside unit in a multi-unit building	13.2%
Restrict access to outdoor work area by constructing barriers and/or placing warning signs	23.0%
Clean-Up	
Sweep work area daily	74.6%
Mop work area daily	21.1%
Vacuum work area with a shop-vac daily	58.1%
Vacuum work area with a two-stage high efficiency filtered vacuum daily	27.2%
Vacuum work area with a HEPA-filtered vacuum daily	18.8%
Wrap debris in impermeable material and duct tape shut prior to removal	23.0%
Place removed carpet in impermeable material and duct tape shut prior to removal	4.8%
Wet mist debris generated by outdoor projects; roll and seal with duct tape before disposal	4.8%

Because of uncertainties about the type of baseline containment and cleaning practices used, how often they are performed, whether they are carried out properly, and how these practices reduce lead levels, benefits are calculated under two different scenarios. The two scenarios both start with the assumption that the more common work practices required by the rule (such as cleaning with a HEPA vacuum at the completion of the renovation) are used in 30 to 40 percent of baseline events.

The first scenario assumes that the equivalent of 20 percent of all at-risk occupants are protected in the baseline commensurate with the results of the rule. This could be because 40 percent of all at-risk occupants receive 50 percent of the full protection benefits provided by the rule, or 31 percent of all at-risk occupants receive 65 percent of the full protection benefits provided by the rule, 25 percent of all at-risk occupants receive 80 percent of the full protection benefits provided by the rule, 20 percent of all at-risk occupants receive the full protection benefits provided by the rule, or some other computational equivalent. This scenario is meant to cover all baseline activities.

The second scenario also assumes that 20 percent of all at-risk occupants are protected in the baseline commensurate with the results of the rule. In this scenario, the 20 percent represents occupants receiving the full protection benefits of the rule, and there are additional occupants who may receive some partial

protection that may not be commensurate with the rule. Given that work practices such as cleaning with a HEPA vacuum at the completion of the job are assumed to be used in 30 to 40 percent of the events, this scenario assumes that additional cleaning activities are performed in another 10 to 20 percent of events. This additional cleaning goes beyond the efficiency of normal contractor or household cleaning, but does not necessarily reach the level of protection achieved by the rule. There are three such activities assumed in Scenario 2:

- **Additional contractor cleaning.** In 15 percent of the baseline events, contractors are assumed to achieve dust reduction levels beyond those credited to normal contractor cleaning. This could be due to the use of a HEPA vacuum, or through a second cleaning with normal cleaning methods immediately after the RRP event. This is assumed to occur in both owner-occupied and rental housing. Computationally, the cleaning efficiency is calculated as two successive cleanings. The first cleaning yields normal contractor efficiencies (a 14 percent to 37 percent removal rate on carpets and a 94.8 percent to 98.5 percent removal rate on non-carpeted surfaces). The second cleaning for carpets is credited with the same cleaning efficiency (14 percent to 37 percent), while non-carpeted surfaces are credited with a 70 percent reduction. Thus, the 15 percent of events in this category achieve a 26 percent to 60 percent cleaning efficiency on carpets and a 98.4 percent to 99.6 percent cleaning efficiency on non-carpeted surfaces. These events are in addition to the baseline activities that protect 20 percent of the population described above. If there are any events where the lead loadings are sufficiently low so that the cleaning efficiency for this additional contractor cleaning reduces lead loadings to below the 40 $\mu g/ft^2$ level in the baseline, then the same level is used in the post-rule analysis. (That is, lead levels are generally assumed to be 40 $\mu g/ft^2$ post-rule, but are not assumed to increase from the baseline as a result of the rule.) Contractors are assumed to cease this additional contractor cleaning after the rule.

- **Contractor cleaning of adjacent room.** In 10 percent of baseline events, contractors are assumed to clean the adjacent room as well as the work room. This is assumed to occur in both owner-occupied and rental housing. These events are independent of the additional contractor cleaning described above. To the extent that an event is in both the 15 percent of events that achieve dust reduction above normal levels and the 10 percent of events where the adjacent room is cleaned, the cleaning efficiency is assumed to be the same in the adjacent room as in the work room. If there are any events where the lead loadings are low enough that the cleaning efficiency for this contractor cleaning of the adjacent room is calculated to reduce lead levels to below 40 $\mu g/ft^2$ in the baseline, the same level is used in the post-rule analysis. (That is, lead levels are generally assumed to be 40 $\mu g/ft^2$ post-rule, but are not assumed to increase from the baseline as a result of the rule.) Contractors are assumed to cease this cleaning of the adjacent room after the rule.

- **Additional household cleaning.** In 15 percent of the events, households are assumed to achieve dust reduction levels beyond those credited to normal household cleaning in their initial cleaning. This could be due to the use of a HEPA vacuum, or through a second cleaning with normal cleaning methods immediately after the RRP event. This is assumed to occur in both owner-occupied and rental housing. Computationally, the cleaning efficiency is calculated as two successive cleanings. The first cleaning yields normal contractor efficiencies (a 14 percent to 37 percent removal rate on carpets and a 94.8 percent to 98.5 percent removal rate on non-carpeted surfaces). The second cleaning for carpets is credited with the same cleaning efficiency (14 percent to 37 percent), while non-carpeted surfaces are credited with a 70 percent reduction.

Thus, the 15 percent of events in this category achieve a 26 percent to 60 percent cleaning efficiency on carpets and a 98.4 percent to 99.6 percent cleaning efficiency on non-carpeted surfaces. These events are independent of the contractor cleaning assumptions. The additional household cleaning in this scenario is assumed to continue after the rule.

The two scenarios are summarized in Table 5-11.

Table 5-11: Scenarios for Benefits Analysis

Category	Scenario 1 Assumption	Scenario 2 Assumption
Treatment of baseline protection commensurate with the rule	Equivalent of 20% of at-risk occupants protected	20% of at-risk occupants protected
Cleaning by contractors in the baseline	Normal contractor cleaning in all events.	In addition to normal contractor cleaning in all events, in 15% of baseline events contractors are assumed to achieve dust reduction levels beyond those credited to normal contractor cleaning. Events in this category achieve a 26% to 60% cleaning efficiency on carpets and a 98.4% to 99.6% cleaning efficiency on non-carpeted surfaces. These events are in addition to the baseline events that protect 20% of the population as described above.
Contractor cleaning of adjacent room in the baseline	Contractor cleans the work room but does not clean the adjacent room.	In 10% of events, contractors are assumed to clean the adjacent room as well as the work room. These events are independent of the additional contractor cleaning described above. The cleaning efficiency is assumed to be the same in the adjacent room as in the work room.
Initial household cleaning	Normal household cleaning for all events	In addition to normal household cleaning, in 15% of the baseline events, households are assumed to achieve dust reduction levels beyond those credited to normal household cleaning. The 15% of events in this category achieve a 26% to 60% cleaning efficiency on carpets and a 98.4% to 99.6% cleaning efficiency on non-carpeted surfaces. These events are independent of the contractor cleaning assumptions.

The resulting number of RRP events where the proposed regulation will provide benefits, and the number of individuals that will benefit from the rule (i.e. are protected by the rule) are shown in Table 5-12. Some of the RRP events and the associated individuals counted in Table 5-12 are not included in the benefit estimates due to data limitations. For example, data are not available on the amount of lead generated by exterior non-painting RRP events, and so they are excluded from the benefits estimations. Thus the populations used in the benefits estimations are smaller than the actual population benefiting from the rule. Because all proposed options cover the same set of housing units in the second year (and beyond), all four options cover the same number of events and protect the same number of children and individuals in the second year.

Table 5-12: Annual Number of RRP Events and Number of Individuals who will Benefit from the Proposed Regulations								
	Number of Events (Millions)				Number of Individuals Protected (thousands)*			
Option	First Year	First Year with LSWP	Second Year	Second Year with LSWP	Children under the Age of Six		All Individuals	
					First Year	Second Year	First Year	Second Year
Option A	10.7	8.1	10.7	4.4	787	783	5,309	5,287
Option B	5.8	4.8	10.7	4.4	668	783	4,529	5,287
Option C	4.3	3.7	10.7	4.4	520	783	3,659	5,287
Option D	5.8	4.8	10.7	4.4	668	783	4,529	5,287
* Number is increment above those occupying units where LSWP are currently practiced in the baseline and assume 75% compliance rate. The number protected may be higher under Scenario 1. Alternative estimates using different development time-frames for the improved test kits are considered in sensitivity analyses presented in Chapter 7.								

5.5.4 Summary of Inputs to the Monte Carlo Model

The input parameters are listed in Table 5-13, along with their value (for those with a point estimate) or their distribution. Certain inputs to the Monte Carlo model account for variability by incorporating a range of possible values. Where all values in this series are assumed to have equal probability of occurring, for example different parameters for contractor cleaning efficiency, these are termed uniform distributions in Table 5-13. Other inputs given by a range of values consist of custom distributions, with specific probabilities for each value in the range. For example, for the variable of soil lead concentration outdoors without the rule, different concentrations are likely depending upon the unit type and the system of paint removal used. These values are not equally likely to occur because of the different frequencies of unit types. The specific distributions used for the custom distribution parameters are given in Appendix 5D. Uncertainties in the quantification of adult effects, including the age of the data used, are addressed in Section 5.5.5.

Table 5-13: Monte Carlo Analysis Inputs				
	Blood-lead Assump-tions	**Units**	**Value or Distribution**	**Reference or Report Section**
Population Assumptions				
Populations Exposed	All	Number of People	Single value for each age and sex category	Section 5.4.1
Lead Loading Assumptions				
Soil Lead Concentration Outdoors without Rule	All	mg/kg	Custom Distribution (Range = 571.6 to 1,123.5)	UIUC, 2002
Soil Lead Concentration Outdoors with Rule	All	mg/kg	490	HUD, 2000
Initial lead dust level in work area after indoor work	All	$\mu g/ft^2$	Custom Distribution (Range = 1,800 to 409,031)	Appendix 5C
Percentage of initial dust loading in rooms adjacent to the work area.	All	unit-less fraction	16%	Derived from U.S. EPA, 1997a
Initial lead dust level outside of work area and adjacent room for interior work.	All	$\mu g/ft^2$	0	Section 5.5
Percentage of area of the home that is a work area	All	unit-less fraction	Custom Distribution (Range = 3% to 30%)	Section 5.5
Lead dust level indoors after contractor cleaning with rule	All	$\mu g/ft^2$	40 maximum or concentration resulting from cleaning, whichever is lower	Toxic Substances Control Act (TSCA) Section 403 Rule
Child Dose-Response Assumptions				
IEUBK Lead Dust to Blood Lead Relationship	1-year Peak	$\mu g/dL$ per $\mu g/ft^2$	Linear regression based on series of IEUBK model results (see Section 5.3.1 for further explanation)	U.S. EPA, 2005
Empirical Lead to Blood Lead Relationship	All	$\mu g/dL$ per $\mu g/ft^2$	See Section 5.3.1	U.S. EPA, 2000a
IQ Reduction Parameter	1-year Peak	IQ points per 1 $\mu g/dL$	Normal Distribution (mean = 0.25, s.d. = 0.04)	Schwartz, 1994
IQ Reduction Parameter	6-year average	IQ points per 1 $\mu g/dL$	Normal Distribution (mean	Canfield, 2003

Table 5-13: Monte Carlo Analysis Inputs				
	Blood-lead Assump-tions	**Units**	**Value or Distribution**	**Reference or Report Section**
			= 0.46, s.d. = 0.15)	
Indoor Cleaning Assumptions				
Percentage of Floors Carpeted	All	unit-less fraction	0.36	Derived from HUD, 2000
Normal Contractor Cleaning Efficiency on Carpet	All	unit-less fraction	Uniform Distribution (Range = 14% - 37%)	Yin, 2002
Additional Contractor Cleaning Efficiency on Carpet where Contractors Achieve Dust Reductions beyond those of Normal Contractor Cleaning	All	unit-less fraction	Same as first carpet cleaning efficiency	Section 5.5.3
Normal Contractor Cleaning Efficiency on Non-Carpet	All	unit-less fraction	Uniform Distribution (Range = 94.8% - 98.5%)	CETL, 2001
Additional Contractor Cleaning Efficiency on Non-Carpet where Contractors Achieve Dust Reductions beyond those of Normal Contractor Cleaning	All	unit-less fraction	70 %	Section 5.5.3
Percent of RRP Events where Contractors Achieve Dust Reductions beyond those of Normal Contractor Cleaning in Work Area	All	unit-less fraction	15 %	Section 5.5.3
Percent of RRP Events where Contractors Clean the Adjacent Room	All	unit-less fraction	10 %	Section 5.5.3
Percent of RRP Events where Contractors Achieve Dust Reductions beyond those of Normal Contractor Cleaning in the Adjacent Room	All	unit-less fraction	15 % of the 10% of Adjacent Rooms that are Cleaned by Contractors (= 1.5%)	Section 5.5.3
Normal Household Cleaning Efficiency on Carpet	All	unit-less fraction	Uniform Distribution (Range = 14% - 37%)	Yin, 2002
Normal Household Cleaning Efficiency on Non-Carpet	All	unit-less fraction	Uniform Distribution (Range = 94.8% - 98.5%)	CETL, 2001
Percent of RRP Events where Households Achieve Dust Reductions beyond those of Normal Household Cleaning	All	unit-less fraction	15 %	Section 5.5.3

Table 5-13: Monte Carlo Analysis Inputs				
	Blood-lead Assump-tions	**Units**	**Value or Distribution**	**Reference or Report Section**
Additional Household Cleaning Efficiency on Carpet where Households Achieve Dust Reductions beyond those of Normal Cleaning	All	unit-less fraction	Same as first carpet cleaning efficiency	Section 5.5.3
Additional Household Cleaning Efficiency on Non-Carpet where Households Achieve Dust Reductions beyond those of Normal Cleaning	All	unit-less fraction	70 %	Section 5.5.3
Frequency of Household Cleaning per year	All	integer	Custom Distribution (Range from 26 to 104)	Simcox, 1995
Adult Exposure Assumptions				
Dust ingested per day (indoors)	All	mg/day	0.56	Hawley, 1985
Dust ingested per day (outdoors)	All	mg/day	50	Hawley, 1985
Loading of dust on surfaces (indoors)	All	mg/m^2	560	Hawley, 1985
Absorption rate for ingested soil lead	All	unit-less fraction	0.12	Adult Lead Methodology, U.S. EPA, 2003
Increase in blood lead per ug/day absorbed from ingestion	All	µg/dL per µg/day	0.4	Adult Lead Methodology, U.S. EPA, 2003
Adult Dose Response Functions				
Blood Lead to Blood Pressure	All	mm Hg per µg/dL	See Table 5-5 for range of relationships.	Section 5.4: Appendix 5B
Blood Lead to Hypertension	All	probability per µg/dL	See Table 5-5 for range of relationships.	Section 5.4: Appendix 5B
Adult Health Endpoint Relationships				
Blood Pressure to CHD	All	probability per mm Hg	See Table 5-5 for range of relationships.	Section 5.4: Appendix 5B
CHD Fatality Rates	All	unit-less fraction	33%	Shurtleff, 1974
Blood Pressure to Atherothrombotic Brain Infarction	All	probability per mm Hg	See Table 5-5 for range of relationships.	Section 5.4: Appendix 5B
Atherothrombotic Brain Infarction Fatality Rate	All	unit-less fraction	30%	Shurtleff, 1974
Blood Pressure to Cerebrovascular Accident	All	probability per mm Hg	See Table 5-5 for range of relationships.	Section 5.4: Appendix 5B
Cerebrovascular Accident Fatality Rate	All	unit-less fraction	30%	Shurtleff, 1974
Blood Pressure to Mortality	All	probability per mm Hg	See Table 5-5 for range of	Section 5.4: Appendix 5B

Table 5-13: Monte Carlo Analysis Inputs				
	Blood-lead Assump-tions	**Units**	**Value or Distribution**	**Reference or Report Section**
			relationships.	
Adult Health Assumptions				
Average PbB - Men 20-59	All	µg/dL	2	CDC, 2005b, Table 2
Average PbB - Men >60	All	µg/dL	2.7	CDC, 2005b, Table 2
Average PbB - Women 20-59	All	µg/dL	1.2	CDC, 2005b, Table 2
Average PbB - Women >60	All	µg/dL	1.9	CDC, 2005b, Table 2
Average DBP - Men 45-54	All	mm Hg	85	HHS, 1986, Table C
Average DBP - Men 55-64	All	mm Hg	85	HHS, 1986, Table C
Average DBP - Men 65-74	All	mm Hg	83	HHS, 1986, Table C
Average DBP - Women 45-54	All	mm Hg	82	HHS, 1986, Table C
Average DBP - Women 55-64	All	mm Hg	82	HHS, 1986, Table C
Average DBP - Women 65-74	All	mm Hg	82	HHS, 1986, Table C
Economic Assumptions				
Discount Rate	All	unit-less fraction	0.03 and 0.7%	
IQ cost per point lost	All	Dollars	12,953	Salkever, 1995
Adult Value of Statistical Life	All	Dollars	6,980,000	EPA, 2000b
Cost per case: hypertension - men	All	Dollars	14,613	Cropper and Krupnick, 1990 and Hartunian, 1981
Cost per case: hypertension women	All	Dollars	12,524	Cropper and Krupnick, 1990 and Hartunian, 1981
Cost per case: CHD - men 40-59	All	Dollars	79,161	Wittels, 1990
Cost per case: CHD - men 60-64	All	Dollars	79,161	Wittels, 1990
Cost per case: CHD - men 65-74	All	Dollars	79,161	Wittels, 1990
Cost per case: CHD - women	All	Dollars	79,161	Wittels, 1990
Cost per case: stroke - men	All	Dollars	295,704	Taylor, 1996
Cost per case: stroke - women	All	Dollars	221,777	Taylor, 1996

5.5.5 Uncertainties in Adult Benefit Estimates

In the 1989 analysis of the health effects associated with lead exposure (US EPA, 1989), EPA concluded that there is a positive association between blood lead and increased blood pressure, as well as between blood lead and cognitive function as measured by intelligence quotient. Since then, new data have become available that are summarized in the 2005 external draft of the Air Criteria Document for Lead (US EPA, 2005c). The EPA draft document states that the data provide stronger evidence for a relationship between lead exposure and blood pressure for adults, and between lead exposure, IQ deficits and other neurobehavioral effects for children. The new data also provide more information on gender and race differences, and on the neurobehavioral effects of lead at lower blood lead levels. EPA believes that the newer data reduces the uncertainties in these health endpoints. EPA's Science Advisory Board (SAB) plans to review these data in March 2006. EPA will revise the draft Air Criteria Document for Lead after the SAB peer review is completed.

There is also some uncertainty associated with the calculations for cardiovascular effects and premature mortality. This analysis estimates these effects based on equations provided by Schwartz (1992), Shurtleff (1974), and McGee and Gordon (1976), and on blood pressure data from the 1976-1980 NHANES. EPA (2005c) cites more recent studies that provide alternate equations. EPA plans to prepare an expanded risk assessment for the lead RRP rulemaking, and will explore the use of more recent equations and more recent NHANES data. The use of newer equations and data is expected to reduce some of the existing uncertainties.

Quantitative Estimate of Benefits

This analysis estimates the benefits of the proposed regulation in terms of IQ deficits in children and increased blood pressure and related health effects in adults. Quantitative estimates of benefits are provided in two scenarios. Scenario 1 quantifies benefits for both children and adults. Scenario 2 quantifies benefits for children alone.[14] This approach is in recognition of the relatively larger uncertainties associated with adult health effects, pending completion of the SAB review, as well as the particular concern about children expressed in Title X of the Residential Lead-Based Paint Hazard Reduction Act of 1992. The Agency is more confident in the estimates for children's IQ effects then it is for the estimates of adult benefits. While recognizing that adults may also benefit from the training and practices required under the rule, Scenario 2 does not try to quantify these benefits due to the uncertainties that currently exist.

5.5.6 Summary of Results

The estimated benefits for this proposed rule are substantial, regardless of which scenario and which set of children's blood-lead modeling assumptions are used. Benefits in the first year for Options B, C and D are somewhat lower than the benefits for Option A, due to the phasing in of coverage in Options B, C and D. Benefits are first presented in terms of number of cases of adverse health effects avoided and the number of IQ points gained, followed by the value of these benefits.

[14] Scenario 2 also assumes additional cleaning in the baseline, as discussed in Section 5.5.3.

The benefits displayed in Table 5-14 through Table 5-18 are annual benefits.[15] They result from the avoided adverse health effects among adults and avoided reductions in IQ among children who are living in units where RRP events occur during a single year's time. Because these benefits occur from avoiding exposure to lead from a single RRP event, and each year a new group of regulated RRP events occurs thus generating a new group of at-risk individuals potentially exposed, every year there will be benefits of approximately this magnitude.[16]

Table 5-14a and b show the number of cases of adverse health effects avoided and IQ points gained under each of the regulatory options, as calculated using Scenario 1 (Table 5-14a) and Scenario 2 (Table 5-14b). (Scenario 2 assumes additional contractor and household cleaning in the baseline, as described in Section 5.5.3.) Due to the differences in assumptions about baseline levels of cleaning after RRP events, the number of cases is lower under Scenario 2 as compared to Scenario 1. Under Scenario 2, the number of cases of IQ points gained is from 78 to 88 percent of the equivalent number of IQ points gained under Scenario 1. Under either scenario, the number of IQ points gained varies widely depending on the blood-lead modeling assumptions used. Starting in Year 2, under Scenario 1, they range from the equivalent of 76 to 429 thousand IQ points gained.[17] Under Scenario 2, the estimate of the number of IQ points gained in Year 2 ranges from 62 to 350 thousand IQ points.

[15] Benefits for Option D are not displayed in the following tables because they are the same as those for Option B; Options B and D cover the same universe of households.

[16] As discussed in more detail in Chapter 4, the number of RRP events covered by the rule will decline slowly as the regulated housing stock declines due to demolitions.

[17] In all cases, these IQ points represent fractions of IQ points gained by a much larger population of children.

Table 5-14a: Total Cases of Avoided Adverse Adult Health Effects and Number of IQ Points Gained – Scenario 1							
		Option A		Option B		Option C	
		Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
	Exposure	Mean	Mean	Mean	Mean	Mean	Mean
Adult Exposures -- Cases of Adverse Health Effects Avoided - Interior and Exterior							
Hypertension	na	44,683	44,499	38,533	44,499	31,134	44,499
CHD	na	188	187	164	187	134	187
Stroke	na	43	42	37	42	30	42
Premature Mortality	na	285	284	249	284	203	284
Child Exposure - IQ Points Gained (thousands) - Interior and Exterior							
Children, age 1-2 years							
Using IEUBK model	Peak	138	137	118	137	94	137
For Interior Estimates	6-Year Average	76	76	66	76	52	76
Using Empirical model	Peak	94	94	81	94	64	94
For Interior Estimates	6-Year Average	112	112	96	112	76	112
Children, age 0-5 years							
Using IEUBK model	Peak	431	429	382	429	294	429
For Interior Estimates	6-Year Average	218	217	187	217	150	217
Based on post-rule compliance rate of 75%.							

Table 5-14b: Total Number of IQ Points Gained – Scenario 2							
		Option A		Option B		Option C	
		Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
	Exposure	Mean	Mean	Mean	Mean	Mean	Mean
Child Exposure - IQ Points Gained (thousands) - Interior and Exterior							
Children, age 1-2 years							
Using IEUBK Model	Peak	108	109	93	109	74	109
For interior estimates	6-Year Average	63	62	54	62	42	62
Using Empirical Model	Peak	83	83	71	83	57	83
For Interior Estimates	6-Year Average	98	98	84	98	67	98
Children, age 0-5 years							
Using IEUBK Model	Peak	352	350	301	350	240	350
For interior estimates	6-Year Average	171	171	147	171	118	171
Based on post-rule compliance rate of 75%. Scenario 2 assumes additional contractor and household cleaning in the baseline as described in Section 5.5.3.							

Looking at first year benefits (either adults or children), Option A (which applies to all renter-occupied target housing units built before 1978 plus all owner-occupied target housing units built before 1978 if a child under the age of six resides there) provides the greatest benefits in terms of number of cases of adult adverse health effects avoided, regardless of which blood-lead assumptions and scenario is used. Under Option B (which applies to all renter-occupied target housing units built before 1960 plus all owner-occupied target housing units built before 1960 if a child under the age of six resides there and any pre-1978 target housing units if a child under six with increased blood-lead resides there), first year benefits are about 14 percent smaller than first year benefits under Option A. Under Option C (which applies to all renter-occupied target housing units built before 1950 plus all owner-occupied target housing units built before 1950 if a child under the age of six resides there and any pre-1978 target housing units if a child under six with increased blood-lead resides there), first year benefits in terms of number of cases of avoided adverse adult health effects are about 30 percent smaller than first year benefits under Option A. These differences are attributable to the greater number of persons protected under Option A in the first year. These differences disappear in the second year when all three options cover the same housing units and thus the same number of people.

Among the categories of adult benefits, by far the largest number of cases avoided is cases of hypertension. The next largest category of adult adverse health effects avoided is Premature Mortality. Stroke has the fewest number of cases avoided. These relative relationships between Scenarios 1 and 2 are consistent across the adult health effect categories.

The tables also show that estimating children's IQ benefits using the IEUBK model yields somewhat higher results than the Empirical Model when considering peak exposures in 1-2 year olds; however, when considering the six-year average exposure, the Empirical Model yields a consistently higher estimate than IEUBK model. This result is likely due to the fact that the Empirical Model is based on data that describes the relationship between dust lead and blood lead in younger children (around the age of two). Using this model to characterize dust and blood lead averaged over the six-year period of ages 0 through 5 assumes that the same behaviors exist and thus the same relationship between dust lead and blood lead exists in younger (up to approximately age two) and older children (ages two and over). In contrast, IEUBK model accounts for differences in behaviors in younger and older children (e.g., dust and soil ingestion rates are lower for children three and older) and yields age-specific blood-lead values for a given dust lead value.

The highest benefits in terms of number of children's IQ points are estimated using peak blood lead as the exposure metric, and attributing the same magnitude of neurological decrement associated with this peak to all children under the age of six years, regardless of the age at which exposure occurs. The lowest benefit in terms of number of children's IQ points gained are derived using IEUBK model to estimate a six-year blood lead average for 1-2 year olds; however, this estimate almost certainly underestimates benefits because it assumes that there are no benefits in avoiding exposures to other age groups.

As with the number of cases of adverse adult health effects avoided, the number of children's IQ points gained in year 1 are highest for Option A and decline for Option B and decline still further for Option C. In the second year, the number of IQ points gained among children is approximately the same for all regulatory options.

Table 5-15 presents the benefits in dollars. In terms of the value of the benefits of the proposed options; they closely track the total number of cases and number of IQ points. Scenario 1 has higher benefits, in

terms of dollar value, than Scenario 2; Option A first year benefits are greater than Option B first year benefits, which are greater than Option C first year benefits. Year 2 benefits are the same across all options within a scenario. Under Scenario 1 Option A, children's IQ benefit estimates range from $0.99 billion to $5.6 billion. For Scenario 2 the range of estimated values for Option A is from $0.81 billion to $4.6 billion. As with number of IQ points, the lowest value almost certainly underestimates benefits because it assumes that there are no benefits in avoiding exposures for children other than those age 1 to 2 years.

Year 2 adult benefits are approximately $2.4 billion under Scenario 1. Depending on the blood-lead modeling assumptions used, adult benefits make up 30 to70 percent of total benefits. While premature mortality account for only a few cases, they are the largest source of adult dollar benefits.

Table 5-15a: Total Benefits of Avoided Exposures – Scenario 1 ($ millions)

		Option A		Option B		Option C	
		Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
	Exposure	Mean	Mean	Mean	Mean	Mean	Mean
Adult Exposure - Interior and Exterior							
Hypertension	na	$602	$599	$519	$599	$419	$599
CHD	na	$13	$13	$12	$13	$10	$13
Stroke	na	$11	$11	$9	$11	$8	$11
Premature Mortality	na	$1,741	$1,734	$1,517	$1,734	$1,239	$1,734
Total	na	$2,367	$2,357	$2,057	$2,357	$1,676	$2,357
Child Exposure - Interior and Exterior							
Children, age 1-2 years							
Using IEUBK Model for Interior Estimates	Peak	$1,783	$1,776	$1,526	$1,776	$1,220	$1,776
	6-Year Average	$990	$986	$849	$986	$668	$986
Using Empirical Model for Interior Estimates	Peak	$1,222	$1,217	$1,047	$1,217	$833	$1,217
	6-Year Average	$1,455	$1,449	$1,247	$1,449	$989	$1,449
Children, age 0-5 years							
Using IEUBK Model for Interior Estimates	Peak	$5,583	$5,560	$4,945	$5,560	$3,810	$5,560
	6-Year Average	$2,828	$2,816	$2,419	$2,816	$1,945	$2,816
Total Exposure - Interior and Exterior							
Adult and Children (age 1-2 years)							
Using IEUBK Model for Interior Estimates	Peak	$4,150	$4,133	$3,583	$4,133	$2,896	$4,133
	6-Year Average	$3,357	$3,343	$2,906	$3,343	$2,344	$3,343
Using Empirical Model For Interior Estimates	Peak	$3,589	$3,574	$3,104	$3,574	$2,509	$3,574
	6-Year Average	$3,822	$3,806	$3,304	$3,806	$2,664	$3,806
Adult and Children (age 0-5 years)							
Using IEUBK Model for Interior Estimates	Peak	$7,949	$7,917	$7,002	$7,917	$5,485	$7,917
	6-Year Average	$5,194	$5,173	$4,476	$5,173	$3,621	$5,173

Based on post-rule compliance rate of 75%.

Table 5-16b: Total Benefits of Avoided Exposures – Scenario 2 ($ millions)							
		Option A		Option B		Option C	
		Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
	Exposure	Mean	Mean	Mean	Mean	Mean	Mean
Child Exposure - Interior and Exterior							
Children, age 1-2 years							
Using IEUBK Model or Interior Estimates	Peak	$1,403	$1,410	$1,201	$1,410	$959	$1,410
	6-Year Average	$810	$807	$695	$807	$545	$807
Using Empirical Model For Interior Estimates	Peak	$1,075	$1,073	$921	$1,073	$733	$1,073
	6-Year Average	$1,274	$1,268	$1,091	$1,268	$865	$1,268
Children, age 0-5 years							
Using IEUBK Model or Interior Estimates	Peak	$4,555	$4,537	$3,901	$4,537	$3,105	$4,537
	6-Year Average	$2,220	$2,211	$1,899	$2,211	$1,526	$2,211
Based on post-rule compliance rate of 75%. Scenario 2 assumes additional contractor and household cleaning in the baseline, as described in Section 5.5.3.							

The full range of monetized benefits from reducing lead exposure is shown in Table 5-16 for each analytic scenario and each regulatory option. In addition to the median values, this table presents the 5th and 95th percentile values derived in the Monte Carlo analysis. The 5th and 95th percentile provide information on the range of the distribution of estimates by showing the benefit estimate below which are 5 percent of the estimates (the 5th percentile) and above which are 5 percent of the estimates (the 95th percentile). For adult benefits, 95th percentile estimates are about 69-74 times higher than the 5th percentile estimates. The range for children's IQ benefits is even larger. These results reflect highly skewed distributions. In other words, the mean values are higher than the median values because there are a few very large values. This relationship holds for both Scenario 1 and 2.

Table 5-16a: Total Benefits for Adult and Child Exposure – Scenario 1 ($ billions)																			
		Option A						Option B						Option C					
		Year 1			Year 2			Year 1			Year 2			Year 1			Year 2		
			Percentiles			*Percentiles*			*Percentiles*			*Percentiles*			*Percentiles*			*Percentiles*	
	Exposure	Median	*5th*	*95th*	Median	*5th*	*95th*	Median	*5th*	*95th*	Median	*5th*	*95th*	Median	*5th*	*95th*	Median	*5th*	*95th*
Adult Exposure - Interior and Exterior																			
Total	na	$1.2	*$2.16*	*$160.6*	$1.2	*$2.15*	*$160.0*	$1.0	*$1.868*	*$138.4*	$1.2	*$2.15*	*$160.0*	$0.8	*$1.446*	*$112.8*	$1.2	*$2.15*	*$160.0*
Child Exposure - Interior and Exterior																			
Children, age 1-2 years																			
Using IEUBK Model	Peak	$0.7	*$0.019*	*$4.0*	$0.7	*$0.019*	*$4.0*	$0.6	*$0.017*	*$3.4*	$0.7	*$0.019*	*$4.0*	$0.5	*$0.013*	*$2.7*	$0.7	*$0.019*	*$4.0*
	6-Year Average	$0.4	*$0.024*	*$2.6*	$0.4	*$0.024*	*$2.6*	$0.3	*$0.021*	*$2.2*	$0.4	*$0.024*	*$2.6*	$0.3	*$0.016*	*$1.7*	$0.4	*$0.024*	*$2.6*
Using Empirical Model	Peak	$1.2	*$0.057*	*$2.8*	$1.2	*$0.057*	*$2.8*	$1.1	*$0.049*	*$2.4*	$1.2	*$0.057*	*$2.8*	$0.9	*$0.038*	*$1.9*	$1.2	*$0.057*	*$2.8*
	6-Year Average	$1.2	*$0.035*	*$4.1*	$1.2	*$0.035*	*$4.1*	$1.1	*$0.030*	*$3.5*	$1.2	*$0.035*	*$4.1*	$0.9	*$0.023*	*$2.8*	$1.2	*$0.035*	*$4.1*
Children, age 0-5 years																			
Using IEUBK Model	Peak	$2.4	*$0.073*	*$17*	$2.4	*$0.073*	*$17*	$2.1	*$0.063*	*$15*	$2.4	*$0.073*	*$17*	$1.6	*$0.047*	*$12*	$2.4	*$0.073*	*$17*
	6-Year Average	$0.9	*$0.0090*	*$6.9*	$0.9	*$0.0090*	*$6.9*	$0.8	*$0.0078*	*$5.9*	$0.9	*$0.0090*	*$6.9*	$0.6	*$0.0059*	*$4.8*	$0.9	*$0.0090*	*$6.9*
Total Exposure - Interior and Exterior																			
Adult and Children (age 1-2 years)																			
Using IEUBK Model	Peak	$1.9	*$2.18*	*$165*	$1.9	*$2.17*	*$164*	$1.6	*$1.885*	*$142*	$1.9	*$2.17*	*$164*	$1.3	*$1.458*	*$115.6*	$1.9	*$2.17*	*$164*
	6-Year Average	$1.6	*$2.18*	*$163*	$1.6	*$2.17*	*$163*	$1.4	*$1.89*	*$140.6*	$1.6	*$2.17*	*$163*	$1.1	*$1.461*	*$114.6*	$1.6	*$2.17*	*$163*
Using Empirical Model	Peak	$2.4	*$2.21*	*$163*	$2.4	*$2.21*	*$163*	$2.1	*$1.92*	*$140.8*	$2.4	*$2.21*	*$163*	$1.7	*$1.48*	*$114.8*	$2.4	*$2.21*	*$163*
	6-Year Average	$2.4	*$2.19*	*$165*	$2.4	*$2.18*	*$164*	$2.1	*$1.90*	*$142*	$2.4	*$2.18*	*$164*	$1.7	*$1.469*	*$115.6*	$2.4	*$2.18*	*$164*
Adult and Children (age 0-5 years)																			
Using IEUBK Model	Peak	$3.6	*$2.23*	*$178*	$3.6	*$2.22*	*$177*	$3.1	*$1.93*	*$153*	$3.6	*$2.22*	*$177*	$2.5	*$1.49*	*$124*	$3.6	*$2.22*	*$177*
	6-Year Average	$2.1	*$2.17*	*$168*	$2.1	*$2.16*	*$167*	$1.9	*$1.88*	*$144*	$2.1	*$2.16*	*$167*	$1.5	*$1.451*	*$118*	$2.1	*$2.16*	*$167*
Based on post-rule compliance rate of 75%.																			

Table 5-16b: Total Benefits for Child Exposure – Scenario 2 ($ billions)																		
		Option A						Option B						Option C				
		Year 1			Year 2			Year 1			Year 2			Year 1			Year 2		
			Percentiles			*Percentiles*			*Percentiles*			*Percentiles*			*Percentiles*			*Percentiles*	
	Exposure	Median	*5th*	*95th*	Median	*5th*	*95th*	Median	*5th*	*95th*	Median	*5th*	*95th*	Median	*5th*	*95th*	Median	*5th*	*95th*
Child Exposure - Interior and Exterior																		
Children, age 1-2 years																		
Using IEUBK Model	Peak	$0.5	*$0.017*	*$3.3*	$0.5	*$0.017*	*$3.3*	$0.5	*$0.015*	*$2.9*	$0.5	*$0.017*	*$3.3*	$0.4	*$0.011*	*$2.3*	$0.5	*$0.017*	*$3.3*
	6-Year Average	$0.3	*$0.022*	*$2.2*	$0.3	*$0.022*	*$2.2*	$0.3	*$0.019*	*$1.9*	$0.3	*$0.022*	*$2.2*	$0.2	*$0.014*	*$1.5*	$0.3	*$0.022*	*$2.2*
Using Empirical Model	Peak	$1.1	*$0.033*	*$2.5*	$1.1	*$0.033*	*$2.5*	$0.9	*$0.029*	*$2.2*	$1.1	*$0.033*	*$2.5*	$0.7	*$0.022*	*$1.7*	$1.1	*$0.033*	*$2.5*
	6-Year Average	$1.1	*$0.027*	*$3.6*	$1.1	*$0.026*	*$3.6*	$0.9	*$0.023*	*$3.1*	$1.1	*$0.026*	*$3.6*	$0.7	*$0.017*	*$2.5*	$1.1	*$0.026*	*$3.6*
Children, age 0-5 years																		
Using IEUBK Model	Peak	$2.4	*$0.066*	*$14.3*	$2.4	*$0.066*	*$14.2*	$2.1	*$0.057*	*$12.2*	$2.4	*$0.066*	*$14.2*	$1.6	*$0.042*	*$9.7*	$2.4	*$0.066*	*$14.2*
	6-Year Average	$0.9	*$0.008*	*$5.7*	$0.9	*$0.008*	*$5.7*	$0.8	*$0.007*	*$4.9*	$0.9	*$0.008*	*$5.7*	$0.6	*$0.005*	*$3.9*	$0.9	*$0.008*	*$5.7*
Based on post-rule compliance rate of 75%.																		
Scenario 2 assumes additional contractor and household cleaning in the baseline, as described in Section 5.5.3.																		

Another way to look at the benefits is in terms of what proportion is attributable to reductions in interior event exposures and what proportion is due to reductions in exterior event exposures. Table 5-17 presents the number of cases of adverse adult health events avoided, and the number of IQ points gained, due to the various regulatory options. The first table presents results for Scenario 1; the second presents Scenario 2. The majority of IQ points gained, under any option and either scenario, are due to reductions in interior event exposures. For adult adverse health effects, however, while the interior number is greater than the exterior number, the difference is smaller. In the case of hypertension, the number of cases avoided due to interior event reductions is only slightly greater than the number avoided due to exterior event reductions. For the other adult health effects, however, the number of interior cases avoided is 25 to 30 percent greater than the number of exterior event cases. Table 5-19 presents the dollar values of these benefits. Again, the majority of the value of children's IQ points gained is attributable to reductions in interior event exposures. For adult health effects, under all options and in any year, the benefits due to reductions in interior event exposures are somewhat greater than the value of benefits from reductions in exterior event exposures.

Table 5-17a: Total Cases of Avoided Adverse Adult Health Effects and Number of IQ Points Gained per Year – Scenario 1													
		Option A				Option B				Option C			
		Year 1		Year 2		Year 1		Year 2		Year 1		Year 2	
	Exposure	Mean		Mean		Mean		Mean		Mean		Mean	
		Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior	Indoor	Exterior
Adult Exposures -- Cases of Adverse Health Effects Avoided													
Hypertension	na	22,604	22,079	22,510	21,989	19,419	19,114	22,510	21,989	16,352	14,782	22,510	21,989
CHD	na	106	82	105	82	92	72	105	82	78	56	105	82
Stroke	na	25	18	24	18	21	16	24	18	18	12	24	18
Premature Mortality	na	160	125	159	125	140	109	159	125	118	85	159	125
Child Exposure - IQ Points Gained (thousands)													
Children, age 1-2 years													
Using IEUBK model For Interior Estimates	Peak	121	17	120	17	104	14	120	17	83	11	120	17
	6-Year Average	51	25	50	26	44	22	50	26	35	17	50	26
Using Empirical model For Interior Estimates	Peak	78	16	78	16	67	14	78	16	53	11	78	16
	6-Year Average	86	26	85	26	74	22	85	26	60	16	85	26
Children, age 0-5 years													
Using IEUBK model For Interior Estimates	Peak	361	70	359	70	322	60	359	70	249	45	359	70
	6-Year Average	208	10	207	10	178	9	207	10	144	6	207	10
Based on post-rule compliance rate of 75%.													

Table 5-18b: Total Number of IQ Points Gained per Year – Scenario 2													
		Option A				Option B				Option C			
		Year 1		Year 2		Year 1		Year 2		Year 1		Year 2	
	Exposure	Mean		Mean		Mean		Mean		Mean		Mean	
		Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior
Child Exposure - IQ Points Gained (thousands)													
Children, age 1-2 years													
Using IEUBK Model For interior estimates	Peak	93	15	94	15	80	13	94	15	64	10	94	15
	6-Year Average	39	24	39	23	34	20	39	23	27	15	39	23
Using Empirical Model For Interior Estimates	Peak	68	15	68	15	58	13	68	15	47	10	68	15
	6-Year Average	75	23	75	23	64	20	75	23	52	15	75	23
Children, age 0-5 years													
Using IEUBK Model For interior estimates	Peak	288	64	286	64	246	55	286	64	198	42	286	64
	6-Year Average	162	9	162	9	139	8	162	9	112	6	162	9
Based on post-rule compliance rate of 75%. Scenario 2 assumes additional contractor and household cleaning in the baseline as described in Section 5.5.3.													

Table 5-19a: Total Benefits of Avoided Exposures per Year – Scenario 1 ($ millions)													
		Option A				Option B				Option C			
		Year 1		Year 2		Year 1		Year 2		Year 1		Year 2	
	Exposure	Mean		Mean		Mean		Mean		Mean		Mean	
		Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior
Adult Exposure													
Hypertension	na	$304	$298	$303	$296	$261	$258	$303	$296	$220	$199	$303	$296
CHD	na	$7	$6	$7	$6	$7	$5	$7	$6	$6	$4	$7	$6
Stroke	na	$6	$5	$6	$5	$5	$4	$6	$5	$5	$3	$6	$5
Premature Mortality	na	$979	$762	$975	$759	$850	$667	$975	$759	$719	$520	$975	$759
Total	na	$1,297	$1,070	$1,292	1,065	$1,124	$933	$1,292	1,065	$949	$727	$1,292	1,065
Child Exposure													
Children, age 1-2 years													
Using IEUBK Model	Peak	$1,569	$214	$1,562	$214	$1,341	$185	$1,562	$214	$1,082	$138	$1,562	$214
for Interior Estimates	6-Year Average	$657	$333	$655	$331	$562	$287	$655	$331	$454	$214	$655	$331
Using Empirical Model	Peak	$1,007	$215	$1,003	$214	$862	$185	$1,003	$214	$695	$138	$1,003	$214
for Interior Estimates	6-Year Average	$1,122	$333	$1,118	$331	$960	$287	$1,118	$331	$775	$214	$1,118	$331
Children, age 0-5 years													
Using IEUBK Model	Peak	$4,675	$908	$4,656	$904	$4,166	$779	$4,656	$904	$3,226	$584	$4,656	$904
for Interior Estimates	6-Year Average	$2,698	$130	$2,687	$129	$2,307	$112	$2,687	$129	$1,862	$83	$2,687	$129
Based on post-rule compliance rate of 75%.													

Table 5-20b: Total Benefits of Avoided Exposures per Year – Scenario 2 ($ millions)													
		Option A				Option B				Option C			
		Year 1		Year 2		Year 1		Year 2		Year 1		Year 2	
	Exposure	Mean		Mean		Mean		Mean		Mean		Mean	
		Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior	Interior	Exterior
Child Exposure													
Children, age 1-2 years													
Using IEUBK Model or Interior Estimates	Peak	$1,206	$197	$1,213	$197	$1,031	$170	$1,213	$197	$832	$127	$1,213	$197
	6-Year Average	$505	$305	$503	$304	$432	$263	$503	$304	$349	$196	$503	$304
Using Empirical Model For Interior Estimates	Peak	$878	$197	$880	$193	$751	$170	$880	$193	$606	$127	$880	$193
	6-Year Average	$969	$305	$965	$303	$828	$263	$965	$303	$669	$196	$965	$303
Children, age 0-5 years													
Using IEUBK Model For Interior Estimates	Peak	$3,723	$832	$3,708	$829	$3,184	$717	$3,708	$829	$2,569	$536	$3,708	$829
	6-Year Average	$2,101	$119	$2,093	$118	$1,797	$102	$2,093	$118	$1,450	$76	$2,093	$118
Based on post-rule compliance rate of 75%.													
Scenario 2 assumes additional contractor and household cleaning in the baseline, as described in Section 5.5.3.													

Table 5-21 and Table 5-22 present total estimated benefits over a 50-year period and annualized benefits for both scenarios. Table 5-21 presents values calculated with a 3 percent discount rate and Table 5-22 with a 7 percent discount rate. Because Year 1 is the only year in which there is a difference among the regulatory options in terms of in population covered and thus benefits, the annualized benefits are nearly the same across the options within a scenario. Using a 3 percent discount rate, Scenario 2 monetary benefits for children's IQ point gained range from 75 to 88 percent of those gained under Scenario 1, depending on which blood-lead model and exposure assumptions are used. Using a 7 percent discount rate, the results are even closer, with the value of children's IQ points gained ranging from 77 to 93 percent of the value estimated under Scenario 1.

Table 5-21a: Total 50- Year and 50-Year Annualized Benefits for Adult and Child Exposure – Scenario 1 (3 Percent Discount Rate, $ billions)																			
		Option A						Option B						Option C					
		Total 50-Year Benefit			Annualized Benefit			Total 50-Year Benefit			Annualized Benefit			Total 50-Year Benefit			Annualized Benefit		
			Percentiles			Percentiles			Percentiles			Percentiles			Percentiles			Percentiles	
	Exposure	Median	5th	95th	Median	5th	95th	Median	5th	95th	Median	5th	95th	Median	5th	95th	Median	5th	95th
Adult Exposure - Interior and Exterior																			
Total	Na	$30	*$53.1*	*$3,950*	$1.2	*$2.1*	*$154*	$28	$52.8	$3,928	$1.1	*$2.1*	*$153*	29	$52.4	$3,902	1.1	*$2.0*	*$152*
Child Exposure - Interior and Exterior																			
Children, age 1-2 years																			
Using IEUBK Model	Peak	$17	*$0.5*	*$99*	$0.7	*$0.0*	*$4*	$17	*$0.5*	*$98*	$0.7	*$0.0*	*$4*	$17	*$0.5*	*$97*	$0.6	*$0.0*	*$4*
	6-Year Average	$10	*$0.6*	*$63*	$0.4	*$0.0*	*$2*	$10	*$0.6*	*$63*	$0.4	*$0.0*	*$2*	$10	*$0.6*	*$62*	$0.4	*$0.0*	*$2*
Using Empirical Model	Peak	$31	*$1.4*	*$70*	$1.2	*$0.1*	*$3*	$30	*$1.4*	*$69*	$1.2	*$0.1*	*$3*	$30	*$1.4*	*$69*	$1.2	*$0.1*	*$3*
	6-Year Average	$31	*$0.9*	*$101*	$1.2	*$0.0*	*$4*	$31	*$0.9*	*$100*	$1.2	*$0.0*	*$4*	$30	*$0.9*	*$99*	$1.2	*$0.0*	*$4*
Children, age 0-5 years																			
Using IEUBK Model	Peak	$59	*$1.8*	*$418*	$2.3	*$0.1*	*$16*	$58	*$1.8*	*$416*	$2.3	*$0.1*	*$16*	$58	*$1.8*	*$412*	$2.3	*$0.1*	*$16*
	6-Year Average	$23	*$0.2*	*$171*	$0.9	*$0.0*	*$7*	$23	*$0.2*	*$170*	$0.9	*$0.0*	*$7*	$23	*$0.2*	*$169*	$0.9	*$0.0*	*$7*
Total Exposure - Interior and Exterior																			
Adult and Children (age 1-2 years)																			
Using IEUBK Model	Peak	$47	*$53.5*	*$4,049*	$1.8	*$2.1*	*$157*	$46	*$53.2*	*$4,026*	$1.8	*$2.1*	*$156*	$46	*$52.8*	*$4,000*	$1.8	*$2.1*	*$155*
	6-Year Average	$40	*$53.7*	*$4,013*	$1.6	*$2.1*	*$156*	$39	*$53.4*	*$3,991*	$1.5	*$2.1*	*$155*	$39	*$52.9*	*$3,965*	$1.5	*$2.1*	*$154*
Using Empirical Model	Peak	$61	*$54.5*	*$4,020*	$2.4	*$2.1*	*$156*	$60	*$54.2*	*$3,997*	$2.3	*$2.1*	*$155*	$59	*$53.7*	*$3,971*	$2.3	*$2.1*	*$154*
	6-Year Average	$61	*$53.9*	*$4,051*	$2.4	*$2.1*	*$157*	$60	*$53.6*	*$4,028*	$2.3	*$2.1*	*$157*	$59	*$53.2*	*$4,002*	$2.3	*$2.1*	*$156*
Adult and Children (age 0-5 years)																			
Using IEUBK Model	Peak	$90	*$54.9*	*$4,368*	$3.5	*$2.1*	*$170*	$88	*$54.6*	*$4,344*	$3.4	*$2.1*	*$169*	$87	*$54.1*	*$4,315*	$3.4	*$2.1*	*$168*
	6-Year Average	$4	*$4.3*	*$330*	$0.2	*$0.2*	*$13*	$4	*$4.0*	*$306*	$0.2	*$0.2*	*$12*	$4	*$3.5*	*$280*	$0.1	*$0.1*	*$11*
Based on post-rule compliance rate of 75%. Scenario 2 assumes additional contractor and household cleaning in the baseline, as described in Section 5.5.3.																			

Table 5-21b: Total 50- Year and 50-Year Annualized Benefits for Child Exposure – Scenario 2 (3 Percent Discount Rate, $ billions)																		
		Option A						**Option B**						**Option C**					
		Total 50-Year Benefit			**Annualized Benefit**			**Total 50-Year Benefit**			**Annualized Benefit**			**Total 50-Year Benefit**			**Annualized Benefit**		
			Percentiles			***Percentiles***			***Percentiles***			***Percentiles***			***Percentiles***			***Percentiles***	
	Exposure	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***
Child Exposure - Interior and Exterior																			
Children, age 1-2 years																			
Using Indoor IEUBK	Peak	$14	*$0.4*	*$82*	$0.5	*$0.0*	*$3*	$13	*$0.4*	*$82*	$0.5	*$0.0*	*$3*	$13	*$0.4*	*$81*	$0.5	*$0.0*	*$3*
	6-Year Average	$8	*$0.5*	*$54*	$0.3	*$0.0*	*$2*	$8	*$0.5*	*$54*	$0.3	*$0.0*	*$2*	$8	*$0.5*	*$53*	$0.3	*$0.0*	*$2*
Using Indoor Empirical	Peak	$27	*$0.8*	*$62*	$1.0	*$0.0*	*$2*	$26	*$0.8*	*$62*	$1.0	*$0.0*	*$2*	$26	*$0.8*	*$61*	$1.0	*$0.0*	*$2*
	6-Year Average	$26	*$0.7*	*$89*	$1.0	*$0.0*	*$3*	$26	*$0.6*	*$89*	$1.0	*$0.0*	*$3*	$26	*$0.6*	*$88*	$1.0	*$0.0*	*$3*
Children, age 0-5 years																			
Using Indoor IEUBK	Peak	$59	*$1.6*	*$351*	$2.3	*$0.1*	*$14*	$58	*$1.6*	*$349*	$2.3	*$0.1*	*$14*	$58	*$1.6*	*$347*	$2.3	*$0.1*	*$13*
	6-Year Average	$23	*$0.2*	*$141*	$0.9	*$0.0*	*$5*	$23	*$0.2*	*$140*	$0.9	*$0.0*	*$5*	$23	*$0.2*	*$139*	$0.9	*$0.0*	*$5*
Based on post-rule compliance rate of 75%.																			
Scenario 2 assumes additional contractor and household cleaning in the baseline, as described in Section 5.5.3.																			

Table 5-22a: Total 50- Year and 50-Year Annualized Benefits for Adult and Child Exposure – Scenario 1 (7 Percent Discount Rate, $ billions)																		
		Option A						**Option B**						**Option C**					
		Total 50-Year Benefit			**Annualized Benefit**			**Total 50-Year Benefit**			**Annualized Benefit**			**Total 50-Year Benefit**			**Annualized Benefit**		
			Percentiles			***Percentiles***			***Percentiles***			***Percentiles***			***Percentiles***			***Percentiles***	
	Exposure	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***
Adult Exposure - Interior and Exterior																			
Total	Na	$18	*$30.3*	*$2,255*	$1.3	*$2.2*	*$163*	$17	$30.0	$2,233	$1.2	*$2.2*	*$162*	$16	$29.6	$2,207	$1.2	*$2.1*	*$160*
Child Exposure - Interior and Exterior																			
Children, age 1-2 years																			
Using Indoor IEUBK	Peak	$10	*$0.3*	*$56*	$0.7	*$0.0*	*$4*	$10	*$0.3*	*$56*	$0.7	*$0.0*	*$4*	$9	*$0.3*	*$55*	$0.7	*$0.0*	*$4*
	6-Year Average	$6	*$0.3*	*$36*	$0.4	*$0.0*	*$3*	$6	*$0.3*	*$36*	$0.4	*$0.0*	*$3*	$5	*$0.3*	*$35*	$0.4	*$0.0*	*$3*
Using Indoor Empirical	Peak	$17	*$0.8*	*$40*	$1.3	*$0.1*	*$3*	$17	*$0.8*	*$39*	$1.3	*$0.1*	*$3*	$17	*$0.8*	*$39*	$1.2	*$0.1*	*$3*
	6-Year Average	$18	*$0.5*	*$57*	$1.3	*$0.0*	*$4*	$17	*$0.5*	*$57*	$1.3	*$0.0*	*$4*	$17	*$0.5*	*$56*	$1.2	*$0.0*	*$4*
Children, age 0-5 years																			
Using Indoor IEUBK	Peak	$34	*$1.0*	*$238*	$2.4	*$0.1*	*$17*	$33	*$1.0*	*$236*	$2.4	*$0.1*	*$17*	$33	*$1.0*	*$233*	$2.4	*$0.1*	*$17*
	6-Year Average	$13	*$0.1*	*$98*	$1.0	*$0.0*	*$7*	$13	*$0.1*	*$97*	$1.0	*$0.0*	*$7*	$13	*$0.1*	*$95*	$0.9	*$0.0*	*$7*
Total Exposure - Interior and Exterior																			
Adult and Children (age 1-2 years)																			
Using Indoor IEUBK	Peak	$28	*$30.6*	*$2,311*	$2.0	*$2.2*	*$167*	$26	*$30.3*	*$2,289*	$1.9	*$2.2*	*$166*	$26	*$29.8*	*$2,262*	$1.9	*$2.2*	*$164*
	6-Year Average	$24	*$30.6*	*$2,291*	$1.7	*$2.2*	*$166*	$22	*$30.3*	*$2,269*	$1.6	*$2.2*	*$164*	$22	*$29.9*	*$2,243*	$1.6	*$2.2*	*$162*
Using Indoor Empirical	Peak	$36	*$31.1*	*$2,295*	$2.6	*$2.3*	*$166*	$34	*$30.8*	*$2,272*	$2.5	*$2.2*	*$165*	$34	*$30.4*	*$2,246*	$2.4	*$2.2*	*$163*
	6-Year Average	$36	*$30.8*	*$2,312*	$2.6	*$2.2*	*$168*	$34	*$30.5*	*$2,290*	$2.5	*$2.2*	*$166*	$34	*$30.1*	*$2,263*	$2.4	*$2.2*	*$164*
Adult and Children (age 0-5 years)																			
Using Indoor IEUBK	Peak	$53	*$31.3*	*$2,494*	$3.9	*$2.3*	*$181*	$50	*$31.0*	*$2,469*	$3.6	*$2.2*	*$179*	$49	*$30.6*	*$2,440*	$3.6	*$2.2*	*$177*
	6-Year Average	$4	*$4.2*	*$324*	$0.3	*$0.3*	*$23*	$4	*$3.9*	*$300*	$0.3	*$0.3*	*$22*	$3	*$3.5*	*$274*	$0.3	*$0.3*	*$20*

Based on post-rule compliance rate of 75%.
Scenario 2 assumes additional contractor and household cleaning in the baseline, as described in Section 5.5.3.

Table 5-22b: Total 50- Year and 50-Year Annualized Benefits for Child Exposure – Scenario 2 (7 Percent Discount Rate, $ billions)																		
		Option A						**Option B**						**Option C**					
		Total 50-Year Benefit			**Annualized Benefit**			**Total 50-Year Benefit**			**Annualized Benefit**			**Total 50-Year Benefit**			**Annualized Benefit**		
			Percentiles			***Percentiles***			***Percentiles***			***Percentiles***			***Percentiles***			***Percentiles***	
	Exposure	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***	Median	***5th***	***95th***
Child Exposure - Interior and Exterior																			
Children, age 1-2 years																			
Using Indoor IEUBK	Peak	$8	*$0.2*	*$47*	$0.6	*$0.0*	*$3*	$8	*$0.2*	*$47*	$0.5	*$0.0*	*$3*	$7	*$0.2*	*$46*	$0.5	*$0.0*	*$3*
	6-Year Average	$5	*$0.3*	*$31*	$0.3	*$0.0*	*$2*	$5	*$0.3*	*$31*	$0.3	*$0.0*	*$2*	$5	*$0.3*	*$30*	$0.3	*$0.0*	*$2*
Using Indoor Empirical	Peak	$15	*$0.5*	*$36*	$1.1	*$0.0*	*$3*	$15	*$0.5*	*$35*	$1.1	*$0.0*	*$3*	$15	*$0.5*	*$35*	$1.1	*$0.0*	*$3*
	6-Year Average	$15	*$0.4*	*$51*	$1.1	*$0.0*	*$4*	$15	*$0.4*	*$50*	$1.1	*$0.0*	*$4*	$15	*$0.4*	*$50*	$1.1	*$0.0*	*$4*
Children, age 0-5 years																			
Using Indoor IEUBK	Peak	$34	*$0.9*	*$200*	$2.4	*$0.1*	*$15*	$33	*$0.9*	*$198*	$2.4	*$0.1*	*$14*	$33	*$0.9*	*$196*	$2.4	*$0.1*	*$14*
	6-Year Average	$13	*$0.1*	*$80*	$1.0	*$0.0*	*$6*	$13	*$0.1*	*$80*	$1.0	*$0.0*	*$6*	$13	*$0.1*	*$79*	$0.9	*$0.0*	*$6*
Based on post-rule compliance rate of 75%.																			
Scenario 2 assumes additional contractor and household cleaning in the baseline, as described in Section 5.5.3.																			

Table 5-23 summarizes the annualized benefit estimates presented in the prior tables. Using a 3 percent discount rate, children's IQ benefits under Scenario 1 range from about $940 to $5,300 million; under Scenario 2 they range from about $700 to $4,300 million. Under Scenario 1, the adult benefits are estimated to be about $2,200 million, bring the sum of estimated adult and children's benefits to a range of $3.2 to $7.6 billion. Using a 7 percent discount rate, all the annualized values are slightly higher than they are when a 3 percent discount rate is used.

Table 5-23: Summary of the Range of Benefits Estimate, by Scenario 1 and Option, using 3 Percent and 7 Percent Discount Rates

	Scenario 1			Scenario 2
	Children's IQ Benefits – Annualized (millions 2005$)[a]	**Adult Health Benefits – Annualized (millions 2005$) [a]**	**Sum of Children's IQ and Adult Benefits -- Annualized (millions 2005$)**	**Children's IQ Benefits – Annualized[a] (millions 2005$)**
	Annualized using 3 Percent Discount Rate			
Option A	$947 - $5,336	$2,262	$3,209 - $7,599	$774 - $4,354
Option B	$941 - $5,311	$2,250	$3,191 - $7,562	$770 - $4,329
Option C	$934 - $5,267	$2,235	$3,170 - $7,503	$764 - $4,298
Option D	$941 - $5,311	$2,250	$3,191 - $7,562	$770 - $4,329
	Annualized using 7 Percent Discount Rate			
Option A	$1,008 - $5,680	$2,408	$3,415 - $8,087	$824 - $4,635
Option B	$997 - $5,633	$2,385	$3,383 - $8,019	$816 - $4,587
Option C	$984 - $5,551	$2,358	$3,342 - $7,909	$805 - $4,530
Option D	$997 - $5,633	$2,385	$3,383 - $8,019	$816 - $4,587

[a] From Table 5-17 and Table 5-18 – range reflects alternative models for blood lead, exposure estimates and population of children

As with the first year adult benefits, premature mortality contributes the largest amount to total annualized adult benefits, under both the 3 percent and the 7 percent discount rate. As can be seen in Table 5-24, the relative values of each of the adult health effects is relatively constant across the regulatory options.

Table 5-24: Annualized Benefits from Adult Exposures Avoided - Interior and Exterior, by Adverse Health Effect Avoided – Scenario 1 ($ millions)

		Option A		**Option B**		**Option C**	
		3 Percent	**7 percent**	**3 Percent**	**7 percent**	**3 Percent**	**7 percent**
	Exposure	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**
Hypertension	na	$575	$612	$572	$606	$568	$599
CHD	na	$13	$14	$13	$14	$13	$13
Stroke	na	$10	$11	$10	$11	$10	$11
Premature Mortality	na	$1,664	$1,771	$1,655	$1,755	$1,645	$1,735

Based on post-rule compliance rate of 75%.

As shown above, regardless of which scenario is considered, the estimated benefits are substantial. In addition, in both scenarios a number of benefit categories have been excluded from the estimated benefits. Among the categories of benefits excluded from either scenario are:

- Other health and developmental effects for which there were not adequate data to develop a dose-response curve, and thus a benefits estimate,
- Benefits that accrue to much of the exposed population (e.g., teenagers, adults younger than 40 years old, exposed individuals that do not live in the housing units with RRP events),
- Adverse effects on plants and animals, and
- Willingness-to-pay values – values based on medical costs and lost income are used instead.

Appendix 5A: Lead-Related Health Effects and Ecological Effects

Most of this appendix consists of two chapters from the First External Review draft of EPA's 2005 Air Quality Criteria Document (AQCD) for Lead. The chapters that are reproduced here are Chapter 5, "Toxicological Effects of Lead in Laboratory Animals, Humans, and in Vitro Test Systems" and Chapter 6, "Epidemiologic Studies of Human Health Effects Associated with Lead Exposure." This is followed by a summary of the ecological effects from renovation, repair, and painting activities involving lead-based paint.

5A.1 Health Effects to Children and Adults, Excerpted from Chapters 5 and 6 of the First External Review Draft of EPA's Air Quality Criteria Document for Lead

The Clean Air Act mandates periodic review of the National Ambient Air Quality Standards (NAAQS) for six common air pollutants, including lead, referred to as criteria pollutants. Under the review process, EPA's Office of Research and Development develops a "criteria document" -- a compilation and evaluation by U.S. EPA scientific staff and other expert authors of the latest scientific knowledge useful in assessing the health and welfare effects of the air pollutant. In this case, the Lead Criteria Document presents the latest available pertinent information on atmospheric science, air quality, exposure, dosimetry, health effects, and environmental effects of lead. In developing criteria documents, EPA must consider the advice of its Clean Air Scientific Advisory Committee (CASAC).

The following is a brief history of the development of the Air Quality Criteria Document for Lead.

- 2004 - EPA begins the mandated periodic revision of the Lead Criteria Document.
- 2005 - CASAC and the public review and comment on the Project Work Plan for the document.
- 2005 - EPA conducts peer consultative workshops in August 2005.
- 2005 - EPA releases the first external review draft of the Lead Criteria Document

The AQCD was released for public comment and for review by CASAC in a Federal Register notice on December 2, 2005 (70 FR 72300). Comments were due by February 15, 2006 in order to be considered by CASAC during their review.

CASAC will hold a public meeting to review the second external review draft of the Air Quality Criteria Document for Lead in March 2006. A Federal Register Notice will announce the date of the meeting and its location. EPA will then review their feedback and recommendations with plans to publish the second external review draft by May 2006. EPA intends to reflect revisions to the AQCD in the economic analysis for the final lead RRP rule.

The full text for the draft AQCD is available at http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=141779 The docket for the external review of the draft AQCD is available at the Regulations.gov Web site under docket ID ORD-2005-0018.

5. TOXICOLOGICAL EFFECTS OF LEAD IN LABORATORY ANIMALS, HUMANS, AND IN VITRO TEST SYSTEMS

5.1 INTRODUCTION

As noted in Chapter 1, air quality criteria documents evaluate scientific knowledge of relationships between pollutant concentrations and their effects on the environment and public health. Chapters 2 and 3 of this document discussed the chemistry and physical properties of lead (Pb); sources, emissions, transport, and deposition of Pb; and environmental concentrations and pathways to human exposure. Chapter 4 discussed models of human exposure that predict tissue distribution of lead. This chapter (Chapter 5) assesses information regarding the toxicological effects of Pb in laboratory animals, humans, and in vitro test systems. Emphasis is placed here on qualitative characterization of various Pb-induced effects, with attempts to define dose-effect relationships for the key health effects that are thought to occur at ambient exposure levels encountered by the general population of the United States. Chapter 6 follows with a discussion of epidemiologic studies of ambient Pb-exposure effects. Chapter 7 provides an integrative synthesis of information on Pb exposures and health effects. The environmental effects of Pb are discussed in Chapter 8.

The framework used here for presenting the toxicologic effects of Pb is subdivided mainly according to organ systems. As noted in the 1986 Pb AQCD, this facilitates presentation of the information, but it must be stressed that all systems are interdependent, functioning in delicate concert to preserve the physiological integrity of the whole organism.

The information discussed in this chapter is derived from a very wide body of literature on studies in humans, laboratory animals, and in vitro test systems of animal cell lines and organ systems that may mimic responses in intact animals. This chapter is not intended to be a compendium of all that is known about lead; rather, it is an update of the reported biological effects from the last previous Pb AQCD (U.S. Environmental Protection Agency, 1986), the Addendum to that document (Lead Effects on Cardiovascular Function, Early Development, and Stature) (U.S. Environmental Protection Agency, 1986), and the Supplement to the 1986 Addendum (U.S. Environmental Protection Agency, 1990). The historical Pb literature is briefly

summarized at the opening of each section or subsection and is intended as a very concise overview of previous work The reader should refer to the previous documents listed above for more detailed discussion of the literature prior to the late 1980s. Each section then continues with brief discussions of key studies published since 1986. Longer discussions of the newly available studies are included where warranted. Sections are ended with comparisons of data from the 1986 AQCD with new data, and basic conclusions are drawn. More detailed summaries of newly available studies and results are provided in tables in Annex AX5.

5.2 EFFECTS OF LEAD ON HEME SYNTHESIS

5.2.1 Effects of Lead on Erythrocyte Biology and Function

Lead poisoning is one of the most common acquired environmental diseases, because of physical properties of the metal and its widespread distribution in the environment. It is a complex disorder affecting several organs in the body, including developing erythrocytes (red blood cells [RBCs]). Anemia is frequently observed with Pb poisoning and is thought to result from the shortening of erythrocyte life span and is also due to the effects of Pb on hemoglobin synthesis. However, the exact mechanisms by which Pb affects the red blood cell (RBC) life span and heme synthesis are not clear. It is postulated that the mechanisms may be due to the effects of Pb on iron uptake; Pb poisoning also causes an increased urinary excretion of porphyrins and 5-aminolevulinic acid (ALA), the first precursor for heme synthesis. In addition, the striking similarities between Pb poisoning and acute intermittent porphyria (the disease associated with lesions in the heme biosynthetic enzyme, porphobilinogen deaminase) strongly suggests that one of the major sites of Pb intoxication is the heme biosynthetic pathway.

The 1986 Pb AQCD presented a concise summary of literature available at that time from both animal and human studies indicating potential effects of Pb intoxication on enzymes and precursors involved in heme synthesis, erythrocyte morphology and function as well as the influence of these perturbations on the nervous system and vitamin D metabolism and associated physiological process. In summary, these studies reported an association between increased Pb exposure and increased ALA-S activity (which is increased in kidney with acute exposure and in spleen with chronic exposure, while it decreased in liver tissue in both the exposure scenarios). The activity of ALA-D appeared to be inversely correlated to blood Pb values and was found to

be inhibited in several tissues. It was also inferred from several animal studies that the effect of Pb on heme formation involved both ferrochelatase inhibition and impaired mitochondrial transport of iron. Human studies indicated that occupational exposure to Pb results in decreased erythrocyte cell survival and alterations in erythrocyte membrane integrity and energetics. The vast scientific literature on the effects of Pb on various aspects of heme metabolism in diverse organ systems both in human and animals has accumulated over the past two decades. Recognizing the magnitude of this literature, this chapter is primarily concerned with discussions of data from animal and in vitro studies, while the human studies are dealt with in Chapter 6.

5.2.2 Effects of Lead on Erythrocyte Functions

The cellular membrane is one of the main targets for toxic effects of heavy metals, including Pb. Anemia, one of the clinical symptoms of Pb intoxication, can develop because of impairment of hemoglobin synthesis and damage of erythrocyte membranes by Pb ions. Although, erythrocyte membrane is not as specialized as other cell membranes are, it carries out important functions common to other cell membranes, such as active and passive transport and the production of ionic and electric gradients. Changes in erythrocyte membrane lipid and protein profiles can alter the membrane fluidity, potentially affecting enzymatic activity and the functionality of receptors and ion channels present on the plasma membrane and also can influence the ionic and molecular composition of intracellular spaces.

Lead Uptake, Binding, and Transport

Studies by Simons (1986a) indicated that the uptake of Pb into human RBCs is a passive process, i.e., it does not require the use of energy in the form of ATP. In addition, Pb may be able to cross the membrane passively in either direction. This process involves anion transport mechanisms, as the characteristic anion exchange inhibitors have been found to inhibit the passive uptake of Pb by RBCs (Simons, 1986a,b). It has also been demonstrated that the transport of Pb across the membrane depends on the presence of another anion, the bicarbonate ion, and is transported as Pb-carbonate (Simons, 1986a). When Pb enters the cell, it binds mainly to hemoglobin, and the ratio of bound to free Pb in cytoplasm has been estimated to be 6000:1. Simons (1986a,b) carried out studies using citrate buffers, which may cause hemolysis of RBCs. To avoid the influence of a citrate buffer, Sugawara et al. (1990) measured the uptake

of Pb into human RBCs by adding Pb directly into plasma. These investigators also found that the transport of Pb across the erythrocyte membrane is energy-independent (passive) and carrier mediated. Little release of Pb from the cells was observed, suggesting absence of any hemolysis of the cells in this protocol. Furthermore, the progressive accumulation of Pb was not observed. More than 98% of the Pb was found accumulated in the cytoplasm in protein-bound form, while only 2% was found in the membrane fraction. Sugawara et al. (1990) also reported finding 45 Pb-binding sites on human hemoglobin. On the other hand, studies reported by Bergdahl et al. (1997) using liquid chromatography coupled with inductive plasma mass spectrometry analysis suggested aminolevulinic acid dehydratase (ALAD), the enzyme involved in the heme synthesis pathway, to be the principle Pb-binding protein, not hemoglobin, as previously thought.

Additional studies carried out by Simons (1993a) evaluated the transport of Pb into RBCs for cell Pb contents in the range of 1 to 10 μM and reported that ^{203}Pb uptake was mediated by an anion exchanger and the efflux was mediated through a vanadate-sensitive pathway identified with the calcium pump (Simons, 1988). He further concluded that the high ratio of RBC to plasma Pb observed in vivo was due to a labile Pb-binding component within the cytoplasm. Simons (1993a) also observed that exit of Pb ions from the RBC was much lower than expected based on his earlier work with erythrocyte ghosts. Utilizing a group of drugs that modify anion exchange and thiol groups in the cytoplasm, Lal et al. (1996) showed that anion exchange mechanisms and thiol groups were critical factors in how Pb stimulates calcium-dependent processes in erythrocytes. Once the role of anion exchanger proteins had been implicated in Pb transport in erythrocytes, Bannon et al. (2000) investigated whether similar anion exchange processes are involved in the uptake and transport of Pb in other cells, such as Madin-Darby canine kidney epithelial cells. Based on a comparative in vitro study using human erythrocytes and canine kidney epithelial cells, these authors reported transport of Pb in kidney epithelial cells, suggesting similar anion exchange involvement.

Erythrocyte Survival, Mobility, and Membrane Integrity

It is well recognized that Pb intoxication interferes with RBC survival by shortening the life span and altering the mobility of the erythrocytes; however, the molecular mechanisms behind these effects of Pb on erythrocyte functions are not well understood. The shape and deformability of the human erythrocyte, or RBC is maintained by several factors including low

concentration of free intracellular Ca^{2+} (<0.1 μM) and a replenished ATP level. An elevated interfacial Ca^{2+} concentration inside the RBC activates the passive ion efflux via a K^+ selective (voltage independent) channel and a concomitant water transport (Gordos effect). Low concentrations of Pb ions can mimic Ca^{2+} and activate the same channel in the RBC.

Intraperitonially injected Pb significantly decreases rat erythrocyte membrane mobility (Terayama et al., 1986), an effect evident to some extent even below blood Pb concentration of 100 μg/100 ml. This decrease in rat erythrocyte mobility was found simultaneous or prior to changes in hematological parameters such as hemoglobin (Hb) levels and hematocrits (Hct). The same group (Terayama and Muratsugu, 1988) also reported a significant decrease in erythrocyte membrane sialic acid content at the same levels of blood Pb with exposure to Pb (20 mM Pb-acetate once a week for 5 weeks). Additional studies by the same group reported that other hematological parameters, such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), were also significantly decreased upon Pb exposure, along with decreased mobility, sialic acid content, and deformability of rat RBCs. It was speculated that Pb-induced decreases in sialic acid content and deformability of RBCs shorten RBC survival time and may lead to anemia in Pb poisoning. Jehan and Motlag (1995) reported Pb exposure caused significant change in RBC membrane cholesterol and phospholipid contents along with sialic acid. Coexposure to Zn was found to reduce these alterations.

Pb-induced morphological changes in human RBC were studied by Eriksson and Bering (1993) using electron paramagnetic resonance imaging. These authors reported that Pb ions (a) induced time-dependent changes in MCV and cell shrinkage and (b) inhibited the Gardos effect. Trialkyl-Pb compounds have also been reported to induce hemolytic activity in erythrocytes, with intensity increasing with hydrophobicity of the compounds (Kleszcynska et al., 1997). Serrani et al. (1997) reported that Pb ions confer protection against RBC lysis in hypotonic low ionic strength media, presumably be due to interaction of Pb with certain constituents in the cell membrane. This resistance to erythrocyte lysis was found to significantly increase with Pb (20 to 25 μM) compared to other metals such as Al, Cd, and Zn (Corchs et al., 2001). The Pb-induced reduction in MCV (RBCs derived from umbilical cord) was found to be reversed when the cells were treated with quinidine, an inhibitor of a potassium channel activator, without any effect on resistance to cell lysis, suggesting changes in cell membrane

structure. This effect may also be involved in membrane deformability (Mojzis and Nistiar, 2001).

Heavy metals, including Cd, Zn, and Pb, have been found to alter RBC membrane microviscosity and fluidity (Amoruso et al., 1987). These authors labeled RBC membranes with fluorescent lipid probe all trans 1, 6-diphenyl-1,3,5-hexatriene (DPH) and demonstrated increased polarization with increased membrane lipid viscosity on exposure to heavy metals. They also postulated that such alterations in cell membrane lipid and possibly also protein fluidity may contribute to abnormal cellular function. Similar changes in RBC fluidity were observed in the RBC collected from workers exposed to Pb (Cook et al., 1987). The RBC ghost membranes isolated from Pb- exposed workers exhibited a significant increase in phosphotidylcholine to phosphotidylethanolamine ratio (an established correlate of membrane fluidity) along with an increase in RBC cholesterol levels, as also reported by Jehan and Motlag (1995) discussed above. These authors predict that such alterations in phospholipid composition of the membrane are responsible in biochemical instability of RBC in Pb-exposed workers. Zimmermann et al. (1993) investigated the potential of such membrane lipid alterations to cause resistance to oxidation. These authors induced hyperlipidemia by treating Pb-exposed Wistar rats with triton. They observed an increase in erythrocyte choline phospholipid levels together with a significant decrease in membrane lipid resistance to oxidation. These authors postulated that such a decrease in resistance might cause RBC fragility, and ultimate destruction, leading to anemic conditions. It has been also reported that exposure to Pb may also increase the levels of fatty acids, e.g., arachidonic acid, in the RBC membrane in humans exposed to Pb (Osterode and Ulberth, 2000). Based on the negative correlation between serum calcium and increased arachidonic acid content, these authors postulated that Pb ions might have substituted for calcium in the activation of phospholipase enzymes, leading to increased synthesis of arachidonic acid. Suwalsky et al. (2003) investigated the interaction of Pb with the RBC membrane, utilizing intact as well as isolated unsealed RBC membrane models (representing phospholipids present in the inner and outer layers of the membrane). Electron microscopy, fluorescence spectroscopy, and X-ray diffraction analyses of these models by the authors indicated that Pb particles adhere to both external and internal surfaces of the membrane. Pb ions also have been found to disturb the lamellar organization by causing considerable molecular disorder within lipid layers.

Recently, it has been shown that osmotic shock, oxidative stress, and/or energy depletion activate Ca^{2+}-sensitive erythrocyte scramblase, leading to the exposure of phosphotidylserine at the cell surface. This exposure of phosphotidylserine had been implicated in the phagocytosis of RBC by macrophages that can be measured by annexin binding, as determined by fluorescence activated cell sorting analysis. Kempe et al. (2005) carried out experiments to investigate whether anemic conditions reported in Pb intoxication are the result of the decreased life span of RBCs due to the above mentioned mechanisms. These authors reported that when human RBCs were exposed to Pb-nitrate (above 0.3 μM), it caused a significant increase in Pb annexin binding, indicative of phosphotidylserine exposure. Using inhibitors for Ca^{2+}- sensitive potassium channels and whole cell patch clamp experiments, these authors concluded that Pb exposure increased activation of potassium channels, leading to shrinkage of cells and also activation of scramblase, resulting in the exposure of phosphotidylserine on the cell membrane surface. These authors further postulated that this exposure of phosphotidylserine on the membrane might have led to them being engulfed by macrophages and the ultimately decreased life span of RBCs in Pb intoxication.

Membrane Proteins

Earlier studies by Fukumoto et al. (1983) reported the differential profile for RBC-membrane polypeptides determined by SDS-PAGE analysis. These investigators found decreased levels of polypeptides in band 3 and increases in the levels of four other bands (i.e., bands 2, 4, 6, and 7) in the RBCs of human workers exposed to Pb. From these observations, they postulated that such Pb-induced alteration in RBC membrane proteins may lead to membrane permeability changes. Apostoli et al. (1988) also observed similar changes in RBC membrane polypeptides in Pb-exposed workers and suggested that band 3 may represent an anion channel protein; they also found that these changes occurred at blood Pb levels of >50 μg/100 ml.

Lead exposure has been known to increase the amount of membrane-bound protein kinase C in rat brain, endothelial, and glial cells. Belloni-Olivi et al. (1996) reported an increased phosphorylation of RBC membrane proteins on Pb exposure. When human RBCs were incubated with Pb-acetate (>100 nM) for 60 min, it was found to increase phosphorylation of membrane cytoskeletal proteins (120, 80, 52 and 45 kDa). This increase was accompanied by

increase in protein kinase C activity. Membrane proteins were not phosphorylated when treated with protein kinase C inhibitors. Calcium and diacylglycerol were found not to be involved in this process. The authors suggested that this activation of protein kinase was a direct interaction of the enzyme protein with Pb. Slobozhanina et al. (2005) reported that incubation of human RBCs with Pb-acetate (1 to 10 μM for 3 h) caused differential binding of fluorescent probes to the membrane, suggesting alterations in the physicochemical state of the membrane proteins and lipids. Based on these observations, the authors postulated that such alterations in membrane molecular composition may influence the activity of membrane enzymes and function of receptors and channels present on the membrane. These and other related studies are summarized in Annex Table AX5-2.1.

5.2.3 Effect of Lead on Erythrocyte Heme Metabolism

Enzyme studies of the heme pathway have shown that Pb is an inhibitor of several enzymes involved in heme synthesis, including 5-aminolevulinic acid dehydratase (ALAD), coproporphyrinogen oxidase, and ferro chelatase (see Figure 5-2.1 for a schematic representation of heme biosynthesis). ALAD is a cytoplasmic enzyme that catalyzes the second, rate-limiting step of the heme biosynthesis pathway; that is, ALAD catalyzes formation of porphobilinogen through the conjugation of two molecules of δ-aminolevulinic acid. ALAD is a Zn-dependent enzyme, and thiol groups are essential for its activity (Bernard and Lauwerys, 1987). Decreased erythrocyte ALAD is the most sensitive indicator of human Pb exposure, to the extent that measurement of ALAD activity reflects well Pb levels in the blood. Similarly, erythrocyte ALAD activity measurements have been used to assess Pb toxicity in other species.

Erythrocyte ALAD

Terayama et al. (1986) reported decreased ALAD activity in rat RBCs at blood Pb levels of 100 μg/100 mL. Scheuhammer (1987) studied the usefulness of the ALAD ratio (activated/nonactivated enzyme activity) to study Pb effects in avian RBCs. The ALAD activity ratio is a sensitive, dose responsive measure of Pb exposure regardless of the mode of administration of Pb. For example, dietary Pb concentrations as low as 5 ppm (dry weight) can be estimated through the use of the ALAD enzyme activity ratio method. A highly significant

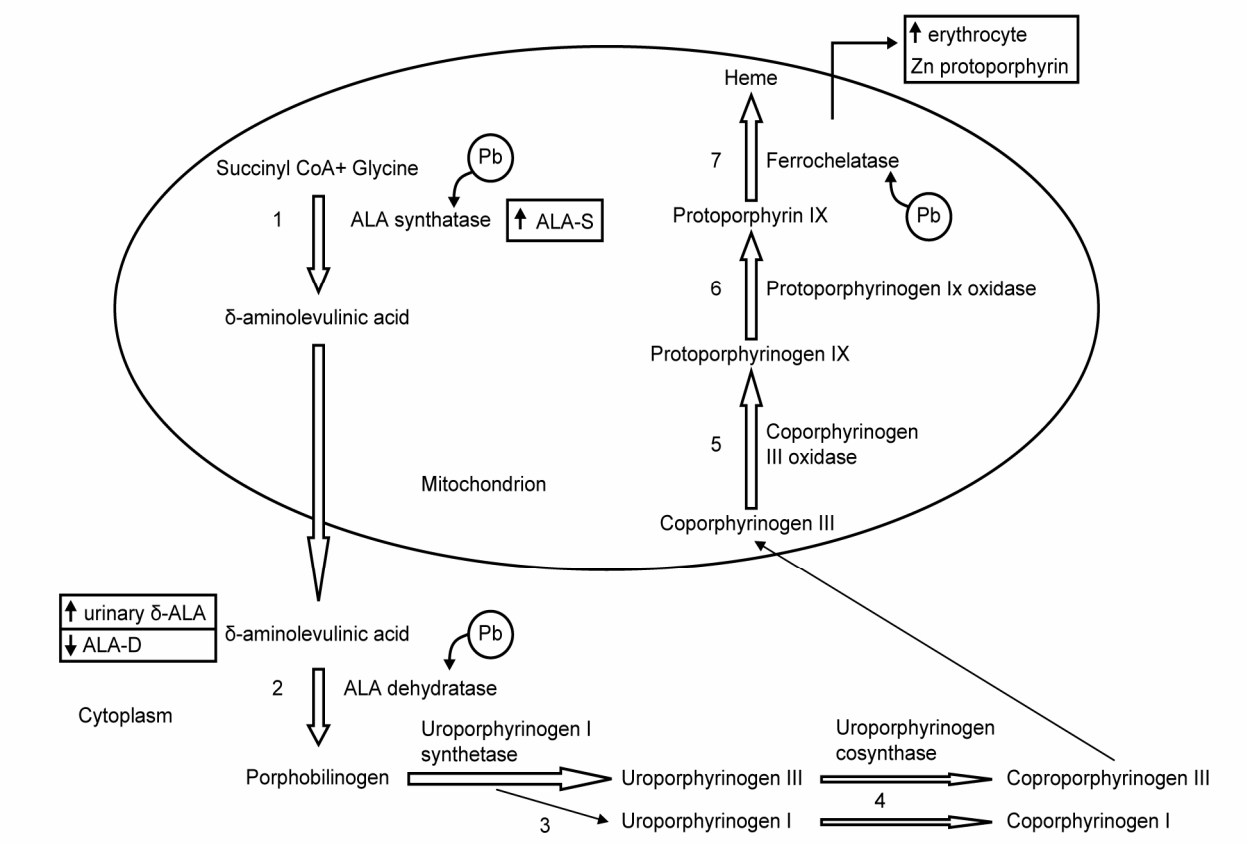


Figure 5-2.1. Schematic presentation of heme synthesis pathway. Potential lead (Pb) interacting sites are indicated by curved arrows (↑ increased, ↓ decreased).

positive correlation was observed between dietary Pb concentration over the 5 to 100 ppm range and the ALAD activity ratio. The author concluded that RBC ALAD ratio may be a useful method for estimating average dietary concentrations of Pb over an environmentally relevant range, in situations where diet is the major source of exposure to Pb or where accurate estimations of dietary Pb are not possible. Redig et al. (1991) reported heme synthetic pathway alterations upon chronic exposure (3 or 11 weeks) to Pb in red-tailed hawks. This treatment resulted in a severe decrease in RBC ALAD activity, which did not return to normal levels until 5 weeks after termination of Pb treatment. Lead exposure also decreased ALAD activity in the bone marrow and in the liver but did not alter aminolevulinic acid synthase activity. Dorward and Yagminas (1994), using comparative enzyme kinetic analysis of ALAD in Pb-exposed female cynomolgus monkeys and human erythrocyte ALAD, found similar inhibition profiles and concluded that ALAD could be a useful model for measuring the biological response in

monkeys. Santos et al. (1999) reported that rat RBC heme biosynthesis was affected by either Pb treatment alone or Pb in combination with ethanol, due to the inhibition of ALAD activity.

Analysis of blood ALAD activity had been used as a powerful clinical biomarker in evaluating Pb toxicity in occupational exposure. Fontanellas et al. (2002) further suggested that this enzyme assay be used in identifying even subclinical Pb poisoning in chronic renal failure (see Section 5.7 for details).

Other Heme Metabolism Enzymes

Taketani et al. (1985) studied the heme synthesizing activity of ferric ion using purified ferrochelatase from rat liver mitochondria and reported that Pb reduced NAD(P)H-dependent heme synthesis by 50% at 10^{-5} M, but that it had no effect when ferrous ion was used as the substrate. Based on these results, the authors concluded that heme synthesis from ferric ion was more susceptible to Pb than the ferrous ion. These studies also revealed that the NAD(P)H oxidizing system reduces ferric ion to ferrous ion, which in turn was used for heme synthesis by ferrochelatase.

The effect of various metals, including Pb, on RBC porphobilinogen synthase (PBG-S) was studied using human RBC hemolysate. Farant and Wigfield (1987) reported that the effect on the enzyme depends on the affinity of the metal for thiol groups at its active sites. Additional studies carried out by the same group utilizing rabbit erythrocyte PBG-S indicated that Pb acts as a potent effector of this enzyme both in vitro and in vivo (Farant and Wigfield, 1990). Human RBC porphobilinogen synthetase activity was found to be inhibited by Pb, while Zn ions activated this enzyme (Simons, 1995). Another enzyme involved in the heme synthetic pathway, porphobilinogen deaminase, was inhibited in human RBC by Pb-nitrate (100 mM) in in vitro studies, but had no effect in vivo (Tomokuni and Ichiba, 1990). Rossi et al. (1992) reported no inhibition of coproporphyrinogen oxidase activity in human lymphocytes on exposure to Pb. Heme synthesis can also be affected in Pb intoxication by interference with Fe transport into reticulocytes. Using a rabbit reticulocyte model, Qian and Morgan (1990) reported that inhibitory effects of Pb on transferrin endocytosis and iron transport across the membrane may also contribute to altered heme metabolism in RBCs. These and other related studies are summarized in Annex Tables AX5-2.2 and 5-2.3.

5.2.4 Effect of Lead on Other Hematological Parameters

The RBC pyrimidine 5-nucleotidase (P5N) catalysis of the hydrolytic dephosphorylation of pyrimidine 5-monophosphates is sensitive to inhibition by Pb. Tomokuni et al. (1989) evaluated the activity of RBC and bone marrow 5-nucleotidase (P5N) and RBC ALAD in mice exposed to drinking water Pb (200 to 500 ppm) for 14 or 30 days. These authors reported that Pb exposure decreased both P5N and ALAD activities in erythrocytes. Additional studies from this group, using a similar exposure regimen, indicated no change in levels of urinary coporphyrins.

Lead exposure (4 mg/kg and 6 mg/Kg body wt/30 days) in splenectomized rats was found to cause depletion of RBC Hb content, to increase numbers of reticulocytes in peripheral blood, and to increase urinary delta aminolevulinic acid excretion (Gautam and Chowdhury, 1987). These authors further reported that the increased number of reticulocytes found in the blood may be due to induced acceleration of the erythropoeitic cell series. Redig et al. (1991) reported biphasic effects of Pb on hematological parameters from their chronic exposure studies in red-tailed hawks over 3 or 11 weeks. These authors observed a rapid and relatively brief increase in RBC free protoporphyrin and a slower, but more prolonged, increase in its Zn complex with 3-week exposure to Pb (0.82 mg/kg body wt). On the other hand, exposure to a higher dose of Pb (1.64 mg/kg body wt) for a longer duration (11 weeks) resulted in a decrease in the Hct and Hb. Panemangalore and Bebe (1996) reported that Zn deficiency increased the Pb-induced accumulation of porphyrin in RBCs to a lesser extent compared to its accumulation in the liver in weaning rats.

The effects of Pb on RBC number and other Hct parameters appear to be dose dependent. Iavicoli et al. (2003) investigated these effects by feeding mice with eight different doses of Pb below (0.6 to <2.0 μg/dL) and above (>2.0 to13 μg/dL) normal background levels. These authors reported that mice receiving below normal background levels of dietary Pb displayed enhanced RBC counts and increased Hb and Hct values, whereas a marked decrease in RBC number occurred when blood Pb levels approached 10 μg/dL. Sivaprasad et al. (2003) also reported significant reductions in RBC Hb content and Hct on Pb exposure (0.02% Pb-acetate in drinking water for 5 weeks). Toplan et al. (2004) observed significant decreases in RBC Hb content and Hct and increases in blood viscosity in Wistar rats after 5-week exposure to Pb. Studies cited above are summarized in Annex Table AX5-2.4.

5.2.5 Effects of Lead on Erythrocyte Enzymes

The toxic effects of Pb on RBCs result from its complexation with the sulfhydryl, carboxyl, and imidazole groups of proteins, particularly enzymes, by competitive binding of Pb^{2+} with Zn^{2+} or Mg^{2+} in metalloenzymes. This binding of Pb to enzyme proteins can inhibit enzymes involved in the glycolytic and pentose phosphate pathway, both of which are sources of energy compounds and intermediates of purine conversion, thus causing a disruption of energy metabolism. Along with these changes, Pb-induced changes in the membrane integrity, as discussed earlier (Section 5.2.1), may also affect the enzymes' associated ion channels and other transport mechanisms.

Energy Metabolism

Erythrocytes generate high-energy ATP by anerobic glycolysis and cycle oxidized and reduced nicotinamide adenine nucleotide phosphate (NADP) by the aerobic pentose phosphate pathway. Anemic conditions associated with Pb poisoning, along with the inhibitory effects of Pb on heme synthesis, may result in increased RBC destruction due to the inhibitory effects of Pb on the activities of the enzyme, pyramidine 5-nucleotidase (P5N). Deficiency of this enzyme is characterized by intracellular accumulation of pyramidine-containing nucleotides, leading to hemolysis. Inhibition of this enzyme along with the perturbations in heme metabolism create imbalances in the energy currency of the erythrocyte. Perturbations in energy metabolism can be followed by changes in the concentration of purine nucleotides. In erythrocytes, these compounds cannot be synthesized de novo, they can only be reconstructed from preexisting free purine bases on nucleosides through salvage type reactions. The cell energy content can be measured by adenylate (ATP + ADP + AMP) and guanylate (GTP + GDP + GMP) nucleotides, and by their sum total. The concentrations of nucleoside monophosphates increase in cases of cell energy deficit, but they quickly degrade to nucleosides and bases.

Cook et al. (1987) compared P5N and deoxypyramidine-5-nucleotidase levels in the RBC of Pb-exposed workers and matched controls and reported significantly lower levels of P5N in Pb-exposed workers. Konantakieti et al. (1986) reported similar observations in neonatal rat RBCs. These authors further indicated that the low levels of nucleotides were due to inhibition of P5N activity by Pb, as the depression in enzyme activity was correlated with blood Pb levels. This was further validated by in vitro inhibition of P5N in a dose-dependent manner. Tomokuni

and Ichiba (1987) found similar results with human RBCs both in vitro and in vivo. They reported activation of Pb-exposed human RBCs. Antonowicz et al. (1990) observed significantly higher levels of glycolytic enzymes and increased production of lactic acid and 2,3-diphospho glycerol, when human RBCs were incubated with Pb. Based on their observations, these authors suggested that Pb exposure may result in anaerobic glycolysis activation in human RBCs. In contrast, Grabowska and Guminska (1996) reported that Pb exposure diminished the ATP levels in human RBCs by inhibiting aerobic glycolysis.

Erythrocyte energy metabolism in workers exposed to heavy metals, but without clinical manifestations of toxicity, was found to intensify and become more pronounced when they were occupationally exposed to Pb. Nikolova and Kavaldzhieva (1991) measured the exposed workers and reported higher ratios of ATP/ADP in Pb-exposed workers. Because the RBC energy pool is perturbed due to Pb exposure, Morita et al. (1997) evaluated the effect of Pb on NAD synthetase and reported an apparent dose-dependent decrease in NAD synthetase activity in the erythrocytes of Pb exposed workers.

Baranowska-Bosiacka and Hlynczak (2003) evaluated Pb effects on distribution profiles of adenine, guanine nucleotide pools and their degradation products in human umbilical cord RBCs. In vitro exposure equivalent (Pb-acetate; 100 to 200 μg/dL) to Pb exposure for 20 h were found to significantly lower the levels of nucleotide pools, including NAD and NADP, accompanied by a significant increase in purine degradation products (adenosine, guanosine, inosine, and hypoxanthine). Associated morphological RBC alterations were also observed, with marked significant increases in stomatocytes, spherocytes, and echinocytes. These investigators also observed similar alterations in the nucleotide pools in Wistar rat RBCs with short-term exposure to Pb (Baranowska-Bosiacka and Hlynczak, 2004). Based on these observations, the authors postulated that decreases in NAD and NADP concentrations in RBCs may be a good indicator of Pb-induced disturbance in the energy process and can serve as a useful marker for chronic Pb exposure. If NAD synthetase activity had been measured in these studies, it might have provided experimental support for the observation of inhibition of NAD synthetase reported by Morita et al. (1997).

Other Enzymes

Lead-induced efflux of K^+ from human RBCs had been recognized as being due to the ability of Pb to selectively increase the membrane permeability for this cation. Studying the efflux of ^{86}Rb using inside-out RBC vesicles, Alvarez et al. (1986) demonstrated that Pb promoted the selective efflux of K^+ ions by altering the sensitivity of Ca^{2+} binding site on the membrane either by direct binding or by altering Mg^{2+}-mediated modulation. Fehlau et al. (1989) indicated that this modulation of the Ca^{2+}-activated K^+ channel in human RBCs coincides with the activation of RBC membrane-bound oxidoreductase. These authors suggested that, even though these two are independent events, the oxidoreductase enzyme activity may influence K channel gating.

Earlier studies by Mas-Oliva (1989) on the potential effects of Pb on the RBC membrane (using RBC ghosts) indicated that Pb has inhibitory effects on Ca^{2+}-Mg^{2+}-ATPase. Further investigations on the role of calmodulin in the inhibition of Ca^{2+}-Mg^{2+}-ATPase indicated that the inhibitory activity on the enzyme may be due either to the effect of Pb on sulfhydryl groups on the enzyme or by direct binding to calmodulin.

Jehan and Motlag (1995) reported that when albino rats were administered Pb i.p (5 or 20 mg/kg body wt) for 14 consecutive days either alone or in combination with Cu (2 mg/kg body wt) or zinc (5 mg/kg body wt), there were severe decreases in RBC membrane enzyme, acetylcholine esterase (AchE), NADH dehydrogenase, and Na^+-K^+ ATPase levels along with decreases in phospholipid content, hexose, and hexosamine. Of the combined metal treatment exposure regimens, Zn was found to considerably reduce such changes. Grabowska and Guminska (1996) assayed three ATPase activities (i.e., Na^+-K^+ ATPase, Mg^{2+}-ATPase, and Ca^{2+}-ATPase) in human RBC in vitro and reported RBC Na^+-K^+ ATPase to be the only enzyme inhibited by Pb, while Ca^{2+} or Mg^{2+}ATPases were not sensitive to Pb. On the other hand, Sivaprasad et al. (2003) observed Pb-induced reductions in RBC activities of the three of those ATPase activities.

Two reports by Calderon-Salinas et al. (1999a,b) indicated Pb effects on calcium transport in human RBC. Initial studies by this group indicated that Pb and Ca are capable of inhibiting the passive transport of other metals in a noncompetitive way. Inhibition studies using N-ethyl-maleimide indicated that Pb and Ca share the same permeability pathway in human RBCs and that this transport system is electrogenic (Calderon-Salinas et al., 1999a). Additional studies by

the same group reported that Pb is capable of inhibiting Ca efflux by inhibiting Ca-ATPase (Calderon-Salinas et al., 1999b). These authors further suggested that under physiological conditions, Pb, via Ca^{2+}-ATPase, alters Ca influx, while chronic Pb intoxication inhibits Ca efflux by altering RBC calcium homeostasis. Silkin et al. (2001) reported Pb-induced activation of K channels in the RBCs of the teleost fish *S. porcus*. Exposure of teleost fish RBCs to 1 to 2 μM Pb led to a minor loss in cellular K^+; but, at 20 to 50 μM Pb, about 70% of cellular K^+ was lost. Based on their observations of Pb-induced K^+ efflux from RBCs under competitive and inhibitory regimens, these authors suggested that Pb activates RBC K^+ channels.

Eder et al. (1990) and Loipfuhrer et al. (1993) investigated activity levels of Ca^{2+}-ATPase and calcium accumulation, respectively, in Pb-depleted rat RBCs. No alteration in Ca^{2+}-ATPase activity or Ca accumulation was observed in the P0 generation (Eder et al., 1990). On the other hand, significant reduction in Ca-ATPase activity was observed in the F1 generation. It was suggested that Pb-induced alterations in the metabolism of phospho- and glycoproteins result from Pb depletion and may be responsible for the reduced enzyme activity. Both of the groups postulated that the decreased MCV observed in Pb depleted rat RBCs could be due to reduced Ca^{2+}-ATPase activity in the RBCs. These and other related studies are summarized in Annex Tables AX5-2.5 and 5-2.6.

5.2.6 Erythrocyte Lipid Peroxidation and Antioxidant Defense

Although several mechanisms have been proposed to explain Pb toxicity, no mechanisms have been defined explicitly. Recent literature on Pb toxicity suggests oxidative stress as one of the important mechanisms for toxic effects of Pb in various organs. Because RBCs accumulate major amounts of Pb compared to other tissues, oxidative stress may also result in the accentuation of lipid peroxidation with concomitant inhibition of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, GSH peroxidase, GSH reductase, and simultaneous increases in oxidized GSH (GSSG) and reduced GSH/GSSG ratios. Pb-induced lipid peroxidation and the mitigating effects of experimental chelation therapy are discussed with relevance to each tissue or organ within this chapter. The discussion focuses on the available literature with reference to studies on erythrocytes.

Patra and Swarup (2000) reported significant changes in RBC lipid peroxide levels and anti oxidant defense (SOD and catalase) levels in RBC hemolysates from male calves exposed to

Pb (7.5 mg/kg body wt for 28 days). These authors suggested the potential role for increased peroxide levels in Pb-induced alterations in RBCs. Mousa et al. (2002) investigated the levels of various antioxidant enzymes, thiols, lipid peroxide in erythrocytes, and total thiol status of plasma in goats exposed to Pb (Pb-acetate, 5.46 mg/kg body wt for 2 weeks). These authors reported that all the parameters referred above were significantly increased in RBCs by day 7 and receded to normal levels by day 14, while peroxides remained significantly increased even by day 14. Based on these observations, it was suggested that Pb-induced lipid peroxide generation in RBCs appears to be a continuous process and can lead to persistent oxidative stress in RBCs with chronic exposure.

Metal chelator agents have been used clinically to reduce internal Pb body burden. These agents form an insoluble complex with Pb and are excreted. Though the majority of studies on the clinical potential of various experimental agents, including certain antioxidants, have been extensively performed mainly in relation to toxicity associated with hepatic and kidney tissues, such studies have also considered their potential effects on heme metabolism and blood Pb levels (see Sections 5.7 and 5.10). In the following paragraphs, two recent representative studies in experimental animals that specifically assessed the protection conferred to erythrocytes are described.

El-Missiry (2000) investigated the protective role of the pineal hormone, melatonin, on Pb-induced suppression of heme synthesis as a consequence of reduced antioxidant status. Intramuscular injection of Pb-acetate (10 mg/kg body wt for 7 days) caused a significant reduction in heme synthesis with decreased blood Hb levels and decreased RBC and liver ALAD. Pretreatment of rats with melatonin (30 mg/kg body wt) intragastrically prevented the suppressive effects of Pb on RBC heme metabolism by conferring protection to the antioxidant capacity of the cells and also by scavenging free radicals generated by Pb intoxication.

Sivaprasad et al. (2003) studied the protective effects of dl-alpha-lipoic acid (LA, 25 mg/kg body wt) and meso-2,3-dimercaptosuccinic acid (DMSA, 25 mg/kg body wt); and they found such treatments, either alone or in combination for a week, had an effect on alterations in RBC functions induced by Pb-acetate (0.02% in drinking water for 5 weeks). These authors reported that treatment with LA or DMSA, alone or in combination, reversed Pb-induced increased LPO and reductions in Hb and Hct, along with changes in other biochemical parameters affected by Pb treatment. These authors further concluded that combined treatment

was much more potent and effective. These and other related studies are summarized in Annex Table AX5-2.7.

5.2.7 Summary

- The 1986 Pb AQCD reported that the activity of ALAD appeared to be inversely correlated to blood Pb values and was found inhibited in several tissues. Human studies reviewed in 1986 Pb AQCD also indicated that occupational exposure to Pb results in decreased RBC survival along with alterations in RBC membrane integrity and energetics.

- More recent studies reviewed in this AQCD indicate that the transport of Pb across the RBC membrane is energy-independent, carrier-mediated and that the uptake of Pb is mediated by an anion exchanger through a vanadate-sensitive pathway.

- Lead intoxication interferes with RBC survival and alters RBC mobility. Hematological parameters, such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), are also significantly decreased upon exposure to Pb. These changes are accompanied by decreased membrane sialic acid content.

- Morphological analyses using electron paramagnetic resonance imaging and spin labeling techniques indicate that changes occur in RBC morphology upon Pb exposure.

- Lead-induced RBC membrane lamellar organization and decreases in membrane lipid resistance to oxidation in rats appear to be mediated by perturbations in RBC membrane lipid profiles. Similarly, Pb-induced altered phosphorylation profiles of RBC membrane proteins have been reported.

- Erythrocyte ALAD activity ratio (ratio of activated/non activated enzyme activity) has been shown to be a sensitive, dose-responsive measure of Pb exposure, regardless of the mode of administration of Pb. Competitive enzyme kinetic analyses in RBCs from both human and Cynomolgus monkeys indicated similar inhibition profiles by Pb.

- Consistent observation of Pb-mediated inhibition of pyramidine 5′-nucleotidase (P5N) suggests this enzyme as a potential biomarker for Pb exposure.

- Significant reductions in levels of nucleotide pools (e.g., NAD and NADP) accompanied by significant increase in purine degradation products have been implicated in the Pb-induced altered energetics of RBCs.

- Lead-induced increased permeability for K^+ in RBCs appears to be due to the selective efflux of K^+ ions on the RBC membrane due to altered sensitivity of the Ca^{2+}-binding site on the membrane. Erythrocyte Na^+-K^+ ATPase appears to be more sensitive to Pb-induced inhibition than Ca^{2+}-Mg^{2+} ATPase.

- Chelation agents and the pineal hormone, melatonin, have been reported to confer protection against Pb-induced lipid peroxidation and increased antioxidant defense in RBCs.

The newly available (since 1986) scientific evidence presented in this section convincingly demonstrates deleterious effects of lead on erythrocyte cell morphology, function, lead uptake and alterations in certain enzymes involved in heme synthetic pathways. However, some of the interesting and important conclusions are derived mainly from in vitro studies, often using short time incubations. It would be useful to substantiate such findings further by more systematic studies employing meaningful experimental designs for in vivo evaluation of laboratory animal models.

5.3 NEUROLOGICAL/NEUROBEHAVIORAL EFFECTS OF LEAD

5.3.1 Neurotoxicological/Neurobehavioral Effects of Lead in Animals

5.3.1.1 Introduction

Since the initial description of Pb encephalopathy in the developing rat in the mid-1960s, (Pentschew and Garro, 1966), a continuing research focus has been on defining the extent of CNS involvement at subencephalopathic, environmentally relevant, levels of exposure. These efforts have primarily addressed the developing organism, consistent with the primary public health concerns for neurotoxicity from Pb during this period. While significant research advances have been made in animal studies over the last four decades, relating these findings to neurotoxicity in children has been challenging and difficult. The barriers to greater progress have primarily been due to Pb's multiple toxic mechanisms of action in brain tissue, which encompasses variable, overlapping, and, at times, opposing dose-effect relationships. One goal of this section is to bring greater clarity to the current state of knowledge.

The Pb neurotoxicity evidence available for assessment in the 1986 Lead AQCD was considerably different in character from current, newly available findings. The literature was dominated by various types of assessments of CNS biogenic amine function in exposed animals, with dopaminergic neuronal systems seeming the most sensitive to the metal and drawing the most attention. In addition, the prevailing wisdom was that the neuronal actions of Pb were best

elucidated by perturbing neurotransmitter systems with CNS agents of known mechanism of action and comparing the responses in exposed animals to those in control subjects, an approach of limited value. Only some of those studies reported blood and/or brain Pb concentrations along with the experimental findings, rendering interpretation of results across different laboratories difficult and somewhat unreliable.

As of 1986, perhaps the most reliable evidence concerned the effects of acute exposure to Pb^{2+} in vitro on voltage-sensitive Ca^{2+} channel function in the nerve cell membrane, developed to a great extent by Cooper and co-workers (Kober and Cooper, 1976; Cooper and Manalis, 1984; Suszkiw et al., 1984). Using neuromuscular endplate or synaptosomal preparations, these studies demonstrated that Pb^{2+} interfered with Ca^{2+} influx through voltage-sensitive channels. These findings significantly advanced the field, though acute exposure in vitro bore little resemblance to environmentally relevant routes and magnitudes of exposure.

In the ensuing two decades, the Pb neurotoxicity literature has reflected an increased focus on cognitive-related mechanisms and the refinement of approaches and methodologies. Exposure-induced alterations at glutamatergic synapses have become a primary substrate of attention. Synaptic plasticity models (e.g., long-term potentiation [LTP]) developed in the 1990s are used in Pb studies in laboratories around the world. Behavioral paradigms, refined to more consistently discriminate Pb effects, aided in identifying optimal testing conditions and developmental periods for exposure. The cumulative result of these advances has lead to clearer understanding of likely mechanisms underlying Pb-induced cognitive impairments found in Pb-exposed children.

The Pb neurotoxicity evidence reviewed in this section is organized largely according to scientific discipline: neurochemical alterations involving glutamatergic, cholinergic, and dopaminergic function; mechanisms defined by neurophysiological approaches; changes in auditory and visual function; modifications in behavioral function; induced alterations in cellular morphology; and findings on cellular disposition of Pb. This type of organization permits a more focused analysis of a very extensive, broad literature.

5.3.1.2 Neurochemical Alterations Resulting from Lead Exposure

The following areas of investigation have drawn the most attention in the Pb neurotoxicity field over the last 20 years. A summary of the key studies evaluating neurochemical alterations resulting from Pb exposure are listed in Table AX5-3.1.

Lead and Neurotransmitter Release Processes

By the mid-1980s, it was evident that acute exposure to Pb^{2+} in vitro reduced the magnitude of depolarization-induced transmitter release, apparently by inhibiting Ca^{2+} influx into the nerve ending through voltage-sensitive Ca^{2+} channels (Kober and Cooper, 1976; Cooper and Manalis, 1984; Suszkiw et al., 1984). Since then, several investigators utilizing various preparations (Shao and Suszkiw, 1991 [cortical synaptosomes]; Tomsig and Suszkiw, 1993 [bovine chromaffin cells]; Braga et al., 1999a,b [cultured hippocampal cells]; Westerink and Vijverberg, 2002 [PC12 cells]), have demonstrated that, in the absence of Ca^{2+}, Pb^{2+} exhibits Ca^{2+}-mimetic properties in stimulating exocytosis and is substantially more potent in doing so. That is, in the absence of Ca^{2+} and depolarization, nM concentrations of Pb^{2+} alone stimulate transmitter release. Many investigators have proposed that this action, in conjunction with the ability of Pb^{2+} to suppress evoked release, produces a higher noise level in synaptic transmission in Pb-exposed animals.

The ability of Pb to diminish stimulated transmitter release has been demonstrated in intact chronically exposed animals via the use of intracerebral microdialysis (Kala and Jadhav, 1995; Lasley and Gilbert, 1996; Lasley et al., 1999). More recently, Lasley and Gilbert (2002) used Ca^{2+}-free perfusate containing a Ca^{2+} channel antagonist for microdialysis to identify the Ca^{2+}-independent component of release. These workers demonstrated that under these conditions high K^{+}-stimulated glutamate and GABA release were *elevated* in chronic high level Pb-exposed animals, suggesting a Pb^{2+}-induced enhancement of evoked release. It was concluded that this pattern of results indicated the presence of two actions of Pb on transmitter release in vivo: (1) a more potent suppression of stimulated release seen at lower exposure levels (associated with blood Pb values of 27-62 µg/dL) combined with (2) Ca^{2+}-mimetic actions that independently induce the exocytosis seen at higher exposure levels (associated with blood Pb values $\geq$62 µg/dL). Together, these two actions produce a biphasic dose-effect relationship (see

Figure 5-3.1). Thus, there is good correspondence between findings in in vitro and in vivo studies with respect to the actions of Pb on transmitter release.

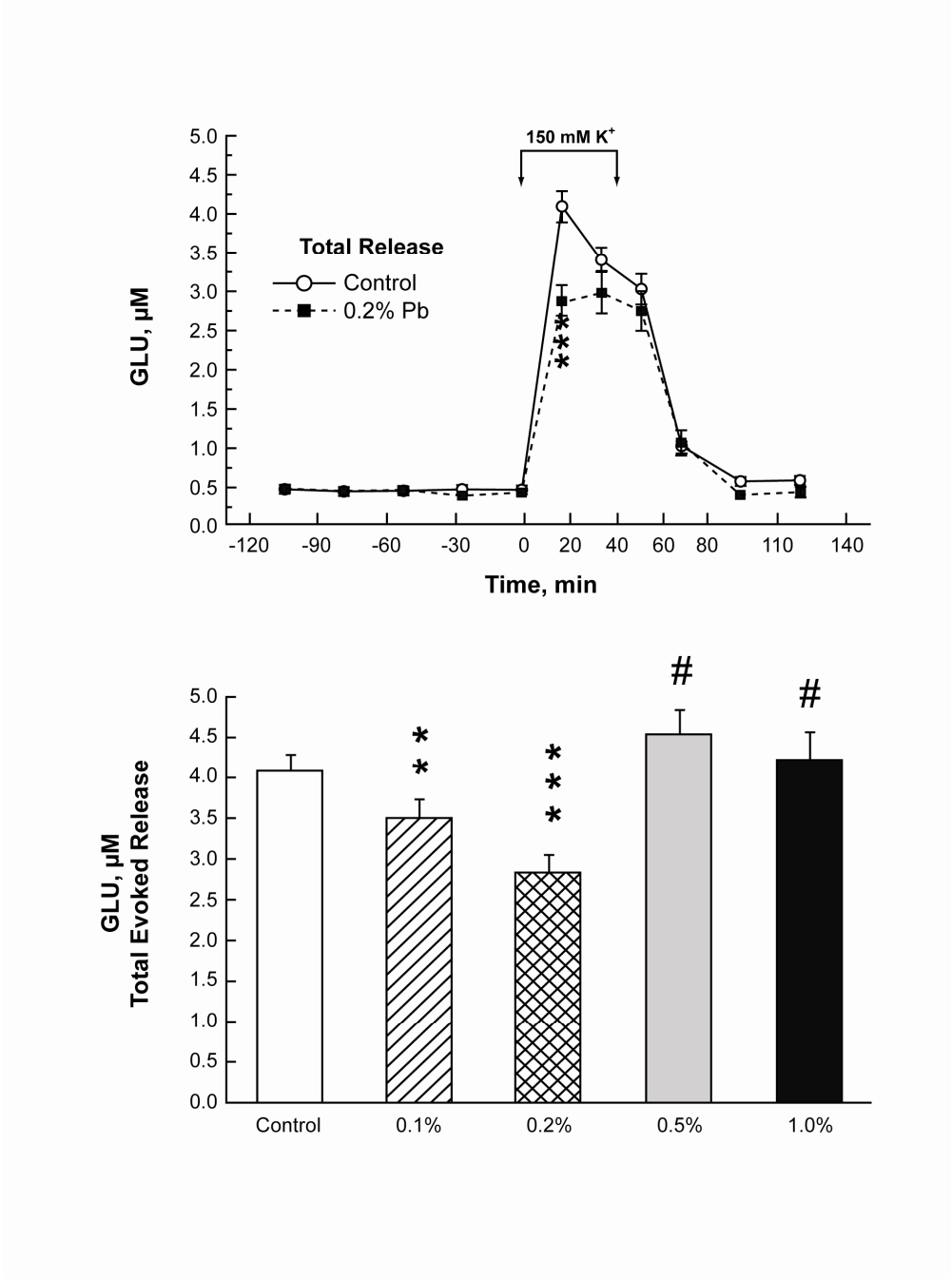


Figure 5-3.1. Time course of extracellular GLU concentration and GLU concentration in response to lead exposure.

*** p<0.001; ** p<0.01 relative to the GLU concentration in control animals; #p<0.0001 relative to the GLU concentration in the 0.2% Pb group.

Source: Lasley and Gilbert (2002).

Lead and Glutamatergic NMDA Receptors

Because of the established importance of the NMDA subtype of glutamate receptor in synaptic plasticity and learning, these receptors have been a focus of intense interest in Pb neurotoxicity for the last 15 years. Using whole cell and single channel patch clamp methodologies, Alkondon et al. (1990) were the first to report that Pb^{2+} inhibited the function of the NMDA receptor channel complex. Guilarte and Miceli (1992) reported similar findings using nominal Pb^{2+} concentrations and receptor binding techniques, and drew parallels between Zn^{2+} Ca^{2+2}- and Pb^{2+}-induced inhibition of the channel. However, Lasley and Gilbert (1999), using free Pb^{2+} ion concentrations and radioligand binding, demonstrated that, despite the similarities, Pb^{2+} did not inhibit the NMDA receptor channel complex by binding to the Zn^{2+} allosteric site. Furthermore, they indicated that the Pb^{2+} IC_{50} of 0.55 μM for inhibition of the channel complex was likely approximately two orders of magnitude greater than the extracellular fluid concentrations of Pb^{2+} associated with environmentally relevant exposure. This does not mean that NMDA receptor function does not change after Pb exposure, but it strongly suggests that the alterations are not based on a direct Pb^{2+} action.

Unfortunately, a consensus on the effects of chronic Pb exposure on NMDA receptor expression and function has not been achieved. Extensive effort has been invested to assess NMDA receptor subunit mRNA and protein expression in exposed animals (Guilarte and McGlothan, 1998; Nihei and Guilarte, 1999; Guilarte et al., 2000; Nihei et al., 2000; Toscano et al., 2002; Guilarte and McGlothan, 2003), but consistent findings have not emerged. An exception was perhaps the work of Nihei et al. (2000) who found decreases in hippocampal NR1 subunit mRNA and protein expression deficits in LTP to be associated with impaired spatial learning in PB-exposed animals. Correlations of this type with functional measures are valuable in validating the biochemical observations.

While exposure-induced alterations of NMDA receptor binding have been observed in multiple laboratories, there has not been uniform agreement as to the direction of change. Upregulation of NMDA receptor density has been observed in rats continuously exposed throughout development (Ma et al., 1997; Lasley et al., 2001), but receptor downregulation has also been reported when exposure was begun immediately postweaning (Cory-Slechta et al., 1997a). The results of behavioral investigations are best explained by increases in NMDA receptor density. Cohn and Cory-Slechta (1993, 1994b), using a repeated learning component of

a multiple reinforcement schedule, observed enhanced performance sensitivity to exogenous NMDA administration and diminished sensitivity to MK-801, an NMDA receptor antagonist in exposed animals. The same findings resulted when the drug discrimination paradigm was utilized (Cory-Slechta, 1995a; Cory-Slechta et al., 1996b): enhanced sensitivity to NMDA and reduced sensitivity to MK-801 in Pb-exposed groups. A decreased sensitivity to MK-801 can result from either increased numbers of NMDA receptors or a diminished access of the antagonist to its binding site in the ion channel. Thus, all these behavioral observations may be accounted for by Pb-induced increases in NMDA receptor density resulting in increased sensitivity to agonists coupled with decreased sensitivity to antagonists. That is, the functional measures suggest that an NMDA receptor upregulation occurs.

Pb^{2+} and Protein Kinase C

Another important focus area for Pb neurotoxicity research has been the interactions of Pb^{2+} with protein kinase C (PKC) activity. Markovac and Goldstein (1988a) were the first to report that Pb^{2+} directly stimulated PKC activity at picomolar concentrations, thereby exhibiting greater potency for this action than Ca^{2+} by 4-5 orders of magnitude. Long et al. (1994) made similar observations using free Pb^{2+} and Ca^{2+} ion concentrations and nuclear magnetic resonance spectroscopy, resulting in an EC_{50} of 55 pM for Pb^{2+} stimulation of PKC. These workers also presented evidence suggesting that the maximal efficacy of Pb^{2+} was less than that of Ca^{2+}, despite its greater potency. Tomsig and Suszkiw (1995) elegantly elucidated multiple interactions of Pb^{2+} with PKC, identifying both stimulatory (affinity in the pM range) and inhibitory (affinities in the nM and μM range) binding sites on the kinase. They also showed that, on the basis of these interactions, Pb^{2+} induced a peak efficacy for stimulation of PKC that was only ~40% of the maximal efficacy produced by Ca^{2+}, leading to their terming Pb^{2+} a partial agonist of the kinase, as reflected in Figure 5-3.2.

Subsequent studies have begun to examine the cellular impact of the Pb^{2+} effects on PKC. Kim et al. (2000) showed that acute Pb^{2+} exposure in vitro stimulated immediate early gene expression in cultured cells by a mechanism that requires PKC. Braga et al. (2004) have demonstrated that Pb^{2+} stimulation of PKC results in inhibition of nicotinic cholinergic modulation of glutamate and GABA synaptic transmission in cultured hippocampal cells. It is anticipated that future studies will further develop this line of investigation.

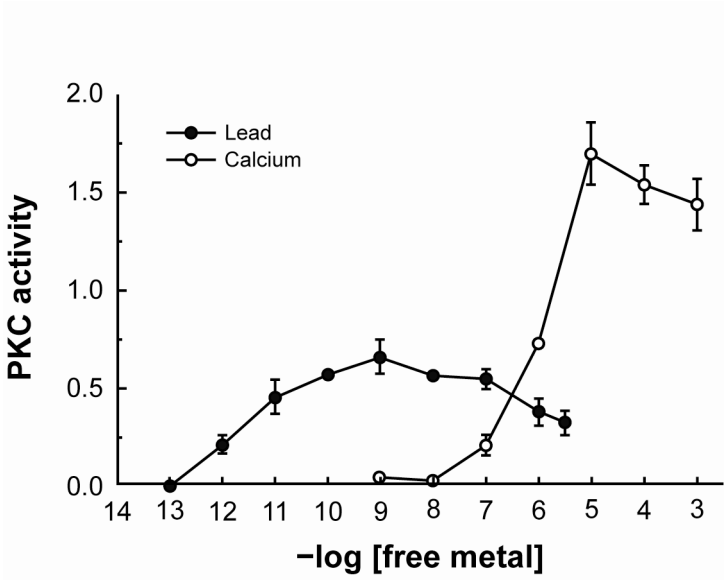


Figure 5-3.2. PKC activity as a function of Ca^{2+} and Pb^{2+} concentrations.

Source: Tomsig and Suszkiw (1995).

The effects of chronic Pb exposure on PKC signaling have been more difficult to discriminate. Most investigators have utilized broken cell preparations and measures of either kinase translocation or enzyme activity; however, a broken cell preparation has not been shown to simulate the intracellular milieu of a chronically exposed intact animal. In the preparation of a tissue extract for determination of kinase activity, the unbound Pb^{2+} is removed or greatly diluted, so that the resulting activity measure largely reflects changes in total PKC expression resulting from the exposure. That is, this measure does not identify a synaptic pool of PKC or necessarily represent the pool of kinase involved in signal transduction. Alternatively, the translocation of kinase from a cytosolic to membrane cellular fraction is a somewhat nonspecific measure and observed changes should be independently confirmed. From the effects of acute Pb^{2+} exposure in vitro it is abundantly clear that PKC is a toxicologically significant intracellular target for Pb^{2+}. However, various investigators have been unable to define how this acute effect translates, if at all, to chronic exposure in the intact animal. Neither is it evident how one could discriminate inhibition of PKC activity (e.g., resulting from decreased efficacy relative to that associated with Ca^{2+}) from downregulation of the enzyme from prolonged stimulation. Resolution of these issues awaits the development of more specific methodologies.

Pb^{2+}-Ca^{2+} Interactions

In general Pb^{2+}-Ca^{2+} interactions have long been proposed as important factors in manifestations of cellular Pb toxicity and have been under investigation since before the 1986 AQCD was prepared. The classical effects of Pb^{2+} mentioned earlier include inhibiting Ca^{2+} influx through cell membrane voltage-sensitive Ca^{2+} channels and exhibiting Ca^{2+}-mimetic properties at multiple intracellular proteins. In addition, Pb^{2+} is known to disturb intracellular Ca^{2+} homeostasis (Simons, 1993b). Ca^{2+}-dependent proteins whose actions have been reported to be stimulated by Pb^{2+} include calmodulin and calmodulin-dependent phosphodiesterase (Goldstein, 1993), calcineurin (Kern and Audesirk, 2000), and Ca^{2+}-ATPase (Ferguson et al., 2000). These actions of Pb^{2+} are thought to be the points of initiation of much of the metal's cellular toxicity.

Lead Exposure and Cholinergic Neuronal Systems

The actions of chronic exposure have also been studied with respect to changes in CNS cholinergic systems, as another substrate thought to underlie cognitive function. Bielarczyk et al. (1996) reported (a) decreased functional cholinergic innervation in the hippocampus and (b) depression of choline acetyltransferase activity in hippocampus and cortex in young adult rats exposed to Pb only during early development. Similar changes were reported by Bourjeily and Suszkiw (1997), leading to the conclusion that perinatal exposure results in a loss of septohippocampal cholinergic projection neurons that persists until testing in young adulthood. Tian et al. (2000) exposed PC12 cells to Pb^{2+} for $\leq$48 h and found that the downregulation of choline acetyltransferase activity reflected the effects of the metal at the level of gene expression. Consistent with these other findings, Jett et al. (2002) employed a similar perinatal exposure protocol and observed increased nicotinic receptor binding in multiple brain regions. These reports reinforce the belief that Pb exposure during early development deleteriously affects cholinergic function and indicate that these actions are an important component of the cognitive impairment resulting from exposure to the metal.

Summary

In reviewing the Pb neurotoxicity literature of the last 20 years and the research focus areas presented above, it is evident that the effects of Pb exposure on components of

neurotransmitter release and Pb^{2+}-Ca^{2+} interactions are closely intertwined. Exposure-induced decreases in glutamatergic, cholinergic, and dopaminergic transmission are most prominent because of the purported role of these neuronal systems in brain development and cognitive function. In contrast, the weight of the data suggest an upregulation of NMDA receptors resulting from chronic exposure, but a consensus on the effects of Pb on expression and function remains to be attained, and it is increasingly apparent that this glutamate receptor subtype may not be a primary target of chronic exposure in the intact animal. While the in vitro interactions of Pb^{2+} and PKC have been carefully described and are broadly relevant to cellular signaling pathways, meaningful and valid observations of the functional effects of these interactions in intact animals have not been achieved.

5.3.1.3 Actions of Lead Exposure Defined by Neurophysiological Approaches

One of the most significant advances in Pb neurotoxicity research over the last two decades is the widespread application of synaptic plasticity models to studies of the effects of exposure. Key studies are listed in Table AX5-3.2. The incorporation of these paradigms into Pb studies could be seen as a natural progression, and one might expect that they would receive greater use in neurotoxicology, as they have in the broader field of neuroscience.

Chronic Lead and Models of Synaptic Plasticity

Throughout the 1990s, the LTP model of synaptic plasticity was utilized in studies of Pb neurotoxicity in laboratories around the world, undoubtedly because it was widely accepted that the model invoked synaptic processes that also were involved in learning and cognitive function. These investigations resulted in large body of evidence that characterized the actions of chronic exposure across several experimental parameters (see Table 5-3.1). Furthermore, at least in the hippocampal subregions, CA1 and dentate gyrus, there was uniform agreement as to the alterations that resulted.

Chronic developmental Pb exposure decreased the magnitude of LTP and increased the threshold for induction (Altmann et al., 1993; Gilbert et al., 1996; Gutowski et al., 1998; Ruan et al., 1998). Simultaneous assessments of paired-pulse functions also uncovered reductions in paired-pulse facilitation, indicative of reduced glutamate release (Lasley and Gilbert, 1996;

Table 5-3.1. Chronic Lead Exposure and LTP

Recording Site	Exposure Period[1]	Blood Pb[2]	Brain Pb[3]	Preparation	Effect of Exposure on LTP
Hippocampal Dentate Gyrus					
Gilbert et al. (1996)	P0 – P90-120	37.2	ND	in vivo	elevated induction threshold
Ruan et al. (1998)	P0 – P90-115	30.1	180	in vivo	diminished magnitude
Gilbert et al. (1999a)	G16 – P130-210 P30 – P130-210	40.2 38.7	378 350	in vivo	elevated induction threshold and diminished magnitude
Gilbert et al. (1999b)	G16 – P120-180	26.8[4] 40.2 61.8	220 378 670	in vivo	elevated induction threshold and diminished magnitude
Gilbert and Mack (1998)	G16 – P210-540	ND	ND	in vivo	accelerated decay
Hippocampal CA1					
Altmann et al. (1993)	G0 – P70-210	14.3	160	slices	blocked, required exposure during early development
Gutowski et al. (1998)	G0 – P90-130	16.0	135	slices	diminished magnitude
Hippocampal CA3					
Gutowski et al. (1997)	G0 – P13-140	28.5	180	slices	no effect across 4 ages
Gutowski et al. (1998)	G0 – P90-130	16.0	135	slices	no effect

[1]Exposure duration in terms of gestational (G) or postnatal (P) days of age; P0 = day of birth.
[2]Values expressed as μg/100 ml.
[3]Values expressed as ng/g tissue.
[4]Different blood Pb values generated by differing levels of exposure.

Ruan et al., 1998). It was also shown that the potentiation produced in Pb-exposed animals decayed more rapidly than in controls (Gilbert and Mack, 1998).

Gilbert et al. (1999a) compared the effects on LTP when exposure occurred during different developmental periods. These workers found that animals whose exposure began shortly after weaning exhibited the same impairments in LTP as animals continuously exposed from late gestation when testing in both groups occurred well into adulthood. A smaller effect on potentiation was observed when exposure was restricted to the late gestation/weaning period.

Gilbert et al. (1999b) also examined the effects of Pb on LTP as a function of chronic exposure level, utilizing a range of 0.1–1.0% Pb in the drinking water (corresponding to blood Pb values of 26 to 117 μg/dL). A reduced capacity for LTP was found at all exposure levels except in the 1.0% groups, indicative of a biphasisc dose-effect relationship (Figure 5-3.3). The 1.0% Pb-exposure level was clearly less effective than the lower exposure groups in reducing LTP magnitude and did not differ significantly from control values. Blood Pb values were elevated as a function of increasing exposure and could not account for the lack of effect in the 1.0% exposure group.

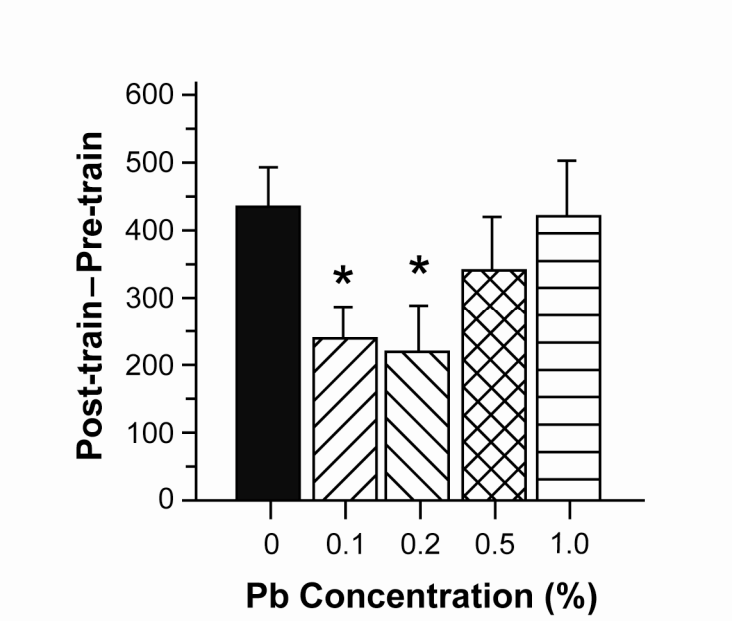


Figure 5-3.3. I/O function difference score–PS amplitude.

Source: Gilbert et al. (1999b).

Zhao et al. (1999) utilized low frequency electrical stimulation in the paradigm of long-term depression (LTD) and found that chronic Pb exposure depressed the magnitude of this form of synaptic plasticity in both hippocampal CA1 and dentate gyrus subregions. The authors also made the point that in combination with the reduced magnitude of LTP reported by other workers, the decrease in LTD magnitude results in a reduced range of synaptic plasticity in chronically exposed subjects.

While the effects of Pb on synaptic plasticity are quite similar in the CA1 and dentate gyrus regions, they are not uniformly present throughout this brain area. Gutowski et al. (1997, 1998) were unable to find any effect of chronic Pb exposure on LTP in hippocampal CA3 (i.e., mossy fiber LTP), even when the investigation was extended across multiple ages. The bases for this distinction await future investigation.

Lead Exposure, Glutamatergic Transmission, and Synaptic Plasticity

Investigation of the synaptic processes underlying LTP has provided insight into the bases for Pb exposure-related impairment of potentiation and cognitive ability (Lasley and Gilbert, 2000). Biochemical and neurophysiological approaches (Lasley and Gilbert, 1996; Gilbert et al., 1996; Ruan et al., 1998) have found stimulated glutamate release to be diminished in hippocampus at blood Pb values where deficits in LTP have been observed. Multiple actions of Pb may be involved at this exposure level because animals exposed postweaning exhibited similar decrements in evoked glutamate release to those exposed continuously from conception (Lasley et al., 1999), similar to the observations for measures of LTP. A biphasic dose-effect relationship was also found in which stimulated glutamate release in hippocampus was decreased at intermediate exposures, but not at higher levels (Lasley and Gilbert, 2002). On the basis of these observations, it is apparent that decreases in stimulated glutamate release are a significant contributing factor to the Pb exposure-related changes seen in LTP.

In comparison to the concordance across laboratories with regard to effects of chronic Pb exposure on LTP and the notable similarities to its actions on glutamate release, the effects of exposure on the NMDA receptor are relatively variable. That is, there is not widespread agreement as to the nature of the exposure-induced changes. Alterations in receptor function occur readily in response to externally applied treatments and might be expected to vary in a dynamic fashion as a function of exposure parameters (e.g., Lasley et al., 2001). However, most studies have involved measures of NMDA receptor integrity in adult animals exposed to constant levels of Pb for at least three, and more commonly 6 to 15, months, so that receptor-mediated effects should have stabilized. Consequently, the following alternative conclusions could be proposed regarding the actions of Pb exposure on the NMDA receptor that are related to its effects on LTP. First, changes in NMDA receptor function may depend on specific Pb exposure conditions. For example, a postweaning exposure protocol may not necessarily produce similar

effects to an exposure protocol initiated during earlier development. Alternatively, exposure effects on LTP may be produced at signal transduction or other cellular loci that exert regulatory influences on the NMDA receptor. This latter conclusion implies that changes in the NMDA receptor do not mediate the primary action of Pb on LTP. In addition, this indicates that identification of some site of direct Pb effect that has regulatory influence on the receptor would produce more consistently observable findings.

Lead and Electrophysiological Changes in Dopaminergic/Cholinergic Systems

Electrophysiological approaches have been employed to delineate other interesting findings in Pb-exposed animals not directly related to synaptic plasticity. Using standard extracellular recording methods, Tavakoli-Nezhad et al. (2001) identified an exposure-dependent decrease in the number of spontaneously active dopamine cells in the substantia nigra and ventral tegmental area, but they found no evidence that this decrease was related to a physical loss of cells. In subsequent work, Tavakoli-Nezhad and Pitts (2005) determined that the decrease in the number of active dopamine cells was not based on depolarization inactivation. However they were able to discern a reduced impulse flow in dopamine neurons and a diminished sensitivity of D_1 receptors in the nucleus accumbens.

The actions of Pb^{2+} on cholinergic nicotinic receptors have been investigated in acutely dissociated or cultured hippocampal cells using the patch clamp technique in whole cell mode (Ishihara et al., 1995). These workers found that Pb^{2+} potently inhibits activation of fast-desensitizing nicotinic currents in a noncompetitive and voltage-dependent manner. The nicotinic receptors affected (methyllycaconitine-sensitive) were more sensitive to Pb^{2+} than other nicotinic subtypes and are known to be highly permeable to Ca^{2+}. This latter observation likely explains the potency for their inhibition by Pb^{2+}.

5.3.1.4 Lead Exposure and Sensory Organ Function

Another focus area for Pb neurotoxicity research that has generated valuable and relevant scientific findings has been sensory organ function. Visual and auditory systems have received the most attention, have generated results closely resembling clinical observations, and have been successful in defining some of the mechanisms underlying the exposure-induced alterations. These studies are summarized in Table AX5-3.3.

Sensory Organ Assessments in Nonhuman Primates

Lilienthal and Winneke (1996) tested monkeys continually exposed to Pb from gestation through 8 to 9 years of age and found increased latencies for waves I, II, and IV in brainstem auditory evoked potentials. These effects persisted for at least 18 months after exposure was terminated and blood Pb values had declined nearly to control levels, leading to the conclusion that these actions of Pb were not dependent on current exposure. Rice (1997) determined pure tone detection thresholds in monkeys exposed continually from birth to 13 years of age, and reported that half of the subjects exhibited thresholds outside of the control range at some frequencies. These findings are consistent with reported alterations in auditory function in humans exposed to Pb developmentally (Otto and Fox, 1993).

Visual function was assessed in monkeys by Reuhl et al. (1989), who exposed a high- and a low-dose group from birth to 6 years of age. This investigation uncovered a decrease in neuronal volume density in cortical areas V1 and V2 in the high-exposure compared to the low-exposure group. These workers also found a decrease in dendritic arborization in pyramidal neurons in these brain areas, leading to the conclusion that chronic developmental Pb exposure produces changes in cytoarchitecture in visual projection areas.

Retinal Function in Rodents

The actions of Pb on retinal cells have been a focus of research for more than two decades. It has long been recognized that Pb^{2+} exhibits a selective effect on rod cells (Fox and Sillman, 1979) and, more recently, that the associated loss of rod and bipolar cells was due to exposure-induced apoptotic changes (e.g., Fox et al., [1997]). These observations have been linked with exposure-related alterations in rod-mediated visual function. In vitro studies utilizing free Pb^{2+} ion concentrations have done much to elucidate the mechanistic bases of these observations.

These latter efforts have established the concentration-dependent inhibition of cyclic GMP (cGMP) hydrolysis by free Pb^{2+}, in addition to increases in retinal cGMP and rod Ca^{2+} levels (e.g., Srivastava et al., [1995]). Kinetic studies utilizing purified rod cGMP phosphodiesterase have shown that pM Pb^{2+} concentrations competitively inhibit the enzyme relative to mM concentrations that are required for Mg^{+2} cofactor activity, thus binding with 10^4-10^6-fold higher affinity than Mg^{+2} and preventing cGMP hydrolysis (Srivastava et al., 1995).

When retinas are incubated in Ca^{2+} and/or Pb^{2+} in vitro, the rods selectively die by apoptosis associated with mitochondrial depolarization, release of mitochondrial cytochrome *c*, and increased caspase activity (He et al., 2000). He et al. (2003) have proposed that apoptosis is triggered by Ca^{2+} and Pb^{2+} overload due to translocation of cytosolic Bax to the mitochondria, which likely sensitized the overloaded mitochondria to release cytochrome *c*. Subsequent work found the elevations in free Ca^{2+} and Pb^{2+} to be localized to photoreceptors and determined that the effects of the two ions were additive and blocked by a mitochondrial permeability transition pore inhibitor (He et al., 2000). This suggested that the two ions bind to the internal metal binding site of this pore and, thereby, initiate the apoptosis cascade.

These mechanisms are entirely consistent with electroretinogram (ERG) changes observed in animals chronically exposed during early development: decreases in maximal ERG amplitude, decreases in absolute ERG sensitivity, and increases in mean ERG latency that were selective for rod photoreceptors (Fox and Farber, 1988). Also in agreement with these mechanisms are observed elevations in retinal cGMP levels and reductions in light-activated cGMP phosphodiesterase activity. Moreover, the exposure level-dependent degeneration of rod and bipolar cells exhibited the classical morphological features of apoptotic cell death (Fox et al., 1997). Other measures of visual function in chronically exposed animals also have been found to be consistent with the mechanistic data. Long-term dose-dependent elevations in response thresholds are present but only at scotopic (i.e., rod-mediated) backgrounds, and dark adaptation is delayed (Fox et al., 1994). In addition, exposure-induced decreases in rhodopsin content that were proportional to the loss of rod cells have been reported (Fox et al., 1997) as well as dose-dependent decreases in retinal Na^+, K^+-ATPase activity (Fox et al., 1991).

These studies investigating rod photoreceptors are perhaps the best examples of the ability to correlate data obtained in vitro with findings derived from in vivo exposure and with changes in visual physiology. In multiple instances, the same cellular mechanisms are affected with each approach and are consistent with ERG and rod-mediated functional measures. These relationships are summarized in Table 5-3.2.

5.3.1.5 Neurobehavioral Toxicity Resulting from Lead Exposure

The breadth of research examining Pb neurotoxicity utilizing behavioral approaches is quite diverse with respect to test paradigms, exposure parameters, test species, and

Table 5-3.2. Mechanisms of Pb-Induced Impairment of Retinal Function

In Vitro Evidence	In Vivo Evidence	Physiological Changes
Competitive inhibition of cGMP PDE	Increased retinal cGMP	
Increased retinal cGMP	Decreased stimulated cGMP PDE activity	Decreased maximal ERG amplitude Decreased absolute ERG sensitivity Increased mean ERG latency
Increased rod [Ca^{2+}]		
Apoptosis from increased photoreceptor Ca^{2+}/Pb^{2+} via binding to mitochondrial permeability transition pore	Morphological features of apoptotic rod, bipolar cell death Decreased rhodopsin proportional to cell loss Translocated cytosolic Bax to the mitochondria, cytochrome *c* released	Increased response thresholds at scotopic backgrounds Delayed dark adaptation
Decreased retinal Na^+, K^+-ATPase activity	Decreased retinal Na^+,K^+-ATPase activity	

Abbreviations: PDE, phosphodiesterase; ERG, electroretinogram.

neuropharmacological agents used. This large literature, summarized in Table AX5-3.4, has permitted development of insightful generalizations while, at the same time, providing focused descriptions of specific behaviors. In addition, the accumulated evidence has supported the development of more effective and refined methodologies.

Lead-Induced Alterations of Behavior – Nonhuman Primates

In reviewing the results of behavioral investigations of Pb neurotoxicity in nonhuman primates conducted over the last two decades, it is abundantly clear that the results are shaped by the nature of the test paradigm and the developmental exposure periods utilized. Thus, studies employing nonspatial discrimination reversal (Rice and Gilbert, 1990a), spatial delayed alternation (Rice and Gilbert, 1990b), and spatial discrimination reversal (Rice, 1990) produced observations that are distinctly different. Experimental groups continually exposed to Pb from birth to testing as adults typically exhibit learning deficits, but groups continually exposed beginning after weaning or whose exposure from birth is terminated during development may or

may not display differences from control animals depending on the sensitivity to exposure of the test paradigm.

Nonetheless, some characteristics of experimental subjects can be gleaned from investigations of neurobehavioral toxicity in nonhuman primates. Modifications of experimental parameters that make task acquisition or retention more challenging (Rice and Gilbert, 1990b; Rice, 1990) are more likely to elicit exposure-related changes in responding. In test paradigms based on fixed interval reinforcement or differential reinforcement of low rate responding schedules, Pb-exposed subjects displayed decreased inter-response times and a greater ratio of responses per earned reinforcement (Rice, 1992a,b). Exposed animals also are less sensitive to changing reinforcement contingencies and, therefore, commit more perseverative errors in responding (Rice, 1992c; Newland et al., 1994). Not surprisingly, it has been noted that these experimental behavioral effects correspond reasonably well to epidemiologic observations in Pb-exposed children (Rice, 1996; Lasley and Gilbert, 2000), thus validating the use of this species as an exposure model.

Lead-Induced Alterations of Behavior – Rodents

The observations of Pb's neurobehavioral effects in rodents in many ways resemble those conclusions attained with nonhuman primates. However, the test paradigms utilized for rats have been somewhat more refined, and the behavioral data have been subjected to more detailed analyses. As a result, valuable insights into the component mechanisms underlying the exposure-related changes have been achieved.

An olfactory serial reversal paradigm was utilized to demonstrate Pb-induced impairments in learning reversals (Hilson and Strupp, 1997; Garavan et al., 2000). These workers found that, when presented with altered reinforcement contingencies for the reversals, rats whose exposure was limited to early development exhibited a shortened initial period of responding to the previously correct cue coupled with a prolonged postperseverative learning phase for the new task. Hilson and Strupp (1997) concluded that the impaired reversal learning was due to a deficiency of learning new contingencies of the task (i.e., an associative deficit), and not based on inflexibility or deficient inhibitory control. Subsequent work by Garavan et al. (2000) determined that this associative deficit was based on a response bias and an impaired ability to associate cues and/or actions with their affective consequences.

Employing a visual discrimination task, Morgan et al. (2000) found that as the level of Pb exposure restricted to early development increased, learning of the task slowed and the number of defined "impaired" animals increased. The authors concluded that the deficits were not limited to attentional function and that an associative deficit had resulted along with a tendency to respond more rapidly. Subsequent work with visual discrimination vigilance tasks found that animals exposed only during gestation and/or lactation exhibited impaired response initiation and increased omission errors, indicating a lasting deficiency in sustained attention and an increased reactivity to errors (Morgan et al., 2001). The authors concluded that the effects of exposure are determined not only by the paradigm, but also by the timing and intensity of exposure. Cory-Slechta (2003) came to a similar conclusion on the factors underlying the manifestation of Pb effects but suggested that the alterations in attention may be due to impulsivity or aversion to delays.

The actions of early Pb exposure on memory appear to be task-dependent, but this issue has not been clearly defined. Alber and Strupp (1996) found that exposed rats performed more poorly on a series of spatial alternation tasks but that the deficit did not vary across intertrial delays, suggesting that memory was not impaired. Murphy and Regan (1999) used a one-trial, light/dark, passive avoidance paradigm and observed a decrease in recall latency on post-training day 5 in rats whose exposure was restricted to early development. Since there was no exposure effect evident during the first 48 h after training, these authors concluded that the impairment was associated with long-term memory storage. Further studies are needed to more clearly characterize the effects of chronic Pb on memory function.

Interactions of Lead Exposure and Responding to Cocaine

Behavioral responses to a number of neuropharmacological agents have resulted in important and useful insights into Pb neurotoxicity. One approach that has been unique and has produced scientifically important results has been investigation of the interactions of chronic Pb exposure and responses to cocaine. Chronic exposure of adult male rats has been shown to attenuate cocaine-induced locomotor activation (Grover et al., 1993) and result in a slower development and reduced magnitude of cocaine-induced sensitization of locomotor activity (Nation et al., 1996). The latter observations are consistent with other evidence of impaired synaptic plasticity that were presented earlier in this chapter. These actions of exposure are not

specific to cocaine, as a similar exposure regimen attenuated the reinforcing effect of brain stimulation of the medial forebrain bundle (Burkey and Nation, 1994), the nerve tract conveying nigrostriatal and mesolimbic dopaminergic neurons to forebrain regions.

Using the drug discrimination paradigm, Miller et al. (2001) restricted Pb exposure to the gestational and lactational periods of early development and observed decreased sensitivity to dopamine D_1 and D_2 receptor agonists when the animals were tested as adults. These findings may be taken as evidence of receptor downregulation, but, in this behavioral task, subjects received chronic intermittent doses of the training drug, which in this study was a low dose of cocaine. Thus, the actions of exposure on dopaminergic systems may be confounded with the receptor changes induced by chronic drug administration.

In contrast to the attenuating effects of chronic Pb administration to adults described above, exposure restricted to the gestational and lactational periods exerts potentiating effects on other types of responses to cocaine when animals are tested long after exposure is terminated. Nation et al. (2003) trained rats to self-administer cocaine intravenously, extinguished the response, and then used a systemically administered priming dose of the drug to initiate a relapse response. Exposed animals were found to have an increased sensitivity to cocaine relapse compared to identically treated controls. When multiple cocaine doses were provided, identically exposed animals were found to self-administer more of a low dose of the drug and less of a high dose than controls, again suggesting an enhanced sensitivity to the actions of cocaine (Nation et al., 2004). Finally, animals exposed to Pb in this manner were found to have an accelerated rate of acquisition of cocaine self-administration behavior (Rocha et al., 2005).

Lead Exposure and the Stimulus Properties of Neuropharmacological Agents

The drug discrimination paradigm has been utilized more widely in Pb neurotoxicity research to characterize postsynaptic receptor status for multiple neurotransmitter systems and has resulted in some useful findings. Rats chronically exposed beginning at weaning and tested as adults were trained to discriminate either a systemically administered D_1 or D_2 receptor agonist (Cory-Slechta and Widzowski, 1991). Exposed rats learned the discrimination task more rapidly than controls and exhibited greater levels of response to lower doses of the training drugs and less blockade by a D_2 receptor antagonist, consistent with generalized dopaminergic receptor supersensitivity. In groups of animals exposed only from birth to weaning and trained to

discriminate the same drugs, the D_2-D_3 subtype receptor supersensitivity in exposed animals was again present, but no changes in responding to the D_1 agonist were apparent (Cory-Slechta et al., 1992). Further work with this test paradigm employing the postweaning exposure protocol failed to demonstrate any D_1-D_2 receptor interactions in the supersensitivity displayed by Pb animals (Cory-Slechta et al., 1996a).

To test cholinergic sensitivity in animals chronically exposed after weaning, rats were trained to discriminate a muscarinic agonist (Cory-Slechta and Pokora, 1995) and were tested in the added presence of a muscarinic antagonist. The results suggest an increased sensitivity to at least one subtype of muscarinic receptor in Pb-treated rats.

Glutamatergic functioning also has been assessed by use of the drug discrimination paradigm. Rats chronically exposed beginning at weaning and tested as adults exhibited diminished responsiveness to an NMDA subtype receptor antagonist (Cory-Slechta, 1995b) but enhanced responsiveness to lower doses of NMDA (Cory-Slechta et al., 1996b). When exposure was limited to the period between birth and weaning, the diminished sensitivity to the NMDA receptor antagonist was less evident, but still present (Cory-Slechta, 1997b).

Thus, the drug discrimination paradigm appears to provide useful insights into the status of some neurotransmitter systems in chronically Pb-exposed animals. The reports cited above indicate an upregulation of dopaminergic, cholinergic, and glutamatergic receptors that are generally consistent with findings of diminished presynaptic function described earlier in this section of the current Lead AQCD. Nonetheless, this paradigm has some limitations. As all drugs in the cited studies were administered systemically, the results provide no evidence on brain regional sites of action. In addition, the chronic intermittent administration of the training drug has the potential to induce compensatory neuronal changes by itself, and thusly may mask or otherwise alter the manifestation of the effects of Pb exposure. Future use of this paradigm in Pb neurotoxicity studies must acknowledge this latter consideration.

Other Effective Behavioral Test Paradigms

Another test paradigm effectively utilized at least transiently to distinguish changes in chronically Pb-exposed animals is the repeated acquisition and performance schedule (Cohn et al., 1993). The purpose of this paradigm was to determine the selectivity of Pb-induced changes in learning, as distinct from nonspecific or performance effects, and to explore the

nature of the underlying error patterns contributing to any learning deficits. This schedule required completion of a sequence of three responses for reinforcement, with the correct sequence for the learning (i.e., repeated acquisition) component changing with each successive experimental session, while the performance component sequence remained constant across sessions.

The use of this schedule in animals chronically exposed to Pb beginning at weaning uncovered significant decrements in accuracy on the learning component, but not on the performance component, in Pb groups compared to controls (Cohn et al., 1993). A detailed analysis of subjects' behavior indicated that Pb exposure impaired learning by increasing perseverative responding on a single lever, even though such repetitive responding was not directly reinforced. In a subsequent study, dose-effect curves for the NMDA receptor antagonist MK-801 were determined in controls and animals tested in this paradigm in which chronic exposure began at weaning (Cohn and Cory-Slechta, 1993). The decline in learning accuracy and the increases in perseverative responding produced by MK-801 were attenuated by Pb exposure, and dose-effect curves relating MK-801 dose to changes in rates of responding were shifted to the right in exposed rats compared to control animals. These observations, therefore, demonstrated a subsensitivity of Pb-exposed animals to both the accuracy-impairing and response rate-altering properties of the antagonist. An additional investigation utilized the same Pb exposure protocol and administration of doses of NMDA as a receptor agonist to rats undergoing this test paradigm (Cohn and Cory-Slechta, 1994b). In control animals, NMDA was found to decrease accuracy of response in both the repeated acquisition and performance components of this multiple schedule and to suppress response rates as well. Lead exposure potentiated the accuracy-impairing effects of NMDA by further increasing the frequencies of errors and likewise potentiated the drug's rate-suppressing effects. Thus, as stated earlier in this section, the Pb-induced potentiation of the agonist effects and reduced sensitivity to the antagonist effects in this test paradigm are consistent with an increased density or some other upregulation of NMDA receptors in exposed brain tissue. In other work, Cohn and Cory-Slechta (1994a) were unable to distinguish any evidence of dopaminergic modulation of responding in this behavioral paradigm. Thus, the repeated acquisition and performance schedule proved valuable not only in providing a finer dissection of the animal's behavior, but in elucidating

important aspects of Pb neurotoxicity without some of the limitations inherent with drug discrimination or other behavioral test methods.

Summary

There is general agreement that the important factors in determining behavioral responses of Pb-exposed animals are (a) the nature of the test paradigm and its sensitivity to exposure and (b) the timing and intensity of the Pb exposure. Detailed analyses of responding have shown that Pb-exposed animals are less sensitive to the changing reinforcement contingencies that are integral to series of reversal tasks. They exhibit shortened initial periods of responding to the previously correct cue in combination with prolonged postperseverative learning phases for the new task. These have been proposed to be associative deficits based on deficiencies in learning new response contingencies. In addition, the impaired responding of Pb-exposed animals in vigilance tasks has been attributed to deficiencies in sustained attention and an increased reactivity to errors.

Other test paradigms such as drug discrimination and repeated acquisition/performance tasks have provided useful assessments of the integrity of CNS neurotransmitter systems in Pb-exposed animals. Evidence from both paradigms has been in general agreement in indicating up-regulated neurotransmitter receptor systems. The timing of Pb exposure is critically important in determining the response to cocaine, and the potentiating action of perinatal Pb exposure is of potential importance for public health purposes.

5.3.1.6 Lead-Induced Changes in Cellular Development and Disposition of the Metal

Alterations in cellular differentiation and morphology can be important structural neuronal and glial components of the manifestations of Pb neurotoxicity. While these issues have not been thoroughly addressed by research investigations, there have, nonetheless, been important observations made. This subsection reviews studies concerned with various aspects of this topic.

Lead Exposure and Neural/Glial Progenitor Cells

Studies of the effects of Pb exposure on neural and glial progenitor cells are recent occurrences in the field of Pb neurotoxicity research. Chronic exposure in rats begun at postnatal

day 25 was found to significantly decrease proliferation of new cells in the dentate gyrus compared to the extent of this process in control animals (Schneider et al., 2005). Other workers initiated Pb exposure at birth and determined that continuous exposure to adulthood reduced the total number of labeled cells in the hippocampal dentate gyrus at 28 days, but not 24 h, after the last administration of a DNA synthesis marker (Gilbert et al., 2005). Rats whose exposure was terminated at weaning exhibited no changes in cellular labeling or survival, indicating that chronic exposure reduces the capacity for hippocampal neurogenesis.

Studies have also been conducted to investigate the effects of exposure on glial progenitor cells. Deng et al. (2001) examined cultured oligodendrocytes and their progenitor cells acutely exposed to Pb^{2+} in vitro; they observed an exposure-induced delay in the differentiation of the progenitors, and that the progenitor cultures were more sensitive to Pb^{2+} than the mature oligodendrocytes. These findings suggested interference with the timely developmental maturation of the progenitor cells. A subsequent study found that a low concentration of Pb^{2+} in vitro inhibited proliferation and differentiation of these progenitors without affecting cell viability (Deng and Poretz, 2002). Proliferative capability was decreased and cell-intrinsic lineage progression was inhibited at a late progenitor stage. Thus, acute Pb^{2+} suppresses both the proliferation and differentiation of these cells.

Lead Exposure and Neurite Outgrowth

Neurite initiation is known to be highly sensitive to neurotoxic compounds and has been the focus of studies examining morphological alterations caused by exposure to Pb^{2+} in vitro. Kern and Audesirk (1995) found that 100 nM Pb^{2+} inhibited neurite initiation in cultured rat hippocampal neurons and, on the basis of results with kinase inhibitors, concluded that this occurred by inappropriate stimulation of protein phosphorylation by Ca^{2+}-calmodulin-dependent or cyclic AMP-dependent protein kinases, possibly through stimulation of calmodulin. Intracellular free Ca^{2+} concentrations were not altered by up to 48 h exposure to nominal 100 nM Pb^{2+}, leading these workers to propose that the stimulation of the above kinases or calmodulin were not via increased Ca^{2+} but, instead, were attributable to intracellular Pb^{2+} concentrations. Evidence of Pb^{2+}-induced inhibition of neurite outgrowth is in general agreement with observations made after chronic exposure to Pb employing in vivo models. Cline et al. (1996) employed an exposure protocol of 0.1 nM–100 μM nominal Pb^{2+} for 6 weeks localized to the

retinotectal system of frog tadpoles, and observed a severely reduced area and branchtip number of retinal ganglion cell axon arborizations within the optic tectum at nM Pb^{2+} concentrations. Reuhl (1989) exposed primates to 2 mg lead/kg/day from infancy to 6 years of age and found that neuronal volume density was reduced in primary visual area V1 and in visual projection area V2 compared to a group exposed to 25 μg lead/kg/day. Moreover, a relative decrease in the number of arborizations among pyramidal neurons in both areas V1 and V2 was observed in the higher dose group. Thus, there is good correspondence between reports that acute Pb^{2+} exposure in vitro and extended exposure in animal models in vivo results in diminished neuronal growth and differentiation at Pb levels of apparent environmental relevance. Studies employing intact animals have not progressed to investigation of specific cellular mechanisms underlying these effects.

Lead Exposure and Neural Stem Cells

Given considerable contemporary interest in the use of neural stem cells to treat various neurological diseases, the efforts of Huang and Schneider (2004) to examine the actions of exposure to Pb^{2+} in vitro on these cells is worthy of note. Lead exposure produced no effect on neurosphere viability, but, it did cause a significant dose-dependent inhibition of proliferation. In addition, the number of neurons differentiated from Pb^{2+}-exposed neurospheres was significantly decreased from control, as were the number of oligodendrocytes obtained. However, Pb exposure increased the number of astrocytes obtained. These observations suggest an important Pb^{2+}-induced influence on stem cell proliferation and differentiation that has public health relevance to prenatal metal exposure.

Accumulation of Lead in Brain

Most studies of neurotoxicity involving chronic Pb exposure now report blood and brain Pb concentrations to quantify exposure magnitude and/or as quality control measures. Thus, a sizable amount of data is available on general aspects of Pb toxicokinetics. While brain Pb values vary monotonically with blood Pb concentrations and exposure levels, steady state accumulation/washout times are longer in tissue and are dependent on exposure magnitude and duration. The half-time for the decline of Pb in brain tissue when exposure is terminated is on

the order of 10 days to 2 weeks, while the value for blood leads would be a matter of a few days (Lasley, unpublished observations).

The speciation and distribution of Pb in brain tissue is largely unknown except for indirect indications that only a small fraction of the divalent cation is present in tissue in extracellular fluid in the free ion state. The existence of a lead-binding protein in brain cytosol was reported by Goering et al. (1986) and was invoked to explain the relatively weak inhibition by Pb^{2+} of brain δ-aminolevulinic acid dehydratase activity. But the binding protein was not fully characterized or identified. Pb^{2+} is known to bind to various intracellular Ca^{2+} binding proteins, such as calmodulin, PKC, and synaptotagmin, particularly those with a C2 domain (Sun et al., 1999), but these are low-volume sources that have been studied for their functional importance and would not serve any kind of tissue metal storage function.

Pb^{2+} appears to be taken up into cultured cells by multiple ion channel-based mechanisms including influx through channels activated by depletion of intracellular Ca^{2+} stores, non-L-type Ca^{2+} channels, and NMDA receptor-associated channels (Kerper and Hinkle, 1997; Mazzolini et al., 2001). Astroglia are well known to act as a Pb sink and, in culture, accumulate up to 24 times more of the metal than neuronal cells (Lindahl et al., 1999); and there is evidence that glutathione may regulate Pb uptake into these cells. Only recently has one astroglial protein been identified—a molecular chaperone in endoplasmic reticulum (Qian et al., 2000, 2005), glucose-regulated protein (GRP78). Intracellular levels of this protein are increased in cultured astroglia during one week's exposure to Pb^{2+}, suggesting that this protein is a component of the intracellular tolerance mechanism that handles high intracellular Pb accumulation through a direct interaction. GRP78 depletion significantly increased the sensitivity of cultured glioma cells to Pb^{2+} as indicated by the generation of reactive oxygen species. Thus, it appears that Pb^{2+} directly targets the protein and induces its compartmentalized redistribution, enabling it to play a protective role in Pb neurotoxicity.

5.3.1.7 Integration of Research Findings

It is evident that the Pb neurotoxicity literature is broad and varied and that many valuable observations have been made over the last 20 years. Nevertheless, a few general conclusions are in order so as to help integrate and concisely summarize evidence in at least a few focused areas.

- Lead-induced impairments in glutamatergic neurotransmission appear to underlie the deficits in synaptic plasticity and in learning or acquisition behavior. Cholinergic neurotransmission also serves an important role in impaired learning in exposed subjects, while deficits in dopaminergic function are manifested as alterations in rates of responding or incentive motivation. Exposure-related alterations in structural plasticity appear to be based on interference with Ca^{2+} signaling and/or glutamatergic transmission.
- There is little if any support in the Pb neurotoxicity research community for the notion of thresholds for any of the toxic mechanisms that have been addressed in this section of the document. With the pressure to reduce experimental group sizes to the minimal number necessary and the unspecified notion that rats are somewhat more resistant to Pb than children, most studies performed with in vivo models report blood Pb values in the range of 15 to 35-40 µg/dL. Moreover, in view of the complex and undefined speciation equilibria and distribution of Pb in physiological milieus, there is no way to directly relate a blood Pb value to the levels of free Pb^{2+} ion or to any other complexed active form of the metal, either in extracellular or intracellular fluids. Generally accepted estimates of the free Pb^{2+} ion concentrations produced in brain extracellular fluid by environmentally relevant exposures fall in the low nanomolar range.
- Susceptibility factors for Pb neurotoxicity are poorly defined in laboratory animals, and, thus, have not been studied. A compelling rationale for their investigation has not been provided.

5.3.2 Neurotoxicological/Neurobehavioral Effects of Lead in Humans

This section is divided into three sub-sections, based upon age and exposure scenarios. The sub-sections include (1) children with blood lead levels above and below 10 µg/dL, (2) adult manifestations of neurotoxicity and other disease states as a result of excessive exposure to lead as children, and (3) adults who were exposed to "ambient" levels of lead. In each of these sub-sections, wherever possible, discussion is focused on biochemical markers, bioclinical markers, and reversibility of lead's neurotoxic effects. In addition, for each of the groups cited above, vulnerability to the neurotoxic effects of lead is considered. Topics in this area include developmental toxicology and growth and development in children. For children and adults, other aspects of vulnerability are considered, such as socioeconomic status, nutrition, and genetic polymorphisms. Based upon the body of studies discussed in each sub-section, it is reasonable to draw conclusions relating to dose-response paradigms and clinical extensions of epidemiological data to individual children.

5.3.2.1 Effects of Lead in Young Children to Mid-Adolescence

Since EPA's publication of the Air Quality Criteria Document and Addenda in 1986-1990{EPA-600/8-83/028aF(1986); EPA/600/8-89/049F(1990)}, major studies with new and critical information have substantially extended previous hypotheses expressed by the EPA. These new data are the primary and major departure from EPA's earlier lead criteria reviews. It is now recognized that lead has adverse effects on the developing central nervous system of young children and that these effects on cognition and behavior persist (at least) into the school-aged years and beyond into mid-adolescence. While causal conclusions about effects of lead exposure on cognitive development are made with caution, collectively, the nature and abundance of the evidence is clear and compelling. This new information causally links detrimental effects of lead on behavior and cognition at blood lead levels both above and below 10 µg/dL. Compared to the earlier EPA documents (cited above), there is solid evidence for detrimental effects of lead on neuropsychological functions such as fine motor skills, visual-spatial, and executive functioning and attention in large groups of children. Apparently, there is no threshold below which lead is without adverse effects on the central nervous system of young children to mid-adolescence. This conclusion is also related to dose-response paradigms of lead in children, as well as to extending the results of epidemiological studies to individual children.

Biomarkers

There are three generally recognized types of biomarkers (National Research Council [NRC], 1993; Lanphear and Bearer, 2005). The first of these is relevant to quantifying exposure and, thus, the internal dose of lead. This subject is covered in Section 6.1. The second type of biomarker focuses on *effects*. Biomarkers of effect are biochemical, physiological and/or clinically measurable alterations in normal functioning that reflect an impairment of health or a specific disease. Effects of this nature include early subclinical effects of lead that are of value in quantifying human health risks; as a result, such effects can lead to an understanding of mechanisms of lead toxicity at the cellular and organ level. An example of the latter are the impacts of lead on heme synthesis, which have been extensively studied as discussed in Section 5.2. Other examples include (in children) effects on the electrophysiology and architecture of the brain. In contrast, biomarkers of *susceptibility* or *vulnerability* are native,

inherent or acquired situational characteristics that alter the responses of children (and adults) to lead exposure. Examples of these biomarkers include socioeconomic status, nutrition, developmental aspects of brain functions, and genetic polymorphisms. Ultimately, these biomarkers, collectively, as a constellation, are considered to be contributing factors that assist in determining whether the cognitive effects of lead exposure in children are reversible.

Biochemical Biomarkers

In the AQCD of 1986, reported studies in lead-poisoned children (blood lead levels of 12-120 μg/dL) revealed an inverse correlation (−0.88) between the entire range of blood lead concentrations and plasma levels of the vitamin D hormone (1, 25-dihydroxyvitamin D) in 177 children from 1-16 years of age (Rosen et al., 1980; Mahaffey et al., 1982). These results suggested that lead impairs the biosynthesis of the Vitamin D hormone; and, as a result, calcium absorption, and possibly that of lead, could be inhibited. Because of 1,25-dihydroxyvitamin D's roles in multiple cellular functions, including the calcium-messenger cascade, development and proliferation of multiple cell types, these clinical observations have substantial implications (NRC, 1993). These data from clinical studies were supported in experimental animals (Smith et al., 1981). In animals fed a low calcium or phosphate diet, oral administration of 0.82% lead, as the acetate, yielded plasma levels of 1,25-dihydroxyvitamin D that were substantially reduced. This effect of lead on circulating 1,25-dihydroxyvitamin D disappeared when either a high calcium or phosphate diet, including lead, was administered. Moreover, intestinal lead appeared to block the absorption of calcium in response to administration of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, although there was no influence on calcium mobilization neither from bone nor of mineralization of rachitic bone (Smith et al., 1981).

More recently, in animals and children, this relationship has been examined further. Chicks fed lead concurrently on a low calcium diet replicated the findings in animals and children noted above. However, chicks fed a calcium sufficient diet coupled to dietary lead, failed to exhibit decreased plasma levels of the vitamin D hormone (Fullmer and Rosen, 1990; Fullmer, 1995, 1997). Similar findings were reported in lead poisoned children with adequate dietary intakes of calcium as those in experimental studies (Koo et al., 1991). Compared to the 1980s, when dietary intakes of calcium were marginal (at best) in inner-city children, recent estimates of dietary calcium intakes in inner city children meet or exceed recommended daily

requirements of 1000 mg/day or greater (Markowitz et al., 2004). Thus, in calcium-sufficient children, plasma concentrations of 1,25-dihydroxyvitamin D are not biomarkers of lead's effects on the vitamin D endocrine system. Nonetheless, in at-risk populations of children, whose dietary intakes of calcium are suboptimal, apparent biosynthesis of the vitamin D hormone, evidenced by decreased circulating levels of the hormonal form of the vitamin, 1,25-dihydroxyvitamin D, is expected.

Tang and co-workers (1999) assessed 244 infants on the Brunet-Lezine Scales at 9 months of age to evaluate possible relationships between cord blood lead levels and plasma concentrations of 5-hydroxyindoleacetic acid (5-HIAA) and homovanillic acid (HVA) at 9 months of age. Cord blood lead concentrations were in the range of 2.5-7 μg/dL. At 9 months of age, 5-HIAA and HVA were negatively correlated with blood lead values and with all the neurodevelopmental functions, except for language, on the Brunet-Lezine Scales. The negative correlations between the serotonergic system, coupled to blood lead levels, were found in global scores, sociability, and coordination on the Brunet-Lezine Scales. Although further confirmation of these results is needed, these findings are consistent with the findings in experimental studies linking lead effects to impairments in neurotransmission (Section 5.3).

Clinically Oriented Biomarkers of Effect

Very little information was available in the time frame of 1986-1990 relating to clinically oriented biomarkers of lead's effects on the central nervous system of children. Currently, there is a substantial body of knowledge which focuses on the functional status of the brain in excessively lead-exposed children. This new information includes functional (Bhattacharya et al., 1993; Rothenberg et al., 1995) and electrophysiological (Otto and Fox, 1993; Burchfiel et al., 1992; Poblano et al., 2001; Rothenberg et al., 2000) studies. The most relevant studies of functional and electrophysiologic data, relating to spectral analyses of EEGs, brainstem auditory-evoked potentials or responses (BAEP and BAER) are those based upon prospective designs of a well characterized cohort of children. Another line of important new information is based upon results from assessments of the biochemical and anatomical functions of the central nervous system in lead-exposed children carried out by magnetic resonance spectroscopy (MRS)(Trope et al., 2001; Meng et al, 2005). Some of these studies link observed results to cognitive impairments summarized in the general introduction to this chapter. Although there may be

some overlap in these reported studies, for the purposes of this discussion, studies are categorized as functional, electrophysiologic and biochemical-anatomical.

A functional assessment of postural equilibrium was carried out in 109 children (in the Cincinnati Prospective Study) at 5.8 years of age when the mean blood lead was 5.8 μg/dL (the geometric mean blood lead for the first 5 years of life was 11.9 μg/dL). Postural sway was quantitated with a microprocessor-based platform. A negative correlation was found between blood lead levels and vestibular/proprioceptive systems, suggesting that lead exposure has detrimental effects on posture and balance. Although these data may have potential relevance to psychomotor deficits observed in lead poisoned children, this methodology has not been further developed, and its potential implications to psychomotor skills in children have not evolved (Bhattacharya et al., 1993).

In the Mexico City Prospective Study, analyses of acoustical cries was carried out in a subset of healthy babies at 2, 15, and 30 days of life. The mean maternal blood lead at 12 weeks of pregnancy was 8.2 μg/dL, and the mean cord blood lead level was 7.8 μg/dL (range: 1-38 μg/dL). The percent nasalization, produced by raising the velum of the velopharynx, decreased progressively over the cord blood lead range of 4-40 μg/dL, and the number of cries were inversely related to cord blood lead levels over the same range. In a subset of the babies, decreased nasalization was related to increased BAEP-evoked latencies. These findings suggested that altered baby cries and auditory functions may be associated with developmental delays affecting early communication. However, validation of infant cries as a predictor of subsequent infant development has not yet evolved.

Burchfiel et al., (1992) studied a subset of the Philadelphia children reported on by Needleman et al. (1979). The method used was brain electrical activity mapping (BEAM) coupled to spectral analysis for each individual electrode. Nineteen children in the uppermost 10th percentile for dentine lead (>24 ppm) were compared to children in the lowest 10th percentile (<6 ppm). The spontaneous resting EEG of the high lead children (n = 19) had higher percentages of low frequency delta activity and reduced percentages of alpha activity compared to the lower lead group of 12 children. Qualitatively, these EEG changes are similar to those observed in acute-severe lead poisoning, and, generally, such findings of diffusely increased slow frequency activity and reduced alpha are commonly found in toxic encephalopathies. These results, which are qualitatively similar to results from the Mexico City Prospective Study,

in which BAER were employed in a different age group, indicate that lead may induce neuropathological effects in a dose-response manner over a continuum of exposure (see Section 5.3).

In the Mexico City Prospective Lead Study, 100-113 5 to7 year olds underwent testing by BAER (Rothenberg et al., 2000). The mean blood lead level at 5 years of age was 8 μg/dL. The results indicated that intervals I-V and III-V intervals of BEAR recorded at 5-7 years of age were related to maternal blood lead at 20 weeks of pregnancy, when the geometric mean blood lead was 7.7 μg/dL (range: 1-30.5 μg/dL). This specificity of the lead effect suggests that the CNS is exquisitely sensitive to lead when auditory structures are undergoing rapid development, and this effect appears to persist to 5 or more years later. As indicated in this study, lead-related alterations in auditory brain stem function may underlie verbal deficits in lead-exposed children, as well as impair auditory functions observed in lead-exposed animals (Section 5.3.1). Also, it becomes increasingly important to examine functional deficits in hearing and language development that may be associated with postnatal lead exposure.

Nine to ten year-olds in the Mexico City Prospective Study were evaluated by determining relative theta activity across the scalp. These results, together with life time blood lead concentrations, were assessed by multiple regression models (Poblano et al., 2001). The most significant increases in theta power were associated with blood lead levels (geometric mean: 10.3 μg/dL) measured between 54 and 72 months of age. Spatially weighted regression showed that there was a significant anterior-posterior gradient in the lead-induced increase in relative theta activity associated with postnatal blood leads at 54-72 and 78-96 months. These lead effects occurred at an age during which relative theta power reaches its developmental maximum and then starts to decrease. These data have critical implications in understanding the neurotoxic and developmental impacts of lead exposure. If theta waves continue throughout childhood as one of the most dominant CNS rhythms, this could qualify as a developmental disorder and an "EEG soft sign." Stated differently, persistence of theta activity reflects an 'immature" EEG pattern and/or brain injury. Neuropsychological testing concurrent with this electrophysiological methodology could add important information connecting direct measures of theta activity to CNS development indexed by neuropsychological outcomes (Lidsky, 2003, 2005).

Using MRS, two studies (Trope et al., 2001; Meng et al., 2005) have provided new and important information. Both studies employed MRS with N-acetylaspartate (NAA). MRS has the capability to monitor brain metabolism by detecting NAA, a metabolite that is known to decrease during processes involving neuronal loss. Thus, this methodology provides both biochemical and anatomical information directly related to the neurotoxic effects of lead on the CNS. Trope et al. (2001) studied 16 lead-poisoned children (mean blood lead: 39.9 μg/dL; range: 23-69 μg/dL) who had a mean age of 8 years, 9 months. All of these children received medical attention before 5 years of age. The latter group was compared to 5 children (blood lead levels <10 μg/dL) who had a mean age of 8 years, 6 months. Both groups of children had normal MRIs. The lead-exposed group of children had significant reductions in NAA/creatine and phosphocreatine ratios in frontal gray matter compared to the nonexposed group. Review of medical records in the lead-exposed group failed to reveal an alternative or contributing etiology that could explain this demonstration of brain damage by MRS. These findings, in the regions of the frontal lobes, which are responsible for attention, executive functions and impulse control, are likely to be relevant to neurotoxic outcomes in lead exposed children, who may exhibit impairments in these areas.

Using very similar techniques, Meng et al. (2005) evaluated 6 lead-exposed children (mean blood lead: 37 μg/dL) who lived near a lead-recycling industry for a period of at least 5 years. These children had never been chelated. The lead-exposed children were compared to 6 non-lead exposed children who had blood lead levels <10 μg/dL. On the Wechsler scale, the control children had a Full Scale IQ of 101 compared to 81 in the excessively exposed group. MRIs were normal in both groups of children. These data parallel those reported by Trope et al., (2001). However, Meng et al. (2005) reported decreased levels of NAA in the lead-exposed group in four brain regions: the left and right frontal areas and the left and right hippocampus. This study also found that MRS metabolites in the lead-exposed subjects were significantly reduced as compared with controls, thereby suggesting interference with neuronal functioning after lead exposure.

Collectively, these electrophysiological and biochemical-anatomical data can assist in providing an understanding of the neurotoxicity of lead and neurophysiological outcomes in relatively “low” and “higher” level childhood lead exposure. Collectively, these data also appear

to provide evidence that lead interferes with the hard-wiring and differentiation of the central nervous system in children.

Vulnerability and Susceptibility

The unique susceptibility of children to the adverse health effects of lead were recognized previously by EPA in 1986-1990. Some of these aspects included the specific behaviors of children, including their metabolism of lead, physiological considerations that separate children from adults, greater potential absorption of lead per square meter of body surface, hand-to-mouth activity, and prevalence of nutritional factors that can enhance the absorption of lead from the GI tract.

Since 1986-1990, an enlarged database is now available to construct a somewhat wider approach to understanding not only new information relating to children's susceptibility, but also furthering characterizing interindividual variability as related to manifestations of lead's adverse health effects in children. This section includes topics of developmental toxicology, growth and development, economic status, nutritional aspects of lead and children, and, finally, genetic considerations of children with possibly a biologically based genetic character interacting with exterior environmental realities. Considerations in this section also delve into risk assessment focused on some child-specific factors that affect health outcomes in populations as well as individual children.

Moreover, as a general principle of toxicology and neurotoxicology, it is recognized that a variety of factors can either enhance or decrease an individual's sensitivity to toxic exposures of lead. Besides individual children, there are factors that modify the selective neurotoxic responses of subgroups of children. Some of these variables that increase a child's vulnerability are discussed below.

Developmental Toxicology

In addition to child-specific factors detailed above, it was concluded previously in 1986–1990 that the critical window of adverse health effects of lead in children was at less than 3 years of age, as briefly mentioned below and in greater detail in Section 6.3. This suggestion of age should be extended to children in their school-aged years to mid-adolescence (Chen et al., 2005; Ris et al., 2004; Dietrich et al., 2004) and into the adult years as well (Rice and Barone, 2000).

Developmental toxicity is usually defined by the occurrence of adverse effects on the developing organism prior to conception and/or during prenatal and postnatal development. Manifestations of developmental toxicity include death to the developing organism, structural abnormalities, impaired growth, and functional deficiencies. Moreover, developmental exposures can result in adverse health effects prenatally, postnatally, in childhood, into school-aged years, and into adult age groups to the elderly (Selevan et al, 2000; Weiss, 2000; Rice and Barone, 2000). An important concept in risk management is to identify, whenever possible, developmental windows for evaluating dose-response relationships. Moreover, in risk management, identification of critical windows is aimed at recognizing especially susceptible sub-groups within the general population to provide specific interventions (Selevan et al., 2000). Information on critical windows of development is needed to assess real and potential environmental health risks (Weiss, 2000).

To protect children's health, it is necessary to understand their unique sensitivity to environmental toxicants, and, to further this understanding, functions of risk and exposure must be considered (Faustman et al, 2000). Risk is defined as the probability of an adverse outcome as a function of exposure and toxicity. It is evident that in development of the CNS, unidirectional inhibition at one developmental stage can cause substantial alterations in subsequent processes. In addition, stages of development occur in temporally distinct time frames across regions of the brain (Rice and Barone, 2000; Weiss, 2000). As a result, the CNS has a very limited capability to compensate for cell loss or other injury (Rice and Barone, 2000). Thus, exposure criteria should be based on information relevant to predicting risks and to accounting for toxicokinetic differences that occur during different stages of development (Faustman et al., 2000).

Characterization of critical time frames of development in children are based, in large part, on the results of experimental studies discussed in Section 5.3.1. Initially, the critical time frame for adverse effects of lead on CNS development was considered to be in children <3 years of age (Bellinger et al., 1991, 1992) in that blood lead levels at 2 years of age were correlated with cognitive impairments at 57 months and 10 years of age. However, as indicated in Section 6.3, the age range for time windows for lead's adverse effects on the CNS has been significantly extended to school-aged children, into adolescence, and into adulthood (Dietrich et al., 1993; Tong et al., 1996; Wasserman et al., 2000; Canfield et al., 2003, 2004; Chen et al., 2005;

Lanphear et al., 2000, 2005). Moreover, recapitulation of synaptogenesis in the form of synaptic plasticity is modified by experience and the environment as children become adults and age into the elderly life phase (Rice and Barone, 2000). This concept provides a toxicological framework for identifying latent or persistent expressions of childhood lead exposure in adults as "growing into a lesion" (Ris et al., 2004) or magnification of an earlier insult with aging (Rice and Barone, 2000). This toxicological recognition of latent or persistent expressions of childhood exposure in adults forms the basis of Section 5.3.2.2, discussed below. Additional areas of concern for children related to risk assessment include consideration of lead's deleterious effects on somatic growth, socioeconomic status, nutritional correlates of lead exposure and interactions between biologically inherent genetics and the external environment (discussed below).

Growth and Development

In the Supplement to the 1986 Addendum (EPA/600/8-89/049F), early results from prospective studies in Cincinnati, Boston, Port Pirie, and Yugoslavia were noted in terms of lead's effects on perinatal and postnatal growth and development. However, evidence regarding physical growth effects related to prenatal or early postnatal exposure were inconsistent. Limitations in these early data from prospective studies included definitions of the length of gestation, racial makeup, maternal age, sample sizes, and levels of lead exposure. It appeared likely that prenatal lead exposure did pose a potential hazard to the developing fetus as related to reduced gestational length and possibly other aspects of fetal growth. It proved difficult, however, to define a definite dose-response relationship for fetal outcomes, although there were some indications that pointed to adverse effects on the fetus at blood lead levels of 10-15 µg/dL.

More recently reported data have extended assessments of impacts of lead on early postnatal outcomes (birth weight, early weight gain to 1-month of age, birth length and head circumference) to measurements of maternal bone lead post-delivery by K-XRF. Additional studies have analyzed national data (NHANES III) in terms of the growth patterns of children 1 to 7 years of age. From the same national survey, other studies have focused on sexual maturation as a function of blood lead concentrations.

Gonzalez-Cossio et al. (1997) assessed the possible relationship of blood lead levels in cord blood and maternal bone lead to birth weight in Mexico City. Two hundred seventy-two mother-infant pairs were studied, and the cord and maternal blood lead levels were, on average,

7.1 and 8.9 µg/dL, respectively. Tibial lead (not patellar lead), measured 1-month postpartum by K-XRF, was the only marker related to birth weight, such that, at the highest quartile of bone lead (15.15 µg/g bone mineral), infants were, on average, 156 grams lighter at birth. Although these data appear to extend previously reported information from prospective studies, some caution in the interpretation of these data is indicated: 10% of tibial lead values and 13% of patellar lead levels were below the instrument's detection limit (as defined by the authors), but these negative values were included in the statistical analysis. By necessity, the study design was cross-sectional, because, for ethical reasons, bone lead measurements are precluded during pregnancy due to radiation exposure, and, for unexplained reasons, there were no statistically significant relationships with blood lead values in mothers or infants.

Sanin et al. (2001) studied a similar population in Mexico City comprising 329 mother-infant pairs. The umbilical cord blood lead (mean) was 6.8 µg/dL and the mean value for the infants was 5.6 µg/dL at 1-month of age. A 10 µg/dL increase in infant blood lead levels at 1-month was associated with a 142 gram decrease in weight gain. Thus, lead exposure postnatally had adverse effects on early perinatal weight gain. In addition, maternal patellar lead at 1-month was negatively associated with weight gain as well. The important finding in this study was the inverse correlation between postnatal blood lead and weight gain. However, the significance of maternal patellar lead by K-XRF is limited by the large standard deviation in the measurement of patellar lead (15.2 µg/g bone mineral) and a revised statistical method for calculating bone leads, which was not delineated in this article. Moreover, the failure of maternal blood lead concentration to predict early or subsequent birth weight was unexplained.

In the third of this series of reports from Mexico City, 233 mother-infant pairs were evaluated as described above, but the outcome measures were birth length and head circumference. These results showed that bone lead biomarkers (tibia and patella) were associated positively and significantly with maternal and umbilical cord lead. However, only patellar lead was significantly and negatively associated with birth length and head circumference. These associations were independent of maternal venous blood lead levels, umbilical cord lead levels, and other predictors of birth size, including birth weight. Similar concerns apply here, as those above, relating to K-XRF measurements. Collectively, except for the relationship between postnatal blood lead concentrations and decreases in weight gain (Sanin

et al., 2001), the cumulative findings relating to perinatal and postnatal outcomes, as indexed by bone lead values, fail to provide a consistent or readily interpretable set of conclusions.

Evaluation of 4391 children 1-7 years old was carried out using the nationally representative data from NHANES III. This population study included non-Hispanic white, non-Hispanic African-American, and Mexican-American children, and the outcomes measured were stature, head circumference, weight and body mass index (Ballew et al., 1999). Blood lead levels were significantly and negatively related to stature and head circumference, yielding a predicted decrease of 1.57 cm in stature and a 0.52 cm decrease in head circumference for each 10 μg/dL increase in blood lead values. There was no statistically relevant association between blood lead and weight and body mass index. These robust findings are of considerable importance, because the observations are very similar to those reported earlier for NHANES II by Schwartz et al. (1986). Thus, although blood leads declined substantially in the United States over two decades (NHANES II vs.NHANES III), lead exposure at considerably lower levels continued to affect the growth of some children. Stated differently, there was no attenuation of the negative association between blood lead levels and indices of growth in children despite a substantial decrease in national blood lead values in young children. Collectively, these cross-sectional national surveys (Schwartz et al., 1986; Ballew et al., 1999) indicate the following negative associations with blood lead values: a 1.0-1.5 cm decrease in stature and a 0.50 cm decrease in head circumference coupled to modest increases in blood lead levels within the range of blood lead levels in children in the United States. Over the past two decades, these data provide the most compelling data sets related to the adverse effects of lead on growth patterns in young American children.

Two studies, utilizing NHANES III data, have measured pubertal development, as related to blood lead concentrations, to determine whether sexual maturation may be affected by current environmental lead exposure (Wu et al., 2003; Selevan et al., 2003). In the study by Wu et al. (2003), pubic hair and breast development were evaluated in 1,706 8–16 year-old girls, and information on menarche was delineated in 1,235 girls 10–16 years of age. The blood lead range was 0.7–21.7 μg/dL. This population was categorized into three groups, according to blood lead values: 0.7–2.0, 2.1-4.9, and 5.0–21.7 μg/dL. Sexual maturation markers were self-reported attainment of menarche and physician-determined Tanner stage 2 pubic hair and breast development. The results indicated that girls who had not yet reached menarche or stage 2 pubic

hair had higher blood leads than those girls who had. Negative relationships were found for blood leads with attainment of menarche and stage 2 pubic hair after adjusting for covariates; no relationships were evident for breast development.

Selevan et al. (2003) studied a subset of girls (8-18 years old) from NHANES III that included 600 non-Hispanic white, 805 non-Hispanic African-American, and 781 Mexican-American girls, who, collectively, had a geometric mean blood lead level of 3 μg/dL. For all girls who had blood lead levels of 3 μg/dL compared to those whose blood leads were 1 μg/dL, the higher lead group had a significant decrease in height after adjustment for confounders. Also, in the higher lead group of girls, there were significant delays in breast and pubic hair development, especially in non-Hispanic African-American and Mexican-American girls. Of the latter two groups, the most profound delays were observed in non-Hispanic African-American girls. The delays in reaching Tanner stages 2, 3, 4, and 5 (in all girls) was associated with those whose geometric mean blood lead was 3 μg/dL (as compared to all girls whose geometric mean blood lead level was 1 μg/dL) were 3.8, 5.3, 5.8, and 2.1 months, respectively, for breast and pubic hair development. There were no significant delays found in non-Hispanic white girls. These findings, within a narrow blood lead range, indicate that environmental lead exposure can delay growth and pubertal development in girls. Thus, analyses of these national surveys in children 1-7 years old and in girls 8-18 years old provide strong evidence for adverse effects of lead on the growth of young children and adolescent girls at blood lead concentrations commonly found in the U.S. population today.

Socioeconomic Status

In the U.S. EPA's Supplement to the 1986 addendum (EPA/600/8-89/049F), very little information was discussed relating to socioeconomic status (SES) and the vulnerability of children to lead exposure and resulting deficits in cognitive skills. Primarily as a result of analyses of NHANES III, the importance of SES has reached its appropriate focus and attention. Additional peer-reviewed articles have also contributed to now well-documented interactions between SES and children's vulnerabilities to the neurotoxic effects of lead.

A child's SES clearly has an important influence on the possibility of lead exposure in young children. Disadvantaged children may have an already compromised neuropsychological status that is further impaired by the toxic effects of lead. Although the exact mechanisms of the

impact of SES on lead's neurotoxic effects on the central nervous system are unknown, poverty, pre-1960 housing in segregated communities, ethnicity, and nutritional deficiencies, collectively, can contribute substantially to increased vulnerability of individual children and subgroups of children. The peer-reviewed literature, discussed in this section and in the following section, provides support for these conditions contributing to children's susceptibility to the toxic effects of lead.

An analysis of the early phase (1988-1991) of NHANES III was carried out by Brody et al. (1994), in which 13,201 persons from 1 year of age through elderly adults were assessed via a multiple stage probability design. It was found that the prevalence of elevated blood lead levels for children in low-income families (16.3%) was about four times higher than the prevalence for children with high family incomes. Non-Hispanic African-American children from low-income families had the highest proportion of elevated blood lead values (28.4%).

A comparison of results from NHANES II and NHANES III (Pirkle et al., 1994) extended data reported earlier (Brody et al., 1994). From 1976 to 1991 (NHANES II vs. early NHANES III) there was an overall decline in all children 1-5 years old from 15.0 to 3.2 μg/dL (geometric means). For non-Hispanic white children, the decline was from 13.7 to 3.2 μg/dL, whereas for non-Hispanic African-American children, the decline was from 20.2 to 5.6 μg/dL. Income levels were based upon those previously determined by the U. S. Census Bureau: income level was defined by the poverty-income ratio (PIR), so that the total family income was divided by the current poverty threshold. PIRs were divided into three categories: low ($0 < PIR < 1.30$; mid-range ($1.30 < PIR\ 3.0$) and high ($PIR > 3.00$). Based upon PIRs, it is noteworthy that mean blood lead levels decreased by 60% (24.0 to 9.7) for African-American children from low-income families living in central cities with populations of 1 million or more. The latter value for low-income African-American children was about 3 times the mean value for non-Hispanic white children.

An analysis of phase 2 of NAHANES III showed that it becomes increasingly evident that SES factors, including sociodemographic factors, are closely related to average blood lead concentrations in young children (Pirkle et al., 1998). By phase 2, the average blood lead in all children 1–5 years old was 2.7 μg/dL. The prevalence of elevated blood lead levels in African-American children living in pre-1946 housing was 21.9%; the prevalence in all children of low-income families living in pre-1946 housing was 16.4% (demographic status was

determined by U.S. Department of Agriculture codes populations according to proximity to major metropolitan areas). Low incomes among all ethnic groups, defined by PIRs, were significantly associated with higher blood leads (details of these data were not provided in the article). It is reasonable to conclude that U.S. children, based on ethnicity, housing age, and income, are disproportionately exposed to excessive levels of lead in their environments.

SES was further considered in NHANES III (1988-1994) based upon age and blood lead concentrations (Bernard and McGheehin, 2003). Overall, 25.6% of children 1-5 years old had blood leads equal to or greater than 5 μg/dL; but most of these children (76%) had blood leads less than 10 μg/dL. Of those children who had blood leads greater than 5 μg/dL, 46.8% were non-Hispanic African-American compared to 18.7% non-Hispanic white children. Housing status also played a significant role: 42.5% of children who had blood leads greater than 5 μg/dL lived in pre-1946 housing, 38.9% lived in housing built between 1946-1973, and 14.1% of children in this blood lead group lived in housing built after 1973. Compared to non-Hispanic white children, African-American children were 3 times more likely to have blood leads greater than 5 μg/dL, 7 times more likely to have blood leads of 10-20 μg/dL, and 13.5 times more likely to have blood leads equal to or greater than 20 μg/dL. Low-income families, defined by PIRs, were at substantially elevated risk for having children with blood lead levels above 5 μg/dL, and the odds ratios in these families were the highest when comparing the 10-20 μg/dL group to those children with blood leads <5 μg/dL.

Among Native American children, 1 to 6 years old, living near a Superfund site in Oklahoma, strong interactions were observed between blood lead levels and poverty, suggesting that poor children were especially vulnerable to the toxic effects of lead (Malcoe et al., 2002). Moreover, blood lead levels were significantly higher in 52,407 WIC-enrolled families between 1996-2000 compared to non-WIC-enrolled families indicating the vulnerability of children with low incomes and poorer nutritional status (Zierold et al., 2004).

Similar findings have been reported from the Port Pirie prospective study (Tong et al., 2000); 375 children, 11-13 years of age, were assessed by Daniel's Scale of Occupational Prestige, which is a surrogate for SES. With adjustment for confounders, Wechsler-derived IQ scores were reported in three groups of children according to their lifetime blood lead values of <12, 12.1-17, and >17 μg/dL, respectively. For the less than 12 μg/dL group, the IQ in the high SES children was 105.6 vs. 103.1 in the low SES group. In the mid-range blood lead group

(12.1-17 µg/dL), the IQ score for the high SES group was 104.4 vs. 100.6 in the low SES group. For the higher lead group, the largest differential in IQ scores was apparent: high SES, 101.5 vs. 90.9 in the low SES group. Poor children were especially vulnerable to the neurotoxic effects of lead.

Familial and nonfamilial factors were discerned in 717 children, some of whom lived in Detroit (urban group-low SES) compared with a group of suburban-based middle class children (Breslau et al., 2001) who lived outside Detroit. Children were prospectively tested via the Wechsler at 6 and 11 years of age. Although blood lead levels were not included in this study, the results are of interest. On average, in the urban children, over time, there was a downward shift of 5 IQ points in the disadvantaged children while a negligible change was found in the suburban-middle class group. Income and demographic data for the two groups of children were defined by the 1990 U.S. Census data. Despite the absence of blood lead concentrations, it is reasonable to suggest that compared to the suburban children (according to the 1990 U. S. Census data utilized), that urban Detroit children were more likely to be exposed to lead based paint in their home environments. Familial determinants of IQ, such as maternal IQ, education, and marital status, exerted stable and uniform influences on children's IQ scores across age in both communities; none of these variables were associated with change in IQ scores. Although family factors (maternal IQ specifically) explained about two-thirds of the initial 14 point disparity in IQ scores between urban vs. suburban children, such factor(s) did not account for any part of the IQ decline of 5 points (on average). These authors concluded that IQ is a "joint" product of "genetics" and the environment. The authors emphasized that the disadvantages of inner city children, including ethnicity, housing, segregation, and educational opportunities underscores the need to fully examine extrafamilial factors, including a community's economic resources, to understand predictors of children's IQs. Although family and community factors are not completely separable, these observations reflect, in part, the legacy and vulnerability of children growing up is socioeconomically disparate communities.

Based upon the studies discussed above, there is conclusive evidence that SES has a profound influence on children's vulnerability and susceptibility to the neurotoxic effects of lead exposure.

Nutrition

There was little discussion of nutritional factors and their impacts on children's vulnerability to lead in earlier EPA documents, because very little, if any, information was available at that time. It has become evident that the dangers of lead exposure in children are substantially enhanced by diet deficient in calcium, iron, zinc and other essential nutrients; specific dietary deficiencies are not infrequently coupled to increased susceptibility to lead in low SES children.

In 205 one-year olds, who were low SES infants and who were living in old housing, blood lead levels were measured and related to nutrient intake (primarily of fat). This sample was stratified so that excessive exposure to lead could be analyzed as an independent or dependent variable to account for changes in blood lead values (Gallicchio et al., 2002). Exposure to environmental lead was assessed by measurements of lead in household dust. The authors reported a positive association between household dust levels and blood lead concentrations, and positive associations were also found between dietary intake of total calories and fat. The latter dietary observations were found to be independent of environmental exposure to lead at dust lead values above the 2001 EPA Guideline (Federal Register, 2001). These results implied that dietary control of fat and total caloric intake could have a beneficial effect on children's blood lead levels independent of environmental exposure, although the authors cautioned that control of the external environment was also a critical factor in modulating children's blood lead levels. Similar findings were reported by Lucas et al. (1996). The relationships between blood lead levels and nutritional factors were studied in 296 children who ranged in age from 9 to 72 months from low-SES families in Baltimore. When environmental lead exposure was statistically controlled, dietary fat intake had a positive association with blood lead levels, particularly in children who had blood leads >15 µg/dL.

Several studies have established a negative association between dietary iron intake (as well as biochemical assessments of iron status). Hammad et al. (1996) evaluated 299 children (9 months to 5 years of age) in a cross-sectional study design. The mean blood lead in this group was 11.4 µg/dL, and the mean age of the entire group of children was 26.2 months. After adjustment for confounders, the authors reported that the highest quartile of dietary iron intake had the lowest blood lead values. Bradman et al. (2001) studied 319 1-5 year-old children in Sacramento, CA in terms of iron status as measured by serum levels of ferritin, and

environmental exposure to lead from soil and lead-based paint. 24% of this sample was iron deficient defined as a serum ferritin level <12 ng/dL. Blood lead levels were higher for each tertile of iron-deficient children who were also experiencing excessive exposure to exogenous lead; and the greatest difference between iron-deficient compared to iron-replete children (a mean difference of 3 μg/dL) was in children who had on-going excessive exposure to lead. It was concluded that improvement of iron status, coupled to control of environmental lead sources led to a significant decline in blood lead concentrations.

An important study was carried out in an urban (Boston) primary care setting of 3,650 9-48 month-old children, and comparisons were made between iron status and "low-level" lead exposure. Iron deficiency was defined according to red blood cell indices, including mean corpuscular volume (MCV) and red cell distribution (RDW). During the study period of 1994-1996, 9.9% of the children were iron deficient, defined by cut-offs for MCV and RDW, and 9.4% of these children had blood lead concentrations of 10 μg/dL or greater (Wright et al., 1999). Among lead-poisoned children, 11.6% were iron deficient. Blood lead levels ranged from less than 5 to 44 μg/dL. More than 50% of the children screened had blood lead concentrations below 5 μg/dL; and the median blood lead was 5 μg/dL. Blood lead levels were stratified into 3 categories: less than 5 μg/dL, 5–9 μg/dL, and greater than 10 μg/dL. Chi-square analysis showed a significant association between rising blood lead levels and iron deficiency, as previously defined. In group comparisons, the mean ages of the patients with blood lead levels less than 5 μg/dL and 10 μg/dL or greater differed significantly from each other, as did those of patients with blood lead levels of less than 5 μg/dL and 5-9 μg/dL. In contrast, there was no significant difference in the mean age for patients with blood lead levels of 5-9 μg/dL and those with blood lead values of 10 μg/dL or greater. Odds ratios were calculated based upon the postulate of iron deficiency as a predictor of blood lead levels after controlling for age, hemoglobin, and insurance status. The odds ratios were 1.63 for a blood lead concentration of 5 μg/dL or more and 1.44 for a blood lead concentration of 10 μg/dL or more among iron deficient children. This study concluded that the combination of increased RDW and decreased MCV (markers of iron deficiency) is associated with blood lead concentrations of more than 5 and more than 10 μg/dL. Thus, this important study demonstrated that iron deficiency is associated with even lower blood lead levels than currently found in the United States.

However, it is important to point out that the associations is not as strong as reported in children with more severe lead poisoning, as discussed above.

In this study (Wright et al., 1999), the combined prevalence of lead poisoning and iron deficiency was present in 1.1% of the children tested. Therefore, secondary preventive measures of childhood lead poisoning, such as selective dietary interventions (iron supplementation), to reduce the intestinal absorption of lead can be simultaneously pursued in tandem with primary preventive efforts (Rosen and Mushak, 2001).

Kordas et al. (2004) examined whether iron status could account in part or for all of the negative relationship between cognitive performance and lead exposure in 602 6-8 year old children living near a metal foundry in Torreon, Mexico. The average blood lead level was 11.5 μg/dL with a standard deviation of 6.1, and 50% of this group had blood lead levels above 10 μg/dL. The results showed that the relation between blood lead and cognition was not strongly affected by nutritional status (iron and zinc), indicating that the association between blood lead and cognition was not explained by the presence of iron deficiency in a relatively intact group of children from the standpoint of nutrition (21.7% were iron deficient). However, low serum ferritin values were more prevalent in children who had blood lead concentrations above 15 μg/dL than those below 15 μg/dL (33.0 vs. 18.4%, $p<0.001$). Furthermore, successive addition of iron status did not attenuate lead's negative association with several cognitive outcomes.

Based upon these reports, it is reasonable to conclude that caloric and fat intake have important effects on blood lead levels in children. Furthermore, based on the above evidence, the inverse association between iron status and blood lead levels is clearly documented in children with low-level lead exposure to more severely elevated blood lead values.

Limited information is available concerning effects of iron supplementation on blood lead levels. Rico et al. (2005) have tested the efficacy of iron (and zinc) supplementation in 515 6-8 year-old children living in close proximity to the lead metal foundry in Torreon, Mexico. This was a randomized, double blind, placebo-controlled study with about 125 subjects in each treatment/placebo group. In addition to supplements or placebo paradigms, selective tests of cognitive functioning were also administered at baseline and 6 months later. The overall prevalence of iron and zinc deficiency was 21.7 and 28.9%, respectively. Thus, in relative terms, this was a reasonably well off population from a nutritional standpoint, with a group of children

many of whom had been excessively exposed to lead since birth. The mean blood lead level was 11.5 µg/dL (SD of 6.1). Cognitive improvements were not discerned in any of the 11 measures employed, and there was a very modest decrease in blood lead levels of only 2.6% (or about 0.30 µg/dL) for the iron supplemented group. These negative findings can be explained by the relatively intact iron status in the majority of children at baseline, and the negative results of cognitive testing can be attributed to a population of children who had been excessively exposed to lead for long timeframes. In contrast, 191 children from a community project in Costa Rica, divided into five treatment groups, had an average blood lead level of 10.98 µg/dL (Wolf et al., 2003). Oral iron supplementation led to a mean decrease in blood lead levels of 1.2 µg/dL over 3 months. These authors concluded that iron therapy can have a substantial effect on decreasing blood lead levels, particularly in children whose iron status is the most compromised and if treated promptly. Interpretation of the results of this study require some degree of caution, because of the limited sample size in each of the five groups.

Mahaffey et al. (1986) analyzed calcium intakes in comparison with blood lead levels in NHANES III. The MEAN and 25th, 50th and 75th percentiles for blood lead concentrations in 2,926 children were, respectively, 15.7, 11, 14, and 19 µg/dL, Corresponding dietary calcium intakes were, respectively, 851, 522, 789, and 1,110 mg/day. Dietary calcium intake was a significant explanatory variable for blood lead, and this relationship was inverse. Thus, in this national survey, a significant and independent inverse association was observed between dietary calcium intake, assessed by the 24-h recall method, and blood lead levels.

One hundred sixty-nine Albany-based mother-infant pairs were evaluated every 3 months during the first year of life according to calcium intakes measured by 24-h recall (Schell et al., 2004). The geometric mean value for blood leads in infants at birth was 1.6 µg/dL; this value rose to 5.1 µg/dL by 12 months of age, when 18% of the sample had elevated blood lead levels (Schell et al., 2004). A significant inverse relationship between calcium intake and blood lead values was found at 6 months; but only the inverse relationship with iron and blood leads persisted to 12 months. The majority of infants in this study met the recommended daily allowances for calcium.

Recent studies that have assessed the impact of calcium on blood lead levels have yielded reasonably consistent results. Sargent et al. (1999) studied 103 children 3.5 to 6 months of age; these infants were followed for 9 months, receiving either no treatment of calcium supplements

or treatment to increase daily calcium intake from about 450 mg/day to a supplemented intake of about 1700 mg/day. Through 4 months of supplementation, the median increase in blood leads was 57% compared to the control group. However, beyond 4 months of treatment, the effect on calcium was attenuated. Up to that time, coupled to measurements of household dust lead, calcium supplementation appeared to impair the absorption of lead from the GI tract; but this apparent effect was not sustained.

In a randomized, double blind, placebo-controlled study, 67 children (1-6 years old), whose blood lead values ranged from 10-45 μg/dL, were given a placebo or a calcium supplement to reach a daily intake of about 1800 mg/day. The mean blood lead levels at baseline were 21.4 and 20.7 μg/dL in the placebo and treatment groups, respectively. All children in this study, from an inner-city group of children in the Bronx, NY, were at or above the daily recommended allowance (RDA) for calcium. Blood lead levels declined similarly in placebo vs. treated groups over the 3-month study period without a differential in final blood lead concentrations between the two groups. It appears that there is a negative association between blood lead levels and calcium intake, particularly, in children who fall below the RDA for calcium. However, even in inner-city children, current calcium intakes appear to readily meet expected RDAs, most likely accounting for the failure of calcium supplements to have effects on blood lead values.

Genetic Polymorphisms

A paucity of information was previously available in EPA's documents in the time frame of 1986-1990. Since that time, at least three genes have been identified that may affect the accumulation and toxicokinetics of lead in children and adults. The three genes are ALAD, the vitamin D receptor gene (VDR), and the hemochromatosis gene (HFE). Relatively few studies relating to genetic polymorphisms have been reported in children compared to a substantial body of clinical research studies reported especially in excessively exposed adults. ALAD, VDR and HFE are discussed here in detail to serve as an introduction for clinical research reports in adults.

The primary importance of incorporating a discussion of genetic polymorphisms in the field of environmental health is their usefulness in detecting differences in levels of risk within specific populations (Kelada et al, 2003). The range of responses to toxic environmental exposures can vary, and population attributable risk may be substantial. Furthermore,

understanding the possible role of genetic polymorphisms in risk assessment can lead to an enhanced delineation of mechanisms underlying toxic exposures.

The ALAD gene (chromosome 9q34) encodes for ALAD, which catalyzes the second step of heme synthesis and is polymorphic. This polymorphism yields two codominant alleles, ALAD-1 and ALAD-2, and these have been differentially implicated in some clinical research studies to lead toxicity (Kelada et al., 2001). It is evident that genotypic frequencies differ by ethnicity and geography; and these considerations require careful assessment in the interpretation of research results. It has been suggested in some studies that ALAD-2 may possibly offer some level of "resistance" to the toxic effects of lead by generating a protein that avidly binds to lead, perhaps sequestering lead from its toxic expressions at various tissue sites. Other studies suggest that the rarer ALAD-2 allele has been associated with higher blood lead levels and may, thereby increase the risk of lead toxicity by producing a protein that binds more tightly than the ALAD-1 protein. Some recent studies in adults have reported that individuals homozygous for the ALAD-1 allele have higher cortical bone lead concentrations and may be at higher risk for long-term adverse effects of lead. Occupationally exposed adults have been most frequently studied in terms of the possible interaction of ALAD polymorphism and adverse health outcomes. As discussed below, reports in children concerning ALAD polymorphism and risk assessment are limited.

The vitamin D receptor (VDR) is a ligand-activated transcription factor that modulates the genomic effects of the vitamin D hormone, 1,25-dihydroxyvitamin D, in a wide variety of tissues. The gene encoding for VDR is on chromosome 12q and has common allelic variants (Zmuda et al., 2000). The allelic variants and their halotypes have been extensively studied with regard to osteoporosis susceptibility. Studies involving other disease states, such as breast and prostate cancer, diabetes, coronary artery disease, and primary hyperparathyroidism, have also focused on the role(s) of VDR gene variants. Consideration of VDR gene variants have also been extended to populations with increased lead exposure, particularly within an occupational setting. Very little information is available on these gene variants and lead exposure in the pediatric age group.

Hereditary hemochromatosis (HHC) is an autosomal recessive disorder of iron metabolism characterized by an increase in iron absorption and deposition in the liver, heart, pancreas, joints, and pituitary gland. HFE, the gene for HHC, has been mapped to the short arm

of chromosome 6 (Hanson et al., 2001). Two of the 37 allelic variants of HFE, described to date, C282Y and H63D have been significantly correlated with HHC. Homozygosity for the C282Y mutation has been found in the majority of patients and their probands diagnosed with HHC. Implications of HFE polymorphism have been proposed in studies of adults excessively exposed to lead, particularly in occupational settings. No studies of HFE have been reported in children with varying blood lead concentrations.

As yet, studies have failed to evaluate arylsulfatase (ASA) polymorphisms in lead exposed children and adults. ASA is recognized as playing a significant role in regions of the brain known to be affected by lead, and it has been established in experimental studies that lead produces low levels of ASA at sensitive stages of nervous system development (Poretz et al., 2000). Studies of ASA in children and adults may yield important information that may explain some of the neurocognitve effects of lead in pediatric and adult populations. As yet, no studies of this nature are available.

A group of 142 lead-poisoned children (mean blood lead: 27.1 μg/dL; SD: 15.2) in New York City children who expressed the 2-2 or 1-2 isozyme phenotype were reported to have blood lead levels 9-11 μg/dL higher than children who were homozygous for the ALAD-1 allele (Wetmur et al., 1991). These authors suggested the possibility that, because the ALAD-2 polypeptide binds lead more effectively, these individuals may be more susceptible to lead poisoning. At the time of publication, the lead binding properties of purified ALAD1-1 and 2-2 proteins and tissue distribution of these alleles were unknown.

The relationship was investigated between ALAD isozymes and blood lead levels in 229 Chinese children within the age range of 6-10 years old (Shen et al., 2000). The mean blood lead value was 10.3 μg/dL (SD: 3.3) and for the 92% of children homozygous for ALAD-1, the mean blood lead was 9.7 μg/dL compared with the 8% of children who were heterozygous (ALAD-1-2) and who had a mean blood lead level of 11.7 μg/dL ($p<0.05$). Using step-wise multiple regression, children who had the ALAD-2 allele were shown to be more likely to have higher blood leads compared to children who had the ALAD-1 allele.

In the only published article to date, environmental samples, blood lead levels, and nutritional factors were assessed together with determinations of VDR-Fok1 genotype (Haynes et al., 2003). A significant interaction was found between dust lead, such that at a 1 $\mu g/ft^2$ increase in floor dust lead, children with VDR-FF genotype had a 1.1% increase in blood lead;

VDR-Ff, a 0.53% increase; and VDR-ff; a 3.8% increase. At floor dust levels less than 10 μg/ft^2, children with VDR-ff had the lowest blood lead concentrations. It is noteworthy that only 17 children in this study were homozygous for the ff allele. Nonetheless, the authors suggested that VDR-Fok1 is an effect modifier for the relationship of floor dust lead exposure and blood lead concentrations.

The implications for risk assessment and health significance in these three pediatric studies are limited. Far more detailed studies in this area of investigation are needed before any firm conclusions can be reached.

Dose-Response Paradigms

The aim of this discussion is to bridge the gap between basic neurotoxicology findings assessed in Section 5.3.1 and the neurobehavioral consequences of lead discussed in Section 6.3.

Based upon current neurotoxicological studies in vivo and in vitro (Section 5.3.1) and based upon epidemiological studies of children (Section 6.3), it is biologically implausible that neurotoxic effects of lead do not occur at blood lead concentrations in children above and below 10 μg/dL. Although it is difficult to extrapolate from experimental studies to investigations in children (Manton et al., 2001), some examples are revealing.

In experimental systems, lead dose is typically employed in molar concentrations (Section 5.3.1); 10 μg/dL of lead in whole blood of children is equivalent to a molar concentration of 0.48 μM. In vitro studies have reported effects of lead on cellular regulatory systems in neurons (and other tissues) far below 0.48 μM. Whereas most or all of the lead used in neurochemistry experimental systems can participate in a reaction, only a small fraction of circulating lead in blood enters specific metabolic pathways. It is recognized that the major portion of lead in whole blood is carried by erythrocytes and that the most accessible fraction of circulating lead to other tissues is in plasma. It has been estimated that 0.24 to 0.29% of lead in whole blood is in plasma (Smith et al., 2002) and that the concentration in CSF is about half of the plasma concentration (Manton and Cook, 1984). Thus, a calculation of the latter concentrations in plasma and CSF in 10 μg/dL of whole blood yields concentrations in the low nanomolar range.

It is very unlikely that the plasma concentration of lead in the low nanomolar range is the "dose" that impacts upon the CNS of children at blood lead levels less than 10 μg/dL. The

"dose" that perturbs the central nervous system of children at "low" blood lead levels is likely to be much higher. Lead's half-lives in various tissues is a function of the site of deposition and degree of on-going exposure. In blood (absent excessive external exposure), the half-life is about 30 days and in brain, the half-life is about 2 years (Leggett, 1993). However, in the absence of on-going external exposure, blood lead levels can remain elevated for relatively extended periods of time due to mobilization from internal stores (Roberts et al., 2001; Manton et al., 2000). As a result, lead, which readily penetrates the blood-brain barrier, can continuously enter neural tissue from the blood compartment (Leggett, 1993).

Active transport mechanisms are also important to consider, and these mechanisms cause differential concentrations of lead in the systemic circulation compared to those in neuronal compartments. Metabolic pumps increase concentrations of ions within intracellular organelles to levels that exceed those in the cytosol. Mechanisms affecting Ca^{2+} distribution are the most critical (Section 5.3.1). Lead's toxic effects in the brain and other tissues are based, in large part, on its ability to "mimic" Ca^{2+} in intracellular processes, coupled to its actions to perturb the Ca^{2+} messenger system (Schanne et al., 1989; Lidsky and Schneider, 2003). For example, lead enters neurons and glia by channels that, under physiological conditions, permit the passage of Ca^{2+} (Kerper and Hinkle, 1997; Legare et al., 1998). Lead enters and damages mitochondria via cellular mechanisms that bring calcium into this organelle (Chavez et al., 1987). Thus, transport mechanisms bring about variations in local concentrations of Ca^{2+} and, presumably, lead as well (Schanne et al., 1989).

Based upon these considerations, it is concluded that brain cells in children are likely exposed to concentrations of lead, in the context of "low" blood lead levels, in the mid-nanomolar range and possibly higher, particularly in organelles that depend upon the calcium messenger system for their physiological activities. The experimental literature clearly demonstrates perturbations in fundamental cellular processes in the nanomolar range and considerably lower (Section 5.3.1).

The shape of the dose-response curve(s) of IQ and blood lead concentrations in children below blood lead levels of 10 µg/dL may be considered to be unexpected. However, the above considerations provide a different and reasonable explanation. It is accepted that lead achieves its neurotoxic effects on multi-neuronal targets, and the threshold concentrations of lead to perturb multiple CNS targets differ by orders of magnitude (Lidsky and Schneider, 2003).

For instance, second messenger systems are affected at picomolar to nanomolar concentrations (Schanne et al., 1989; Lidsky and Schneider, 2003). These perturbations can mediate a variety of toxic consequences of lead by perturbing the temporal and spatial resolution of Ca^{2+}. As a result, several loci within the complex Ca^{2+} messenger system may be impaired, thereby explaining toxic effects of lead on multiple cellular processes affecting brain functioning at differential intracellular concentrations. At somewhat higher lead concentrations in the circulation, other critical subcellular processes will be affected and impaired (e.g., heme synthesis and cellular energy metabolism). Thus, based upon various targets in the CNS affected by lead at widely different concentrations, the dose-response curve would tend to be steeper at lower lead "doses," as may be seen when inspecting the relationships between blood lead and IQ, particularly at blood lead levels less than 10 μg/dL.

Neuro-Epidemiological Studies: Implications for Individual Children

Bellinger (2004) pointed out that the clinically evident cognitive outcomes applicable to attributing specific neurobehavioral outcomes to childhood lead poisoning differ from those that are employed more typically to characterize risk in a population of children. The latter type of epidemiological studies have been applied to setting public health standards in children by the EPA and the U.S. Centers for Disease Control and Prevention. However, the clinical presentation of and ultimately the diagnosis of cognitive outcomes caused by excessive exposure to lead in individual children have received little attention. Moreover, the clinical presentation of lead exposure in the individual child cannot be clearly recognized or ascertained from epidemiological data (Lidsky and Schneider, 2005).

The majority of risk assessment studies have reported the averaged performance of large cohorts of children on a traditional IQ test as the neurobehavioral outcome measure. Such studies, after adjustment for appropriate confounders, have consistently reported an inverse correlation between blood lead concentrations and IQ scores (Schwartz, 1994). In addition to IQ as the outcome index, children who have elevated blood lead levels have been shown to lack skills in basic academic subjects (Needleman et al., 1990; Fergusson et al., 1997; Lanphear et al., 2000). As adolescents, such children are at risk for anti-social behavior (Dietrich et al., 2001; Needleman et al., 2002). These reports indicate that the outcomes in a lead-exposed child focus on impairments in intellectual achievement, academic performance, and problematic behavior.

These nonspecific outcomes are of extremely limited diagnostic utility for a pediatrician to understand what measurable outcomes may or may not be attributable to childhood lead exposure in an individual child.

Because lead has neurotoxic effects on a child's developing brain (Bressler et al., 1999; Lidsky and Schneider, 2003; Finkelstein et al., 1998), diagnostic methods are necessary to uncover manifestations of brain dysfunction. IQ tests were not designed to evaluate brain dysfunction; IQ tests are insensitive to the symptoms of brain dysfunction resulting from brain injury (Lezak, 1995). Manifestations of brain injury are manifested by highly specific aspects of impaired functions that involve language, memory, and executive skills (Lezak, 1995). In contrast, IQ is an aggregate, based on the summed performance of several sub-tests that assess an array of cognitive functions, and this array fails to tap into focal deficits that are the stigmata of brain injury. Given the lack of sensitivity of IQ scores to assess the presence of brain damage, the generally consistent findings of lead's adverse affects on IQ reflect the robustness of the reported data (Hill, 1965; Chen et al., 2005; Lanphear, 2005). Whereas the mean IQ in a large group of children has often shown a decrease as a result of brain damage, the size of the decrease fails to reflect the failures of a child's abilities to carry out daily living activities, which are typically brought to the attention of a pediatrician for treatment and management.

Neuropsychology is an applied science focused on the neurobehavioral manifestations of brain dysfunction (Lezak, 1995). Neuropsychological test batteries focus on testing paradigms that are controlled by specific neural systems to detect functional effects of brain injury. Several studies (noted above) have reported impairments in groups of children that have carried out neuropsychological tests of fine motor skills, executive abilities, language, and aspects of learning and memory (Bellinger et al., 1994; Faust and Brown, 1987; Stiles and Bellinger, 1993; Dietrich et al., 1992; Walkowiak et al., 1998; Wasserman et al., 2000; Campbell et al., 2000; Winneke and Kramer, 1997; Canfield et al., 2004; Ris et al., 2004).

Because diffuse neurocognitive "dulling" is not a typical outcome of childhood lead exposure and because a specific pattern of cognitive deficits ("signature injury or injuries") is not apparent in individual children, the clinical-pediatric presentation is specific to each individual child. Thus, a child's specific deficits evidenced by neuropsychological testing are of little assistance in making a clinical diagnosis of past or present exposure to lead and the lack of a

neurobehavioral "signature" is common to other neurotoxic agents that can cause brain injury (Hartman, 1995).

Neuropsychological testing within a clinical framework is designed to measure cognitive and behavioral manifestations of normal and abnormal brain function to arrive at a diagnosis of brain injury, when present. Decisions arriving at evidence for abnormality are based on a pattern of test results tapping specific neural systems, with the understanding that some systems will be affected and diminished as a result of brain injury whereas others will be unaffected (Lezak, 1995; Lidsky and Schneider, 2003, 2005).

From this discussion, it is reasonable to conclude that neuropsychological assessments provide additional and important information to the clinical understanding of an individual child compared to what a pediatrician and neuropsychologist can ascertain from epidemiological data. Clinical neuropsychological evaluations can lead to an etiological conclusion, together with a pediatrician's differential diagnosis, whether a child's cognitive deficits are typical of brain injury and whether, if present, that injury can be diagnostically attributed to lead exposure. When impairments are detected, it is then the task of the pediatrician to carry out a physical examination and to review medical records, radiographs, laboratory data, and environmental-exposure information. Based upon review of all this information and a differential diagnosis to rule out other causes of brain damage, a clinical determination can be made as to the etiology of an individual child's impairments and whether such deficits can be the result of lead exposure. Once alternative or contributing etiologies have been ruled out as the cause of brain damage, a diagnosis can be made causally linking lead exposure to brain damage in an individual child. This describes the collaborative roles of the neuropsychologist and pediatrician in determining the role of lead as the etiological factor (or not) in producing manifestations of brain damage in the context of different patterns of neuropsychological deficits in each individual child.

5.3.2.2 Clinical Manifestations in Adults with Childhood Lead Poisoning

It is reasonable to conclude from the studies discussed in this section that clinical manifestations become manifest in adults as persistent or latent consequences of earlier childhood lead poisoning. Specific effects of lead in this section include impairments in cognitive abilities that directly involve the central nervous system (White et al., 1993). These data have been applied to cognitive outcomes (White et al., 1993) and mortality rates in adults

following severe childhood lead poisoning (McDonald et al., 1996). Data from these analyses also indicate the presence of long-term latent and/or persistent effects on blood pressure in adults several decades after severe childhood lead poisoning (Hu, 1991). These data have been extended to more recent studies of lead's impacts on adults from early excessive childhood exposure, in terms of adverse health impacts on the central and peripheral nervous systems. With current analytical techniques, these data have been applied and connected to bone lead concentrations, as well as to the development of hypertension (Stokes et al., 1998; Gerr et al., 2002).

This section includes new concepts of health impacts of lead on adults from lead exposure during childhood, concepts that were not expressed in the previous 1986 EPA Lead AQCD/Addendum and the 1990 Supplement to that Addendum.

White et al. (1993) evaluated cognitive functioning in 33 adults (mean age of 54 years), all of whom had been admitted to Boston's Children's Hospital during 1930-1942. Because blood lead measurements were not available then, criteria for the diagnosis of lead poisoning included: (1) lead paint exposure and pica; (2) signs and symptoms of childhood lead poisoning (i.e., abdominal pain, vomiting, constipation, anorexia, irritability.) A latter subgroup of 27 adults was considered to have the mildest lead poisoning. The second and third groups had more severe central nervous system symptoms of "nerve palsy" (n = 3) and encephalopathy (n = 3) as well as (3) positive lead lines on skeletal radiographs. The 33 retrieved adults from the Boston area were generally characterized as to the severity of their childhood lead poisoning into three groups (according to the above symptoms) and according to blood lead concentrations estimated as 60–100, 90–120, and greater than 120 μg/dL, respectively. Each adult underwent a 90-m neuropsychological test battery. Compared to matched controls, the 33 adults evidenced widespread cognitive deficits in attention, memory, reasoning, motor speed, visual-spatial-constructional skills, and coordination; previously leaded subjects were lower (compared to controls) in lifetime occupational status. These observations were consistent with the onset of brain damage as children with persistence 50 years later. Exposure of the CNS during their adult years could also have occurred from release of lead from bone stores (Tsaih et al., 2001).

This is the first retrospective report that systematically addressed cognitive outcomes in adults from childhood lead poisoning. Nonetheless, these data are limited by their observational

context, lack of blood lead measurements, the long interval between childhood to the point of study as adults, the limited number of subjects, and the retrospective nature of the design.

McDonald and Potter (1996) assessed ratios of observed (O)/expected (E) deaths in a cohort of 454 adults admitted as lead-poisoned children to Boston Children's Hospital from 1923 to 1966 and traced through December, 1991. These are the only such data reported. As children, the criteria for lead poisoning was based upon the following: (1) a history of "paint pica" or other sources of exposure; (2) positive bone radiographs for lead lines; and (3) GI, neurologic and/or hematologic signs and symptoms. Seventy-six percent of this group met all three criteria and 24% met at least two out of the three criteria for diagnostic inclusion. Data were adjusted for confounders such as age, sex, ethnicity, and calendar period but not for socioeconomic status. As noted, observed deaths were compared to expected deaths; and O/E ratios were computed for hematological deaths (O/E = 9.7), for seizure disorder deaths (O/E = 5.0), for cardiovascular disease deaths (O/E = 2.1), and for cerebrovascular disease deaths (O/E = 5.5). This unique study also has limitations. It was retrospective in design, deaths may have been underestimated, there was an excess of cases dating back to the 1930s, and blood lead measurements did not begin at Boston Children's Hospital until 1963. Moreover, 153 of the original cohort of 454 were lost to follow-up. However, the authors pointed out that (1) blood lead levels measured post-1963 were generally consistent with the classification of the severity of lead poisoning pre-1963; (2) although 153 of the original group were lost to follow-up, the remaining cohort was followed for a total period of 29.5 years; (3) if deaths were missed, this would have artificially lowered the observed O/E ratios; (4) interpretation of these results could be limited by the relatively small number of deaths; but, for each of the mortality outcomes, less than one death was expected. Overall, in this cohort, mortality from all causes was about 70% higher than expected.

Collectively, although the studies reported by White et al. (1993) and McDonald and Potter (1996) have limitations, these are the first reported data to indicate that severe lead poisoning causes brain damage and impacts on mortality in adults from childhood lead poisoning.

Recent reports, utilizing current methodologies, have extended the above data relating to cognitive outcomes (Stokes et al., 1998), as well as hypertension (Gerr et al., 2002) in a cohort of 257 adults (19-29 years old) who had childhood lead poisoning at 9 months to 9 years of age

from lead smelters in Idaho's Silver Valley. In 1974-1975, the mean blood lead level in young children at each of five towns near the smelter activities was in the range of 40 to 65 µg/dL and the standard deviations of the blood lead levels in the five towns ranged from 13.5 to 28 µg/dL (Gerr et al., 2002). Of the 257 adults excessively exposed as children, 43 individual blood lead values were traced back to 1974-1975, and the mean level was 49 µg/dL. The referent cohort was in the Spokane, WA area. The exposed and nonexposed groups were compared in terms of electrophysiological and neuropsychological testing, and the latter results were evaluated with concurrent K-XRF tibial lead measurements.

Fine motor and cognitive outcomes in the exposure group, after adjustment for confounding, were significantly associated with poorer performance on hand-eye coordination, reaction time, trails B, symbol digit, serial digit learning, Raven progressive matrices, and vocabulary tests. The estimated effect of being in the exposed group was negative for all 12 of the motor and cognitive outcomes. Among tests of peripheral nerve function, vibrotactile thresholds of the fingers and standing steadiness were significantly different between the exposed and nonexposed groups; sural sensory amplitude and peroneal motor amplitude were significantly related to the exposure group. Tibial bone lead measurements failed to reach a p value $<.05$ in any of the test paradigms, although there was a trend towards significance in vocabulary and vibrotactile thresholds for fingers and toes in the exposed group. This apparent insensitivity of bone lead measurements to various outcome measures was probably related to the modest precision of K-XRF determinations.

Based on this study, it is reasonable to conclude that excessive accumulation of lead in childhood has latent and/or persistent adverse health effects on both the peripheral and central nervous systems of adults assessed 19-29 years later. The latter report, using currently available methods, is generally consistent with the earlier study by White et al. (1993). Information is needed in less severely exposed children followed longitudinally into adolescence and the adult age group.

5.3.2.3 Adults with Ambient Exposures to Lead

In the previous 1986 EPA AQCD/Addendum, the focus was on adverse health effects in adults at blood lead levels in the range of 30-50 µg/dL. The studies reviewed focused on slowed nerve conduction velocities, altered testicular function, reduced Hg production, and other signs

of impaired heme synthesis evident at somewhat lower blood lead levels. These effects pointed to a generalized impairment of normal physiological functioning as adult lead levels exceeded 30-40 μg/dL. The lowest observed effect levels of 15-30 μg/dL were related to impairments in heme synthesis. In contrast, in the 1990 Supplement to the 1986 Addendum, it was concluded that the relationship between lead and blood pressure held across a wide range of blood lead values, possibly extending down to 7 μg/dL for middle-aged men. In brief, except for effects of lead on heme synthesis down to adult blood lead values of about 15 μg/dL, EPA's emphasis was on adverse health effects in the 30-40-50 μg/dL blood lead range (1986-1990).

Since that time, studies have shown lead's effects in terms of biomarkers and indices of vulnerability and susceptibility in adult populations with blood lead concentrations, on average, less than 10 μg/dL. The number and strength of these studies are limited (see below). Several of these recent studies have also included K-XRF measurements of lead in bone which should be cautiously interpreted.

Biochemical Biomarkers

Plasma total homocysteine (tHcy) is recognized as an independent risk factor for atherosclerosis and cardiovascular disease and has both environmental and genetic risk factors. Homocysteine is an intermediate metabolite in the trans-sulfation pathway that converts methionine to cysteine. Moreover, the addition to homocysteine of serine by the pyridoxal phosphate-dependent enzyme cystathionine βeta-synthase produces cystathionine, which in turn is converted to cysteine by cystathionine gamma-lyase (CTH) (Mudd et al., 1995). Homocysteine can either be methylated back to methionine by the enzyme methionine synthase (MTH) or can undergo trans-sulfuration to produce cystathionine (Mudd et al., 1995). As a result, many enzymes can affect plasma tHcy concentrations, and each enzyme can identify a potential candidate gene for evaluating the genetic determinants of plasma tHcy. Of common gene variants, the thermolabile variant in MTHFR encoding methylenetetrahydrofolate has been associated with elevated plasma tHcy. This and other variants have been connected to the disease states noted above (Weisberg et al., 2003). In this regard, a study of 496 Caucasian adults found that common variants in CTH can be a determinant of plasma tHct levels (Wang et al., 2004).

In view of these interactions and the associations of plasma tHcy with environmental factors, cardiovascular disease and cognitive dysfunction, Schafer et al. (2005) evaluated the possible relationship between blood lead levels, tibia lead (by K-XRF), and tHcy in a longitudinal study carried out within the context of the Baltimore Memory Study. In this study, 1,140 randomly selected adults were assessed. They had a mean age of 59.3 years, an average (SD) blood lead level of 3.5 (2.4) μg/dL, and a mean (SD) tibia lead (μg of Pb/g bone mineral) concentration of 18.9 (12.5). After adjustment for age, sex, ethnicity, educational level, and tobacco and alcohol use, plasma tHcy levels were found to have increased 0.35 μmol/L per 1 μg/dL increase in blood lead concentration. No relationship was found between plasma tHcy and tibia lead levels, perhaps because of the wide standard deviation among the subjects and the modest precision of the K-XRF methodology. At blood lead levels, on average, under 10 μg/dL, these results provide some initial evidence suggesting that tHcy could be a mechanism underlying lead effects on the cardiovascular and central nervous systems. Whether lead directly elevates plasma tHcy, whether lead kinetics may be modified by tHcy, and/or whether one of homocysteine's polymorphic variants may have specific binding properties for lead are all open questions for which further investigation is required.

Vulnerability and Susceptibility

Socioeconomic Status

There was very little information on socioeconomic status (SES) in ambiently exposed adults in previous EPA Documents (1986-1990). Although some data have been published since 1990, it is limited to investigations of a female population in Mexico City (Farias et al., 1996), of male populations from the Normative Aging Study in Boston (Elreedy et al., 1999), and of a minority group of men in the Boston area (Lin et al., 2004).

Determinants of blood lead levels were evaluated in 513 pregnant women in Mexico City: one group of women was enrolled from a public general hospital, and was considered to be low SES. The second group, a high-SES cohort, was enrolled from a private hospital. The geometric mean blood lead values were 6.6 and 11.12 μg/dL from the high and low SES groups, respectively (Farias et al., 1996). The entire population of pregnant women was enrolled in this study during January 1994 to August 1995 and, beside different exposure paradigms, seasonality played an important role in differentiating blood lead concentrations between the high and low

SES groups. The primary determining factor for blood lead levels in the low SES population was the use of lead-glazed ceramics in women from the public hospital; and seasonality was the main factor influencing blood lead levels in the women from the private hospital. A predictive model, fitted to milk consumption, dietary supplements of calcium plus gestational age, was predictive of a 14 μg/dL difference between the best and worst scenarios in women from the public hospital. Seasonal differences in blood lead concentrations, which ranged, on average, from 4.7 to 12.7 μg/dL, from summer to winter, respectively, in the high SES-private hospital-based women, focused on airborne lead as their primary source of exposure, although measurements of air lead levels were not reported.

Elreedy et al. (1999) investigated various factors related to SES in 538 white males (ages 50-92) in the Normative Aging Study or Boston-based adults. Questionnaire data were collected regarding educational and occupational status, and these data were further analyzed using 1990 Census Block Group Data. Men who had four years of college, compared to others who did not graduate from high school, had, on average, lower bone lead levels. These data suggested the possibility of individual SES as having an affect on cumulative lead exposure. Detailed information on the health status of these two groups of Boston men was not provided.

Eighty-four minority individuals living in the Boston area were compared by bone lead measurements to previously studied Caucasian subjects: the mean values for blood lead (SD), tibia lead (SD) and patella lead (SD) for the minority group of males were 3.0 μg/dL, 11.9 μg/g (11), and 14.9 μg/g (15.3), respectively. These results suggest disparities in body burdens of lead in the minority group of men, particularly in those older than 55 years of age. However, the high standard deviations in the bone lead data, the modest precision of the utilized K-XRF system, and lack of information on the health status within the minority group of men require a level of caution in evaluating these outcomes, which, in themselves, based upon the NHANES data from childhood national data, are not surprising.

Nutrition

Studies reported in populations from Mexico City, Boston and Rio de Janeiro provided new information on nutritional parameters in subjects with mean blood and erythrocyte lead levels less than 10 μg/dL. These three studies examined the effects of calcium and vitamin D nutrition in various populations.

Erythrocyte lead concentrations were evaluated in 68 pregnant and 45 lactating Rio de Janeiro women whose dietary intakes of calcium were low on a chronic basis (400-600 mg/day). Whole blood lead concentrations were less than 10 μg/dL in these women, including 33 controls (Pires et al., 2001). Lactating women had significantly higher erythrocyte lead values compared to both pregnant and control subjects. Indices of bone resorption (urinary d-pyridinoline) and formation (plasma bone alkaline phosphatase) were significantly higher in pregnant and lactating women, suggesting that RBC lead was elevated in the ambiently exposed women during lactation with low dietary intakes of calcium.

A larger group of lactating women (617) in Mexico City were examined from 1994-1995 to further understand the potential effects of lowering blood lead levels through dietary calcium supplements (Hernandez-Avilla et al., 2003). The average age was 24 years; the mean blood lead level at baseline was 8.5 μg/dL. Women were randomly assigned to receive either calcium carbonate (1200 mg/day) or placebo in a double-blind study, and blood lead concentrations were measured at 3 and 6 months into the study. A modest decrease of 1.16 μg/dL (mean) was observed at 6 months in the calcium-supplemented group. This relatively small decrease in blood lead values may be explained, in part, by relatively high lead burdens in this Mexico City population, although blood lead levels did not exceed 8.5 μg/dL initially.

A cross-sectional assessment was carried out by Cheng et al. (1998) in 747 males in the context of the Boston Aging Study. In 67-year-old men (average age) the mean (SD) blood lead, tibia lead and patella lead were 6.2 (4.1) μg/dL, 21.9 (13.3) μg/g, and 32 (19.5) μg/g, respectively. After adjusting for age, education, cigarette use, and alcohol consumption, men in the lowest quintile of total dietary intakes of vitamin D (179 IU/day) had higher bone lead content compared to men in the highest quintile for vitamin D intake (IU 589/day). These data are consistent with those discussed above, in that low dietary intakes of vitamin could be expected to decrease calcium and increase lead absorption from the GI tract. However, dietary calcium intakes were not measured in this study.

Genetic Polymorphisms

Since 1986-1990, two reports have been published relating to genetic polymorphisms in ambiently exposed adults: one of these is related to ALAD and the other to HFE. Both of these studies were carried out in the Boston Normative Aging Study in adult males. Hu et al. (2001)

investigated whether ALAD polymorphism may be associated with blood and bone lead values in 726 middle-aged and elderly men from the Boston area. In this group of men, the mean (SD) of blood lead concentrations, tibia lead and patella lead were 6.2 (4.1) μg/dL, 22.1 (13.5) μg/g, and 30.4 (17.2) μg/g, respectively. The ALAD 1-1 genotype was associated with an increase of 2.55 μg/g in cortical bone (tibia), thereby suggesting the possibility that the ALAD 2 allele may decrease the accumulation of lead in bone. Whether this difference of 2.55 μg/g bone mineral was above or below the precision and/or the minimum detection limits of the K-XRF method was not addressed in this report.

Within the same Boston population, Wright et al. (2004) evaluated potential relationships between the HFE gene and bone lead values in 730 men. Of this population, 13 and 25% had the C282Y and H63D variants of HFE, respectively. After adjusting for age, smoking, and education, carriers of the HFE variant allele(s) had lower patella bone lead concentrations compared to all groups by polymorphism analyses. Caution in interpreting these data are expressed, as in other data reported from the Boston Normative Aging Study.

Neurotoxicology of Lead

One study has been reported since 1986-1990 that assessed aspects of cognitive functioning in the Normative Aging Study in Boston within a group of 466 males who had low-level or ambient lead exposure. The purpose was to evaluate whether biomarkers of lead were related to cognitive functioning, and the latter was indexed by the Mini-Mental State Examination (MMSE) (Weisskopf et al., 2004a). On two occasions, 3.5 years apart, MMSE scores were obtained during 1993–2002 in men whose age averaged 67.4 years. Bone lead measurements by K-XRF were assessed on two occasions between 1993–2002. The presented results indicated that a one-interquartile range (20 μg/g) increase in patella lead was associated with a decline in the MMSE equivalent to that of aging 5 years in relation to baseline MMSE scores. Associations were not observed in values for blood lead or tibia lead levels. The authors suggested that this steeper decline in MMSE scores was thus related to lead that is mobilizable from skeletal store (patella lead). These data reflect an important beginning to define effects of ambient lead exposure on cognitive functioning in adults. Although the MMSE has been employed in epidemiological population-based research, it is evident that a comprehensive

neuropsychological test battery has the potential to provide more definitive information related to understanding further the impact of ambient lead exposure on cognition in adults.

5.4 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF LEAD

5.4.1 Summary of Key Findings on the Developmental and Reproductive Effects of Lead in Animals from the 1986 Lead AQCD

The 1986 Pb AQCD presented unequivocal evidence for effects of Pb on reproduction and development in laboratory animals, derived principally from studies of rodents. Fetotoxic effects (spontaneous abortion and fetal death) were reported following chronic exposures to relatively high doses (600 to 800 ppm inorganic lead) in the diet, and more subtle effects (such as changes in ALA-D activity or hematocrit) at lower doses (5 to 10 ppm in drinking water and 10 $\mu g/m^3$ in air). The 1986 Pb AQCD reported that the lowest observed adverse effect level (LOAEL) for reproductive and developmental effects was 64 µg/kg per day (multiple exposures by gavage).

The 1986 Pb AQCD also reported evidence for a variety of sublethal effects on reproduction and development in experimental laboratory animals following Pb exposure. Sublethal effects included changes in levels or function of reproductive hormones as well as effects on the gonads (both male and female) and conception. The animal data also suggested more subtle effects on hormone metabolism and reproductive cell structure. Stowe and Goyer (1971) classified the reproductive effects of Pb as gametotoxic, whether intrauterine or extrauterine.

The data reported in the 1986 Pb AQCD, and more recent studies conducted in experimental animal models, provide convincing evidence that Pb induces temporary and long-lasting effects on male and female reproductive and developmental function. The newer literature supports the earlier conclusions presented in the 1986 Pb AQCD that Pb disrupts endocrine function at multiple points along the hypothalamic-pituitary-gonad axis (Sokol et al., 1985; Stowe and Goyer, 1971; Vermande Van Eck and Meigs, 1960; Junaid et al., 1997; McGivern at al., 1991; Ronis et al., 1996, 1998b,c; Sokol, 1987; Sokol et al., 1985, 1994, 1998; Sokol and Berman, 1991; Kempinas at al., 1988, 1990, 1994; Tchernitchin et al., 1998b; Sant' Ana et al., 2001; Srivastava et al., 2004). A schematic representation of the hypothalamic-pituitary-gonadal axis is shown in Figure 5-4.1.

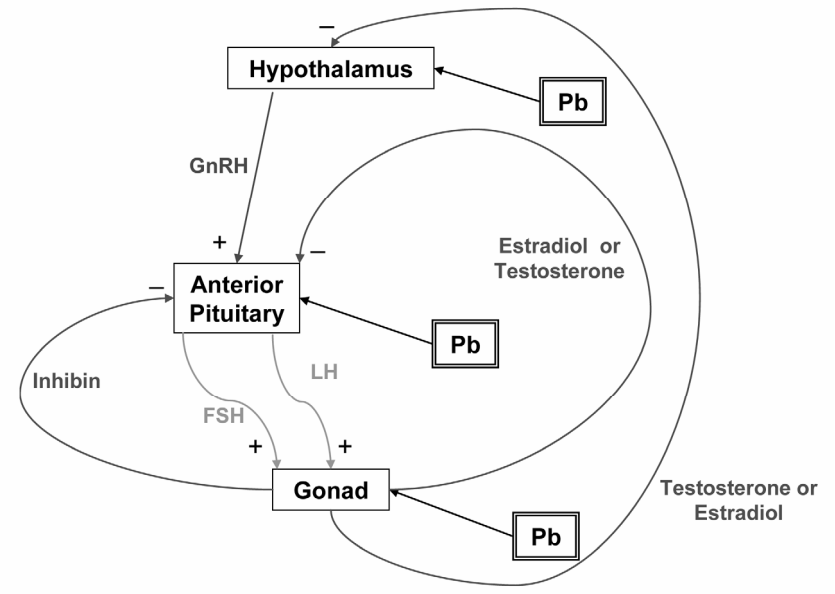


Figure 5-4.1. Data from male and female experimental animals suggests that Pb has multiple targets in the hypothalmic-pituitary-gonadal axis.

The majority of the experimental animal studies on developmental and reproductive effects of Pb examined effects due to inorganic forms of lead; very little is known about the reproductive and developmental effects due to organic forms. In general, the few available studies suggest that effects of organic forms of Pb are similar to those produced by inorganic forms. Administration of triethyl-Pb-chloride during early gestation reduces pregnancy rates in mice (Odenbro and Kihlström, 1977). Growth retardation following organolead exposure has been reported (Kennedy et al., 1975; McClain and Becker, 1972). More recent studies have demonstrated that exposure of mice to triethyl-Pb-chloride during late gestation reduces perinatal growth rate (Odenbro et al., 1988).

This section summarizes the evidence for effects of Pb exposure in developing organisms exposed during the period from conception to maturity that has been reported since 1986. Effects on neurological, immunological, or renal endpoints in developing organisms are discussed in Sections 5.3, 5.9 and 5.7, respectively.

5.4.2 Effects on Male Reproductive Function

The 1986 Pb AQCD reported convincing evidence based on experimental animal studies that Pb acts as an endocrine disruptor in males. Those studies demonstrated an association between reduced male fertility and repeat-dose Pb exposure. Lead exposure had been reported to alter sperm development and function; however, the mechanism underlying these effects was not completely understood. These effects were attributed to either alterations in testicular enzymes important for hormone production or to changes in the hormone receptors. More recent research supports the conclusion that the mechanisms for endocrine disruption in males involves Pb acting at multiple sites along the hypothalamic-pituitary-gonadal axis (see Figure 5-4.1).

Reported effects of Pb on male reproduction differ substantially across studies, with some studies finding profoundly adverse effects and other studies finding no or minimal effects. The variable findings have been attributed to the complex mechanisms involved in hormone regulation and the multiple sites of action for lead. Sokol et al. (2002) suggested that differences in results among studies may be, in part, attributed to an adaptive mechanism in the hypothalamic-pituitary-gonadal axis that may render the expression of some toxic effects dependent on exposure duration. Sokol and Berman (1991) found that timing of exposure was critical to Pb-induced male reproductive toxicity in rats. Studies conducted in nonhuman primates supported the importance of timing, finding that the adverse effects of Pb on male reproduction are dependent upon age (i.e., developmental stage at time of exposure) and duration of exposure (Foster et al., 1993; Singh et al., 1993a).

The adverse effects of Pb on male reproduction may be expressed as perturbations in sexual development and maturation, changes in fertility, endocrine disruption, and alterations in structure of reproductive cells or tissue. Each of these effects is discussed in greater detail in the sections that follow.

5.4.2.1 Effects on Male Sexual Development and Maturation

The 1986 Pb AQCD reported adverse effects of Pb on male sexual development and maturation. Experimental studies conducted in animals demonstrated that high-dose (e.g., dietary exposure to 0.08 to 1.0% Pb-acetate in mice and to 100 ppm in dogs) preadolescent Pb exposure can produce long-lasting detrimental effects on male sexual development. Numerous more recent studies conducted in experimental animals support the earlier findings that Pb

exposure during early development can delay the onset of male puberty and alter reproductive function later in life (McGivern et al., 1991; al-Hakkak et al., 1988; Chowdhuri et al., 2001; Dearth et al., 2002, 2004; Gandley et al., 1999; McGivern et al., 1991; Ronis et al., 1998a,c; Sokol et al., 1994; Yu et al., 1996). Studies that provide the strongest evidence for the dose-response range for typical effects in rodents are discussed below (Table 5-4.1).

McGivern et al. (1991) found that male rats born to dams that received Pb-acetate in drinking water beginning on gestation day 14 and through parturition (PbB 73 µg/dL) exhibited reduced sperm counts, altered male reproductive behavior, and enlarged prostates later in life. Prepubertal exposure of male Sprague-Dawley rats (age 24 to 74 days) to Pb-acetate in drinking water (PbB 30 to 60 µg/dL) resulted in significant reduction in testis weight and in the weight of secondary sex organs; however, these effects were not observed in rats exposed postpubertally (day 60 to 74; Ronis et al., 1996). A dose-dependent delay in sexual maturation was found in male rats, following prenatal Pb exposure that continued until adulthood (age 85 days) (Ronis et al., 1998a,b,c). In these studies, PbBs in the pups between the ages of 21 and 85 days were >100 µg/dL. Additional details concerning these studies are provided in Table 5-4.1.

One possible explanation for the persistent effects of Pb exposure on the male reproductive system is a disruption in pulsatile release of sex hormones during early development (Ronis et al., 1998c). Lead effects on sex hormones are discussed in Section 5.4.2.3.

5.4.2.2 Effects on Male Fertility: Effects on Sperm Production and Function

The 1986 Pb AQCD presented evidence that Pb exposure affects male fertility in various animal species, including rabbits (Cole and Bachhuber, 1915), guinea pigs (Weller, 1915), rats (Ivanova-Chemishanska et al., 1980), and mice (Schroeder and Mitchener, 1971).

Several more recent studies, conducted in various animal species, have demonstrated Pb-induced alteration of sperm parameters (e.g., count, motility, number of abnormal) (Sokol et al., 1985; and eight other studies). These effects, however, have not been reproduced in all studies. For example, Foster et al. (1996a) reported that 15- to 20-year-old cynomolgus monkeys receiving Pb-acetate for their lifetime (mean PbB 56 µg/dL) showed no significant alterations in sperm parameters (i.e., sperm count, viability, motility, and morphology) or circulating levels of testosterone (see Section 5.4.2.3 for discussion of lead-induced changes in testosterone levels).

Table 5-4.1. Selected Studies Showing the Effects of Lead on Reproductive Function in Males

Citation	Species/ Strain	Dose/Route/Form/Duration/Group Size	Endpoint/Magnitude of Effect/p-value	Blood Lead Concentration (PbB)
Foster et al. (1993)	Monkey/ Cynomolgus	0–1500 µg Pb-acetate/kg-d in gelatin capsules p.o. for various durations: 9 control monkeys, 4 monkeys in lifetime group (birth to 9 years), 4 in infancy group (first 400 days of life), 4 in post-infancy exposure (from 300 days to 9 years)	Suppressed LH response to GnRH stimulation in the lifetime group ($p = 0.0370$); Sertoli cell function (reduction in the inhibin to FSH ratio) ($p = 0.0286$) in lifetime and post-infancy groups.	Lifetime group 3–26 µg/dL at 4–5 years Infancy group 5–36 µg/dL at 100–300 days, 3–3 µg/dL at 4–5 years Post-infancy group 20–35 µg/dL
Foster et al. (1996a)	Monkey/ Cynomolgus	0–1500 µg Pb-acetate/kg-d in gelatin capsules p.o. from birth until 9 years of age 8 control monkeys, 4 monkeys in low group (6–20 µg/dL), 7 monkeys in high group (22–148 µg/dL)	Mean PbB of 56 µg/dL showed no significant alterations in parameters of semen quality (count, viability, motility, or morphology).	PbB 10±3 or 56±49 µg/dL
Foster et al. (1998)	Monkey/ Cynomolgus	0–1500 µg Pb-acetate/kg-d in gelatin capsules p.o. for various durations: birth to 10 years (lifetime); PND 300 to 10 years (post-infancy); birth to 300 days (infancy); 3 control monkeys, 4 lifetime, 4 infancy, 5 post-infancy	Circulating concentrations of FSH, LH, and testosterone were not altered by treatment; semen characteristics (count, motility, morphology) were not affected by treatment possibly because not all Sertoli cells were injured; degeneration of seminiferous epithelium in infancy and lifetime groups (no difference in severity between these groups); ultrastructural alterations in seminal vesicles, most prominent in infancy and post-infancy groups.	PbB ~35 µg/dL
McGivern et al. (1991)	Rat/Sprague-Dawley	0.1% Pb-acetate in drinking water from GD 14 to parturition; 8 control litters; 6 Pb-acetate litters (5 males per litter)	Decreased sperm count (21% at 70 days and 24% at 165 days, $p<0.05$); reduced male behavior ($p < 0.05$); enlarged prostate (25% increase in weight; $p<0.07$); irregular release patterns of both FSH and LH ($p<0.05$).	Control PbB <5 µg/dL at birth Maternal PbB 73 µg/dL at birth Pup PbB 64 µg/dL at birth
Ronis et al. (1996)	Rat/Sprague-Dawley	0.6% Pb-acetate in drinking water for various durations: PND 24–74 (pubertal exposure); PND 60–74 (post pubertal exposure); 11 males and females in pubertal exposure group (10 each in control pubertal group); 6 males and females post-pubertal exposure and control groups	PbB >250 µg/dL reduced circulating testosterone levels in male rats 40–50% ($p < 0.05$); reduction in male secondary sex organ weight ($p < 0.005$); delayed vaginal opening ($p<0.0001$); disrupted estrous cycle in females (50% of rats); increased incidence of stillbirth (2% control vs. 19% Pb) ($p < 0.005$).	Pubertal PbB 30–60 µg/dL Post-pubertal PbB 30–60 µg/dL Mean PbBs in male rats 30–60 µg/dL, respectively

Table 5-4.1 (cont'd). Selected Studies Showing the Effects of Lead on Reproductive Function in Males

Citation	Species/ Strain	Dose/Route/Form/Duration/Group Size	Endpoint/Magnitude of Effect/p-value	Blood Lead Concentration (PbB)
Ronis et al. (1998a)	Rat/Sprague-Dawley	0.6% Pb-acetate in drinking water ad libitum for various durations as follows: GD 5 to PND 1; GD 5 to weaning; PND 1 to weaning; 3 control litters, 2 gestation exposure litters, 2 lactation exposure litters, 2 gestation and lactation exposure litters, 2 postnatal exposure litters, 2 chronic exposure litters; 4 male and 4 female pups per litter	Suppression of adult mean serum testosterone levels was only observed in male pups exposed to Pb continuously from GD 5 throughout life ($p < 0.05$).	Group: Male PbB Naïve: 5.5±2.0 µg/dL Control: 1.9±0.2 µg/dL Gest: 9.1±0.7 µg/dL Lact: 3.3±0.4 µg/dL Gest+Lact: 16.1±2.3 µg/dL Postnatal: 226.0±29 µg/dL Chronic: 316.0±53 µg/dL
Ronis et al. (1998b)	Rat/Sprague-Dawley	Lead acetate in drinking water (0.05% to 0.45% w/v); dams exposed until weaning; exposure of pups which continued until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Dose-response reduction in birth weight ($p < 0.05$), more pronounced in male pups; decreased growth rates in both sexes ($p < 0.05$) were accompanied by a statistically significant decrease in plasma concentrations of IGF1 through puberty PND 35 and 55 ($p < 0.05$); increase in pituitary growth hormone during puberty ($p < 0.05$).	Mean PbB in offspring at 0.05% (w/v) 49±6 µg/dL Mean PbB in offspring at 0.15% (w/v) 126 ± 16 µg/dL Mean PbB in offspring at 0.45% (w/v) 263 ± 28 µg/dL
Ronis et al. (1998c)	Rat/Sprague-Dawley	Lead acetate 0.05, 0.15, or 0.45% in drinking water beginning GD 5 continuing until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%); 4 male and 4 female pups per litter	Dose-responsive decrease in birth weight ($p < 0.05$); dose-responsive decrease in crown-to-rump length ($p < 0.05$); dose-dependent delay in sexual maturity ($p < 0.05$); decrease in prostate weight ($p < 0.05$); decrease in plasma concentration of testosterone during puberty ($p < 0.05$); decrease in plasma LH ($p < 0.05$); elevated pituitary LH content ($p < 0.05$); decrease in plasma testosterone/LH ratio at high dose ($p < 0.05$).	Dams: 0, 48, 88, or 181 µg/dL Pups PND 1: <1, 40, 83, or 120 µg/dL Pups PND 21: <1, 46, 196, or 236 µg/dL Pups PND 35: <1, 20, 70, or 278 µg/dL Pups PND 55: <1, 68, 137, or 379 µg/dL Pups PND 85: <1, 59, 129, or 214 µg/dL

Table 5-4.1 (cont'd). Selected Studies Showing the Effects of Lead on Reproductive Function in Males

Citation	Species/ Strain	Dose/Route/Form/Duration/Group Size	Endpoint/Magnitude of Effect/p-value	Blood Lead Concentration (PbB)		
Singh et al. (1993a)	Monkey/ Cynomolgus	0–1500 µg Pb-acetate/kg-d in gelatin capsules for various durations: 3 control monkeys, 4 monkeys in infancy group (exposure first 400 days), 5 in post-infancy group (exposure 300 days to 9 years of age), 4 in lifetime group (exposure from birth until 9 years)	Degeneration of seminiferous epithelium in all exposed groups (frequency not specified); ultrastructural alterations in seminal vesicles, most prominent in infancy and post-infancy groups (frequency not specified).	Chronic PbB <40–50 µg/dL		
Sokol and Berman (1991)	Rat/Wistar	0, 0.1, or 0.3% Pb-acetate in drinking water for 30 days beginning at 42, 52, or 70 days old; 8–11 control rats for each age, 8–11 rats for each age in 0.1% group, 8–11 rats for each age in 0.3% group	Dose-related suppression of spermatogenesis (decreased sperm count and sperm production rate) in the exposed rats of the two highest age groups ($p < 0.05$); dose-related suppression of serum testosterone in 52-day old rats ($p = 0.04$) and in 70-day old rats ($p < 0.003$).	Group	Age	PbB
				0%	All	<7 µg/dL
					42 d	25 µg/dL
				0.1%	52 d	35 µg/dL
					70 d	37 µg/dL
					42 d	36 µg/dL
				0.3%	52 d	60 µg/dL
					70 d	42 µg/dL

FSH, follicle stimulating hormone; GD, gestational day; GnRH, gonadotropin releasing hormone; IGF_1, insulin-like growth factor 1; LH, luteinizing hormone; PbB, blood Pb concentration; PND, post-natal day

Sokol et al. (2002) provided evidence of an adaptive mechanism in the hypothalamic-pituitary-gonadal axis in response to prolonged exposure to lead. The existence of this adaptive mechanism would explain the apparent inconsistency in reported effects on circulating testosterone levels, sperm count, and sperm production following Pb exposure. Because of this adaptive mechanism, changes in testosterone levels and certain sperm parameters may not always serve as reliable endpoints for assessing the effects of Pb on male fertility and reproductive function for all exposure durations.

Although gross changes in sperm parameters were not observed in monkeys in which chronic PbB was approximately 56 µg/dL, Foster et al. (1996a) reported that monkey sperm exhibited a statistically significant, dose-related reduction in chromatin structure (as determined by susceptibility to weak acid denaturation). These changes may have adverse impacts on fertility, and they are thought to be related to dominant lethal effects of Pb (similar to the effects reported by al-Hakkak et al. [1988] in mice). Additional details concerning Foster et al. (1996a) are provided in Table 5-4.1.

The data from Foster et al. (1996a), demonstrating a change in monkey sperm chromatin suggestive of a subtle lead-induced reduction in male fertility (in the absence of gross changes sperm parameters), are consistent with observations of reduced in vitro fertilization capacity of sperm collected from other mammalian species. Sokol et al. (1994) reported that exposure of adult male rats to Pb-acetate in drinking water for 14 to 60 days (PbB 33 to 46 µg/dL) resulted in reduced in vitro fertilization of eggs harvested from unexposed females. No differences were observed in sperm ultrastructure or in the DNA histogram of sperm obtained from lead-exposed rats compared to controls. Consistent with this finding are reports of reduced fertilization capacity of rabbit sperm exposed to high concentrations (25 µM) of Pb chloride in vitro (Foote, 1999) and reduced in vitro fertilization capacity of sperm from mice exposed to Pb in drinking water at 1 g/L for 4 months (PbB not reported) (Johansson et al., 1987).

Two modes of action have been proposed for lead-induced alterations in sperm capacity for fertilization. The affinity of Pb for sulfhydryl groups may explain some of the lead-induced alterations in sperm structure and function. Mammalian sperm possess high concentrations of sulfhydryl groups, which are critical for maintaining normal function (Johansson and Pellicciari, 1988). Reyes et al. (1976) demonstrated that binding of Pb to membrane thiols inhibits sperm maturation. In addition, recent experimental data also suggest that lead-induced generation of

reactive oxygen species (ROS) may contribute to the injury of tissues responsible for sperm formation (see Section 5.4.2.4).

5.4.2.3 Effects on Male Sex Endocrine System

The 1986 Pb AQCD reported that, although the mode of action for the adverse effects of Pb on the male reproductive system was not understood, effects on hormone production or hormone receptors were likely contributors. More recent studies provide convincing evidence that Pb acts as an endocrine disruptor in males at various points along the hypothalamic-pituitary-gonadal axis (Figure 5-4.1). In rats, Pb exposures that decreased serum testosterone levels increased mRNA levels of GnRH and LH in the hypothalamus and pituitary, respectively, and increased levels of LH in pituitary; these changes can occur in the absence of a change in serum gonadotropin levels (Klein et al., 1994; Ronis et al., 1998c; Sokol et al., 2002). In monkeys, chronic Pb exposures (PbB 20 to 35 μg/dL) suppressed GnRH-induced secretion of LH and decreased serum testosterone:LH and inhibin:FSH ratios (Foster et al., 1993). The mechanisms underlying the effects on the hypothalamic-pituitary-gonadal axis have not been elucidated but may involve a suppression of GnRH secretion (Bratton et al., 1994; Sokol, 1987; Sokol et al., 1998).

Although there is evidence for a common mode of action, consistent effects on circulating testosterone levels are not always observed in lead-exposed animals. Rodamilans et al. (1988) and Kempinas et al. (1994) attributed these inconsistencies to the normal biological variation (circannual and seasonal) of testosterone secretion in rats and monkeys. Observations of lead-induced reductions in testosterone levels in some studies, but not others, may be due to enhanced sensitivity to inhibition of the testosterone secretory system during certain periods of development. In addition, the hypothalamic-pituitary-gonadal axis exhibits compensatory mechanisms that may attenuate the effects of Pb during prolonged Pb exposure (Sokol et al., 2002). Taken together, the sensitivity of testosterone secretion during certain periods and potential for modulation of the effects during long-term exposures studies, may explain some of the apparent inconsistencies in the reported effects of Pb exposure on circulating testosterone levels.

5.4.2.4 Effects on Morphology and Histology of Male Sex Organs

The 1986 Pb AQCD reported evidence for histological changes in the testes or prostate in rats, in association with relatively high doses of Pb (Chowdhury et al., 1984; Hilderbrand et al., 1973; Golubovich et al., 1968). More recent studies conducted in animal models provide persuasive support for testicular damage (i.e., ultrastructural changes in testes and cytotoxicity in Sertoli cells) following lower level lead exposure (Foster et al., 1998; Singh et al., 1993a; Batra et al., 2001; Chowdhury et al., 1986, 1987; Corpas et al., 1995; Pinon-Lataillade et al., 1993; Saxena et al., 1990). Studies conducted in nonhuman primates warrant particular attention. These studies found ultrastructural changes in the testes (Sertoli and other spermatogenic cells) of monkeys at PbB 35 to 40 µg/dL (Foster et al., 1998; Singh et al., 1993a).

Foster et al. (1998) reported that chronic Pb exposure (PbB ~35 µg/dL), beginning in infancy, resulted in persistent ultrastructural changes in the testes of cynomolgus monkeys. Electron microscopy showed disruption of the general structure of the seminiferous epithelium involving Sertoli cells, basal lamina, and spermatids in the groups exposed for lifetime and during infancy (with no duration difference in severity). Chronic exposures to Pb beginning after infancy, that achieved similar PbBs, did not produce these effects.

Similarly, Singh et al. (1993a) demonstrated ultrastructural changes in testicular basement membrane and Sertoli cell morphology (seminiferous tubules) in cynomolgus monkeys exposed chronically to Pb (PbB <40 to 50 µg/dL); the effects were most prominent when dosing began in infancy or post-infancy. These results suggest that, in monkeys, Pb exposure during certain periods of development produces persistent testicular alterations. Additional details concerning Foster et al. (1998) and Singh et al. (1993a) are provided in Table 5-4.1.

A possible mode of action for lead-induced testicular injury is oxidative stress. Foster et al. (1998) suggested that lead-induced oxygen free radical generation was a plausible mechanism of testicular injury in primates. This oxygen radical hypothesis is supported by studies conducted in rodents (Chowdhury et al., 1984; Acharya et al., 2003; Adhikari et al., 2001; Batra et al., 2001; Bizarro et al., 2003; Chowdhury et al., 1984; Gorbel et al., 2002; Mishra and Acharya, 2004). Also supporting the oxidative stress hypothesis are observations of increases in the percentage of apoptotic cells in the testes of rodents in response to Pb exposure (Pace et al., 2005; Gorbel et al., 2002; Adhikari et al., 2001).

5.4.3 Effects on Female Reproductive Function

Lead has been shown to disrupt the hypothalamic-pituitary-gonadal axis and to produce ovarian atrophy and reproductive dysfunction in females (Figure 5-4.1). The 1986 Pb AQCD reported that Pb exposure was associated with inhibition of menstruation, ovulation, and follicular growth in monkeys (Vermande-Van Eck and Meigs, 1960), and in rodents Pb exposure delayed vaginal opening, decreased frequency of implantation, and reduced rates of pregnancy (Kimmel et al., 1980; Odenbro and Kihlström, 1977, respectively).

Data from more recent experimental animal studies support these findings. Lead effects on female reproduction may be classified as alterations in female sexual maturation, effects on fertility and menstrual cycle, endocrine disruption, and changes in morphology or histology or female reproductive organs as well as the placenta. Recent literature concerning each of these effects is summarized below.

5.4.3.1 Effects on Female Sexual Development and Maturation

The 1986 Pb AQCD reported that Pb exposure in rodents produced delays in sexual maturation. Grant et al. (1980) reported delayed vaginal opening in female rats exposed in utero and during lactation and maturation (PbB ~20 to 40 μg/dL). More recent studies in experimental animals (primarily rodent studies) provide convincing evidence that Pb exposure before puberty (particularly prenatal and early postnatal exposure) delays the maturation of the female reproductive system (Dearth et al., 2002, 2004; Ronis et al., 1996, 1998b,c).

Dearth et al. (2002) is of particular interest, because it employed a cross-fostering design (to allow comparison of pups exposed during gestation only, lactation only, or both) and because maternal and offspring PbBs were monitored throughout gestation and lactation. Fisher 344 dams were exposed to Pb by gavage beginning 30 days before mating until weaning of the pups at 21 days of age (gavage exposure removes possible confounding of exposure by consumption of Pb in drinking water by pups in those studies where drinking water is the route of exposure for dams). Mean maternal PbB was approximately 40 μg/dL. Pups exposed during gestation and lactation had the highest PbB (38.5 μg/dL) on day 10; at this time, the PbBs in pups exposed during gestation only or lactation only were 13.7 and 27.6 μg/dL, respectively. By postnatal day (PND) 30, all three groups had PbB ≤3 μg/dL. Dearth et al. (2002) reported a statistically significant delay in the onset of puberty (vaginal opening and days at first diestrus) in rats

exposed during lactation, gestation, or during lactation and gestation (with no differences among the groups). In addition, a statistically significant reduction in the circulating levels of insulin-like growth factor 1 (IGF_1), LH, and estradiol (E_2) were reported on PND 30 in all three treatment groups (with no differences among treatment groups). Additional details concerning Dearth et al. (2002) are provided in Table 5-4.2.

A subsequent study in both Sprague-Dawley and F344 rats (Dearth et al., 2004) showed that the F344 strain is more sensitive to maternal Pb exposure than Sprague-Dawley rats to lead-induced delayed puberty, which could, in part, explain the inconsistencies with effect levels observed in Sprague Dawley rats (e.g., Ronis et al., 1998a,b,c; McGivern et al., 1991). Ronis et al. (1998c) suggested that the delayed onset of puberty may arise from a lead-induced disruption of pulsatile release of sex hormones (see Section 5.4.3.3).

5.4.3.2 Effects on Female Fertility

The 1986 Pb AQCD reported convincing evidence from experimental animal studies for lead-induced alterations in female fertility, including interference with implantation and pregnancy (Odenbro and Kihlström, 1977; Wide and Nilsson, 1977). More recent studies have confirmed these effects. In general, Pb exposure does not produce total sterility, although Pb exposure clearly disturbs female fertility (Taupeau et al., 2001). Studies in nonhuman primates and rodents have shown that exposure of gravid females to Pb produces implantation dysfunction and reduces litter size and newborn survival (Lögdberg et al., 1987; Flora and Tandon, 1987; Johansson and Wide, 1986; Pinon-Lataillade et al., 1995; Piasek and Kostial, 1991; Ronis et al., 1996). See Section 5.4.4.1 for details.

5.4.3.3 Effects on the Female Sex Endocrine System and Menstrual Cycle

The 1986 Pb AQCD described numerous studies that found effects of Pb on the female endocrine system and menstrual cycle in various species, including nonhuman primates, and that supported the conclusion that Pb was an endocrine disruptor in females (Grant et al., 1980; Maker et al., 1975; Vermande-Van Eck and Meigs, 1960). Observations of delayed vaginal opening (see Section 5.4.3.1) were attributed to the endocrine disruption effects of Pb on the hypothalamic-pituitary-gonadal axis (Stowe and Goyer, 1971; Vermande Van Eck and Meigs, 1960).

Table 5-4.2. Selected Studies Showing the Effects of Lead on Reproductive Function in Females

Citation	Species/ Strain	Dose/Route/Form/Duration/ Group Size	Endpoint/Magnitude of Effect (% or incidence) /p-value	Blood Lead Concentration (PbB)
Dearth et al. (2002)	Rat/Fisher 344	12 mg/mL Pb-acetate gavage from 30 days prior breeding until pups were weaned 21 day after birth; 10–32 litters per group, control group, gestation and lactation exposure, gestation only exposure, lactation only exposure	Delay in onset of puberty ($p < 0.05$); reduced serum levels of IGF_1 ($p < 0.001$), LH ($p < 0.001$), and E_2 ($p < 0.001$).	Maternal PbB ~40 µg/dL Pups PbB as follows: Gest+lact ~38 µg/dL PND 10 Gest+lact ~15 µg/dL PND 21 Gest+lact ~3 µg/dL PND 30 Gest ~14 µg/dL PND 10 Gest ~3 µg/dL PND 21 Gest ~1 µg/dL PND 30 Lact ~28 µg/dL PND 10 Lact ~15 µg/dL PND 21 Lact ~3 µg/dL PND 30
Foster (1992)	Monkey/ Cynomolgus	Daily dosing for up to 10 years with gelatin capsules containing Pb-acetate (1.5 mg/kg); 8 control group monkeys, 8 lifetime exposure (birth–10 years), 8 childhood exposure (birth–400 days), and 8 adolescent exposure (PND 300-10 years of age)	Statistically significant reductions in circulating levels of LH, ($p < 0.042$), FSH ($p < 0.041$), and E_2 ($p < 0.0001$) during menstrual cycle; progesterone concentrations were unchanged and menstrual cycle was not significantly affected.	PbB <40 µg/dL
Foster et al. (1992)	Monkey/ Cynomolgus	Daily dosing for up to 10 years with gelatin capsules containing Pb-acetate (1.5 mg/kg); 8 control group monkeys, 8 childhood (birth–400 days), 7 adolescent (PND 300–10 years), 7 lifetime (birth–10 years)	No effect on endometrial response to gonadal steroids as determined by ultrasound.	PbB <40 µg/dL
Foster et al. (1996b)	Monkey/ Cynomolgus	Chronic exposure to Pb-acetate 50 to 2000 µg/kg-day p.o. beginning at birth for 15–20 years; 20 control monkeys, 4 monkeys in 50 µg/kg-d group, 3 monkeys in 100 µg/kg-d, 2 monkeys in 500 µg/kg-d group, and 3 monkeys in 2000 µg/kg-d group	Reduced corpora luteal production of progesterone ($p = 0.04$), without alterations in E_2, 20-alpha-hydroxyprogesterone, or menstrual cyclicity.	PbB 10–15 µg/dL in low group (50 or 100 µg/kg-day) PbB 25–30 µg/dL in moderate group (500 or 2000 µg/kg-day)

Table 5-4.2 (cont'd). Selected Studies Showing the Effects of Lead on Reproductive Function in Females

Citation	Species/ Strain	Dose/Route/Form/Duration/ Group Size	Endpoint/Magnitude of Effect (% or incidence)/p-value	Blood Lead Concentration (PbB)
Franks et al. (1989)	Monkey/ Rhesus	Lead acetate in drinking water (2–8 mg/kg-d) for 33 months; 7 control and 10 Pb monkeys	Reduced circulating concentration of progesterone ($p < 0.05$); treatment with Pb did not prevent ovulation, but produced longer and more variable menstrual cycles and shorter menstrual flow.	PbB 68.9 ± 6.54 µg/dL
Laughlin et al. (1987)	Monkey/ Rhesus	Lead acetate in drinking water at 3.6, 5.9, or 8.1 mg/kg-day for 1–2 years 7 control and 10 experimental monkeys per group	Reductions in cycle frequency ($p<0.01$); fewer days of flow ($p<0.01$); longer and more variable cycle intervals ($p<0.025$).	PbB 44–89 µg/dL 51.2 µg/dL (low dose) 80.7 µg/dL (mid dose) 88.4 µg/dL (high dose)
Lögdberg et al. (1988)	Monkey/ Squirrel	Lead acetate (varying concentrations ≤0.1% in diet) maternal dosing from 5-8.5 weeks pregnant to PND 1 11 control monkeys, 3 low Pb exposure group (PbB 24 µg/dL), 7 medium Pb group (PbB 40 µg/dL, 5 high Pb group (PbB 56 µg/dL)	Dose-dependent reduction in placental weight ($p<0.0007$); various pathological lesions were seen in the placentas (n = 4), including hemorrhages, hyalinization of the parenchyma with destruction of the villi and massive vacuolization of chorion epithelium.	Mean maternal PbB 37 µg/dL (22-82 µg/dL) 24 (22–26) µg/dL (low dose) 40 (35–46) µg/dL (mid dose) 56 (43–82) µg/dL (high dose)

E_2, estradiol; FSH, follicle stimulating hormone; GD, gestational day; IGF_1, insulin-like growth factor 1; LH, luteinizing hormone; PbB, blood Pb concentration; PND, post-natal day

More recent studies have provided convincing support for endocrine-mediated alterations of the female reproductive system in rats (Srivastava et al., 2004; Dearth et al., 2002; Ronis et al., 1998a,b,c; Junaid et al., 1997; Ronis et al., 1996), guinea pigs (Sierra and Tiffany-Castiglioni, 1992), and nonhuman primates (Foster et al., 1992, 1996b; Foster, 1992; Franks et al., 1989; Laughlin et al., 1987). The nonhuman primate studies are particularly relevant to extrapolations to humans and provide dose-response information for effects of Pb on female sex hormones and menstrual cycle.

Laughlin et al. (1987) found that exposure to Pb (PbB 44 to 89 μg/dL) alters menstrual cycles (specifically, causing reductions in cycle frequency, fewer days of menstrual flow, and longer and more variable cycle intervals) in female rhesus monkeys. Consistent with these observations, Franks et al. (1989) found that chronic exposure to Pb in the drinking water (PbB 70 μg/dL) reduced circulating concentrations of progesterone (suggesting impaired luteal function), produced longer and more variable menstrual cycles and temporally shorter menstrual flow in female rhesus monkeys. Additional details concerning these studies are provided in Table 5-4.2.

At lower blood Pb levels (PbB <40 μg/dL), female cynomolgus monkeys exhibited statistically significant reductions in circulating levels of LH, FSH, and E_2 during the menstrual cycle; however, serum progesterone concentrations were unchanged and menstrual cycle was not significantly affected (Foster, 1992). Similar exposures and PbB were shown to have no effect on endometrial response to gonadal steroids in cynomolgus monkeys as determined by ultrasound analysis (Foster et al., 1992). At lower blood lead concentrations (25 to 30 μg/dL), reduced corpora luteal production of progesterone occurred in the absence of alterations in E_2, 20-alpha-hydroxyprogesterone, or menstrual cyclicity (Foster et al., 1996b). In contrast to Foster et al. (1992), this study (Foster et al., 1996b) found no statistically significant effect of Pb on serum progesterone levels in cynomolgus monkeys that had lower PbB (10 to 15 μg/dL). Additional details concerning these studies are provided in Table 5-4.2.

Several modes of action for lead-induced, endocrine disruption-mediated alterations in female reproduction have been proposed, including changes in hormone synthesis or metabolism at the enzyme level (Wiebe and Barr, 1988; Wiebe et al., 1988) and changes in hormone receptor levels (Wiebe et al., 1988; Wide and D'Argy, 1986). In addition, Pb may alter sex hormone release and imprinting during early development (Ronis et al., 1998c; Tchernitchin et al.,

1998a,b). The latter effects would be consistent with observations of persistent changes in estrogen receptor levels in the uterus (Wiebe and Barr, 1988) and LH function in the ovary (Srivastava et al., 2004) in lead-exposed animals.

5.4.3.4 Effects on Morphology and Histology of Female Sex Organs and the Placenta

Lead-induced changes in morphology or histology in female sex organs and the placenta may explain reduced fertility and impaired female reproductive success (see Sections 5.4.3.2 and 5.4.4.1.). Lögdberg et al. (1988) reported a dose-dependent reduction in placental weight and an increase in pathological lesions of the placenta in squirrel monkeys that received oral doses of Pb-acetate (0.001 to 0.1% in diet) during the last three-fourths or two-thirds of pregnancy (mean maternal PbB 37 µg/dL; range: 22 to 82 µg/dL). These effects occurred without overt toxicity in the mothers. Additional details concerning Lögdberg et al. (1988) are provided in Table 5-4.2.

Similar effects on placental weight and histology were observed in mice (Fuentes et al., 1996; Nayak et al., 1989). These effects on the placenta may explain the reduced birth weight that has been associated with prenatal Pb exposure (see Section 5.4.5). Exposure to Pb in early pregnancy also produces structural changes in the epithelium of the uterus of mice (Nilsson et al., 1991; Wide and Nilsson, 1979). These changes in uterine tissue may impair successful implantation of the blastocysts (see Section 5.4.4.1).

5.4.4 Effects on Embryogenesis

Lead exposure can increase fetal mortality, produce a variety of sublethal effects, and disrupt the growth and development of the offspring. Many of the lead-induced sublethal developmental effects occur at maternal PbB levels that do not result in clinical toxicity in the mothers.

5.4.4.1 Embryo/Fetal Mortality

The 1986 Pb AQCD concluded that that acute exposure to high doses of Pb interfered with implantation and pregnancy (Wide, 1985; Odenbro and Kihlström, 1977; Wide and Nilsson, 1977; Vermande-Van Eck and Meigs, 1960). This conclusion is supported by results of more recent studies (Lögdberg et al., 1987; Giavini et al., 1980; Jacquet, 1976, 1977; Jacquet et al.,

1975, 1976; Johansson and Wide 1986; Johansson et al., 1987; Johansson, 1989; Maisin et al., 1978; Pinon-Lataillade et al., 1995; Wide and Nilsson, 1977, 1979).

Lögdberg et al. (1987) reported an increase in pre- and perinatal mortality in squirrel monkeys that received Pb-acetate orally during the last two-thirds of pregnancy (45% versus 7 to 8% among controls). Mean maternal PbB was 54 µg/dL (39 to 82 µg/dL). These fetotoxic effects occurred without overt toxicity in the mothers. Additional details concerning Lögdberg et al. (1987) are provided in Table 5-4.3. These effects are consistent with data from rodent studies, wherein gestational exposure to Pb (PbB 32 to >70 µg/dL) resulted in smaller litters and fewer implantation sites (e.g., Pinon-Lataillade et al., 1995; Singh et al., 1993b; Piasek and Kostial, 1991).

Numerous studies have been performed to elucidate the mechanisms by which Pb causes prenatal death (Maisin at al., 1978; Jacquet, 1977, 1976; Jacquet et al., 1976, 1975). The available data suggest that Pb may alter blastocyst development and impair implantation. Hanna et al. (1997) demonstrated that in vitro exposure of 2- and 4-cell mouse embryos to 200 µM Pb-acetate resulted in reduced cell proliferation and blastocyst formation. Additional evidence for an effect on blastocysts is provided by data from in vitro fertilization studies (Chowdhuri et al., 2001; Johansson, 1989; Johansson et al., 1987). Johansson and co-workers (1989, 1987) reported that Pb delayed the timing of escape from the zona pellucida and induced a premature acrosome reaction. These effects could disrupt attachment and implantation of the blastocyst if they were to occur in vivo.

5.4.4.2 Effects on embryo/fetal morphology

The 1986 Pb AQCD summarized numerous reports that found associations between prenatal exposure to high doses of Pb and increased incidences of teratogenic effects (particularly tail stunting) in rodents (Ferm and Carpenter, 1967; Dey et al., 2001; Flora and Tandon, 1987; Ronis et al., 1996; Wide, 1985). More recent studies provide additional support for teratogenic effects of Pb in experimental animals (Flora and Tandon, 1987). Flora and Tandon (1987) demonstrated a dose-dependent effect on the incidence of tail malformations at ≥10 mg/kg i.v. on days 9 to 11 of gestation (PbB 13 to 45 µg/dL) that occurred only in those dams exhibiting "observable maternal toxicity" (not otherwise specified in the report). The few

Table 5-4.3. Selected Studies Showing the Effects of Lead on Mammalian Embryogenesis and Development

Citation	Species/ Strain	Dose/Route/Form/Duration/Group size	Endpoint/Magnitude of Effect/p-value	Blood Lead Concentration (PbB)
Cory-Slechta et al. (2004)	Rat/Long-Evans	Lead acetate in drinking water (150 ppm); 2 months before breeding until the end of lactation; 14 rats no maternal stress with Pb exposure, 15 rats no maternal stress with Pb exposure, 18 rats maternal stress without Pb exposure, 23 rats maternal stress and Pb exposure	Pb alone (in male) ($p<0.05$) and Pb plus stress (in females) ($p<0.05$) permanently elevated corticosterene levels in offspring	PbB 30–40 µg/dL
Dearth et al. (2002)	Rat/Fisher 344	12 mg/mL Pb-acetate gavage during gestation and lactation exposure 4 groups: control group, gestation and lactation exposure, gestation only exposure, lactation only exposure 10–32 litters per group (NOS)	Delayed onset of puberty ($p<0.05$); suppressed serum levels of IGF_1, LH, and E_2 ($p<0.001$); Pb altered translation and/or secretion of IGF_1 ($p<0.001$).	Maternal PbB ~40 µg/dL Pups PbB as follows: Gest+lact ~38 µg/dL PND 10 Gest+lact ~15 µg/dL PND 21 Gest+lact ~3 µg/ PND 30 Gest ~14 µg/dL PND 10 Gest ~3 µg/dL PND 21 Gest ~1 µg/dL PND 30 Lact ~28 µg/dL PND 10 Lact ~15 µg/dL PND 21 Lact ~3 µg/dL PND 30
Flora and Tandon (1987)	Rat/Albino (NOS)	Lead nitrate dissolved in water 2–20 mg/kg-d i.v. on day 9, 10, 11 of gestation; 6 rats in each group (0, 5, 10 , 20, 40 mg/kg lead)	Dose-dependant increase in external malformations at all doses ($p<0.001$), particularly tail defects; dose-dependant decrease in number of live births at 20 and 400 mg/kg ($p<0.001$); dose-dependent increase in number of resorptions per dam at ≤10 mg/kg ($p<0.01$).	PbB 4.13±0.61 µg/dL 0 mg/kg PbB 10.21±0.61 µg/dL 5 mg/kg PbB 13.13±0.27 µg/dL 10 mg/kg PbB 29.41±0.41 µg/dL 20 mg/kg PbB 45.03±0.31 µg/dL 40 mg/kg
Fox et al. (1991a)	Rat/Long-Evans hooded	Lactation exposure via dams exposed to 0.02 or 0.2% Pb in drinking water from PND 1 through weaning (PND 21); 8 female pups per litter (number of litter unspecified) control pups, 8 pups for litter (number of litter unspecified) low-level exposure pups, 8 pups per litter (number of litter unspecified) moderate level exposure pups	Long-term, dose-dependent decreases retinal Na/K ATPase activity in the female offspring (only female pups were used) (-11%; -26%) ($p<0.05$).	PbB 18.8 µg/dL (0.02%) or 59.4 µg/dL (0.2%) at weaning

Table 5-4.3 (cont'd). Selected Studies Showing the Effects of Lead on Mammalian Embryogenesis and Development

Citation	Species/ Strain	Dose/Route/Form/Duration/Group Size	Endpoint/Magnitude of Effect/p-value	Blood Lead Concentration (PbB)
Fox et al. (1997)	Rat/Long-Evans hooded	0.02 or 0.2% Pb-acetate in drinking water from PND 0–PND 21; 8 female pups per litter control pups; 8 pups per litter low-level exposure; 8 pups per litter moderate level exposure (number of litters per dose unspecified)	Developmental and adult Pb exposure for 6 weeks produced age and dose-dependent retinal degeneration such that rods and bipolar cells were selectively lost; at the ultrastructural level, all dying cells exhibit the classical morphological features of apoptotic cell death; decrease in the number of rods was correlated with the loss of rhodopsin content per eye confirming that rods were directly affected by Pb ($p < 0.05$); single-flash rod ERGs and cone ERGs obtained from lead-exposed rats demonstrated that there were age- and dose-dependent decreases in the rod a-wave and b-wave sensitivity and maximum amplitudes without any effect on cones; in adult rats exposed to Pb for three weeks, qualitatively similar ERG changes occurred in the absence of cell loss or decrease in rhodopsin content ($p < 0.05$); developmental and adult Pb exposure for three and six weeks produced age- and dose-dependent decreases in retinal cGMP phosphodiesterase (PDE) activity resulting in increased cGMP levels ($p<0.05$); retinas of developing and adult rats exposed to Pb exhibit qualitatively similar rod mediated ERG alterations as well as rod and bipolar apoptotic cell death ($p<0.05$) Similar biochemical mechanism such as the inhibition of rod and bipolar cell cGMP PDE, varying only in degree and duration, underlies both the lead-induced ERG rod-mediated deficits and the rod and bipolar apoptotic cell death ($p<0.05$).	PbB weanlings 19±3 (low exposure) or 59±8 µg/dL (moderate exposure), adult 7±2 µg/dL (at PND 90)
Iavicoli et al. (2003)	Mouse/Swiss	Lead acetate in food (0.02, 0.06, 0.11, 0.2, 2, 4, 20, 40 ppm); exposure began 1 day after mating until litter was 90 days old; one litter of mice exposed to each dietary concentration	Low-level Pb exposure (PbB 2–13 µg/dL) reduced red cell synthesis ($p<0.05$); high-level exposure (PbB 0.6-2 µg/dL) enhanced red cell synthesis ($p < 0.05$).	PbB 0.6 to <2.0 µg/dL or >2.0–13 µg/dL

Table 5-4.3 (cont'd). Selected Studies Showing the Effects of Lead on Mammalian Embryogenesis and Development

Citation	Species/ Strain	Dose/Route/Form/Duration/Group size	Endpoint/Magnitude of effect/p-value	Blood Lead Concentration (PbB)
Lögdberg et al. (1987)	Monkey/ Squirrel	Lead acetate (5–20 mg/kg daily to maintain PbB) maternal dosing from 5–8.5 weeks pregnant to PND1 20 control; 11 lead-exposed monkeys	Increase in pre- and perinatal mortality among squirrel monkeys receiving Pb-acetate p.o. during the last two-thirds of pregnancy (45% vs. 7–8% among controls). Statistically significant reductions in mean birth weight ($p<0.05$) were observed in Pb exposed monkeys as compared to controls. Effects occurred without clinical manifestation of toxic effects in the mothers.	PbB 54 µg/dL (39–82 µg/dL)
Ronis et al. (1996)	Rat/Sprague-Dawley	0.6% Pb-acetate in drinking water for various durations: PND 24–74 (pubertal exposure); PND 60–74 (post pubertal exposure); 11 males and females in pubertal exposure group (10 each in control pubertal group) 6 males and females post-pubertal exposure and control groups	Reduction in serum testosterone levels in male, not female; in female suppression of circulating E2 ($p<0.05$) and LH ($p<0.05$); reduction in male secondary sex organ weight ($p<0.0005$); delayed vaginal opening and disrupted diestrous in females ($p<0.005$); increased incidence of stillbirth (2% control vs. 19% Pb) ($p<0.005$).	*In utero* PbB 250–300 µg/dL pre-pubertal PbB 30–60 µg/dL post pubertal PbB 30–60 µg/dL PbBs in the dams and offspring in this experiment were >200 µg/dL
Ronis et al. (1998a)	Rat/Sprague-Dawley	0.6% Pb-acetate in drinking water *ad libitum* for various durations; GD 5 to PND 1; GD 5 to weaning; PND 1 to weaning; 3 control litters, 2 gestation exposure litters, 2 lactation exposure litters, 2 gestation and lactation exposure litters, 2 postnatal litters, 2 chronic litters (4 male and 4 female pups per litter)	Dose-dependent delay in sexual maturation (delayed vaginal opening) ($p<0.0002$) following prenatal Pb exposure that continued until adulthood (85 days old); reduced birth weight ($p<0.05$), more pronounced among male pups.	Group: Pup PbB Naïve: ~6 µg/dL Control: <2 µg/dL Gest: ~10 µg/dL Lac: ~3 µg/dL Gest+Lac: ~13 µg/dL Postnatal: ~260 µg/dL Chronic: ~287 µg/dL

Table 5-4.3 (cont'd). Selected Studies Showing the Effects of Lead on Mammalian Embryogenesis and Development

Citation	Species/ Strain	Dose/Route/Form/Duration/Group Size	Endpoint/Magnitude of Effect/p-value	Blood Lead Concentration (PbB)
Ronis et al. (1998b)	Rat/Sprague-Dawley	Lead acetate in drinking water (0.05% to 0.45% w/v); dams exposed until weaning; exposure of pups which continued until PND 21, 35, 55, or 85 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%) (4 male and 4 female pups per litter)	Prenatal Pb exposure that continues until adulthood (85 days old) delays sexual maturation in female pups in a dose-related manner ($p<0.05$); birth weight reduced ($p<0.05$), more pronounced among male pups; decreased growth rates ($p<0.05$) in both sexes accompanied by decrease in plasma concentrations of IGF_1 through puberty ($p<0.05$) and a significant increase in pituitary growth hormone during puberty ($p<0.05$).	PbBs in the pups between the ages of 21 and 85 days were >100 µg/dL and reached up to 388 µg/dL
Ronis et al. (1998c)	Rat/Sprague-Dawley	Lead acetate 0.05, 0.15, or 0.45% in drinking water beginning GD 5 continuing until PND 21, 35, 55, or 85; 5 control litters (0%), 10 low-dose litters (0.05%), 8 mid-dose litters (0.15%), 9 high-dose litters (0.45%) (4 male and 4 female pups per litter)	Dose-responsive decrease in birth weight ($p<0.05$), and crown-to-rump length ($p<0.05$); dose-responsive delay in sexual maturity in male ($p<0.05$) and female ($p<0.05$); neonatal decrease in sex steroids ($p<0.05$); pubertal decrease in testosterone (male) ($p<0.05$), and E_2 (female) ($p<0.05$); decrease estrous cyclicity at high dose ($p<0.05$).	Dams: 0, 48, 88, or 181 µg/dL Pups PND 1: <1, ~40, ~70, or >120 µg/dL Pups PND 21: <1, >50, >160, or ~237 µg/dL Pups PND 35: <1, ~22, >70, or >278 µg/dL Pups PND 55: <1, >68, >137, or ~380 µg/dL Pups PND 85: <1, >43, >122, or >214 µg/dL
Ronis et al. (2001)	Rat/Sprague-Dawley	Lead acetate in drinking water to 825 or 2475 ppm *ad libitum* from GD 4 to GD 55 postpartum; 1 male and female pup/litter (5 litters per group) control group, 1 male and female pup/litter (5 litters per group) 825 ppm Pb-acetate group, 1 male and female pup/litter (5 litters per group) 2475 ppm Pb-acetate group	Dose-dependent decrease of the load of failure in male ($p<0.05$); no difference in plasma levels of vitamin D metabolites; reduced somatic growth ($p<0.05$), longitudinal bone growth ($p<0.05$, and bone strength during the pubertal period ($p<0.05$); sex steroid replacement did not restore skeletal parameters in Pb exposed rats; L-Dopa increased plasma IGF_1 concentrations, rates of bone growth, and bone strength measures in controls while having no effect in Pb exposed groups; DO gap x-ray density and proximal new endostreal bone formation were decreased in the distration gaps of the lead-treated animals ($p < 0.01$); distraction initiated at 0.2 mm 30 to 60 days of age.	PbB at 825 ppm was 67–192 µg/dL PbB at 2475 ppm was 120–388 µg/dL

Table 5-4.3 (cont'd). Selected Studies Showing the Effects of Lead on Mammalian Embryogenesis and Development

Citation	Species/ Strain	Dose/Route/Form/Duration/Group Size	Endpoint/Magnitude of Effect/p-value	Blood Lead Concentration (PbB)
	Rat/Sprague-Dawley	Lead in drinking water at 34 ppm from weaning of mothers through gestation and weaning of offspring until birth; 6 pups control group, 6 pups experimental group	Reduced body weight ($p = 0.04$); parotid function was decreased by nearly 30% ($p = 0.30$); higher mean caries scores than the control pups ($p = 0.005$); pre- and perinatal Pb exposure had significantly increased susceptibility to dental caries ($p = 0.015$).	PbB 48±13 µg/dL

GMP, cyclic guanosine--3',5'-monophosphate; DO, distraction osteogenesis; E_2, estradiol; ERG, electroretinographic; GD, gestational day; IGF_1, insulin-like growth factor 1; LH, luteinizing hormone; NOS, not otherwise specified; PbB, blood Pb concentration; PDE, phosphodiesterase; PND, post-natal day

studies (including those described in the 1986 Pb AQCD and more recent reports) that have demonstrated teratogenic effects of Pb exposure are confounded by maternal toxicity.

5.4.5 Effects on Growth and Endocrine Regulation of Growth

Studies conducted in rodents provide convincing evidence for an association between gestational Pb exposure and reduced birth weight and postnatal growth at doses that produce no clinical toxicity in the mothers (Dearth et al., 2002; Hamilton et al., 1994; Lögdberg et al., 1987; Piasek and Kostial, 1991; Pinon-Lataillade et al., 1995; Ronis et al., 1998a,b,c; Singh et al., 1993b; Watson et al., 1997). In squirrel monkeys, Lögdberg et al. (1987) reported a statistically significant reduction in mean birth weight following oral exposure to Pb-acetate during the latter trimesters of pregnancy (mean maternal PbB 54 μg/dL [39 to 82 μg/dL]). Additional details concerning Lögdberg et al. (1987) are provided in Table AX5-4.3.

In addition, the literature provides convincing support for lead-induced impairment of postnatal growth. Although some early studies (Minnema and Hammond, 1994; Hammond et al., 1993, 1990) ascribed the reduction in postnatal growth to reduced food consumption (suggesting an effect of Pb on the satiety endpoint), more recent studies report impaired growth unrelated to changes in food consumption. Ronis et al. (1996, 1998a,b,c) reported lead-induced reductions in birth weight and postnatal growth that occurred in the absence of a significant alteration in food consumption. Han et al. (2000) found a reduction in the birth length of pups (pup PbB ~16 μg/dL on PND 1) whose mothers had been exposed to Pb up to 1 month before mating (maternal PbB on GD 9, 16, and 21 <40 μg/dL). Berry et al. (2002) reported depressed growth in rats exposed to lead, even though food consumption was higher in the lead-exposed rats.

Ronis et al. (2001) showed that in rats, pre- and postnatal (through PND 55) exposure to Pb reduced somatic longitudinal bone growth and bone strength during the pubertal period (PbB >67 μg/dL). These effects could not be reversed by stimulation of the growth hormone axis by supplemental sex hormone. These results suggest that Pb exposure may impair growth through a mechanism that involves a suppressed pituitary response to hypothalamic stimulation. The mechanism may be related to a reduction in plasma concentrations of IGF_1 following Pb exposure (Dearth et al., 2002; Ronis et al., 1998b). Dearth et al. (2002) exposed F344 rats to Pb by gavage beginning 30 days before mating and continuing until weaning of the pups at 21 days

of age. By PND 30, all three groups had PbB ≤3 μg/dL and all lead-exposed groups exhibited decreased serum levels of IGF_1, LH, and E_2. Since liver IGF_1 mRNA was not affected, it appeared that Pb altered the translation and/or secretion of IGF_1, which in turn decreased LH-releasing hormone at the hypothalamic level. Additional details concerning Dearth et al. (2002) are provided in Table AX5-4.3. An effect on IGF_1 also been demonstrated by Ronis et al. (1998b).

5.4.6 Effects on Other Endocrine Systems during Development

Recent experimental animal studies provide evidence for an interaction between Pb exposure and stress hormones, including glucocorticoids and catecholamines (Cory-Slechta et al., 2004; Yu et al., 1996; Vyskocil et al., 1991; Saxena et al., 1990). Lead has been reported to increase stress hormone levels (Vyskocil et al., 1991).

Cory-Slechta et al. (2004) reported a persistent effect of combined environmental stress (administered as restraint) and maternal Pb exposure (PbB 30 to 40 μg/dL) on corticosteroid levels in adult offspring. Female adult offspring born to these dams exhibited elevated corticosteroid levels only when Pb exposure was combined with environmental stress, whereas their adult male siblings exhibited elevated corticosteroid levels from Pb exposure alone. These data suggest that brief exposures to Pb and stress during development may result in persistent changes in the hypothalamic-pituitary-adrenal axis. Additional details concerning Cory-Slechta et al. (2004) are provided in Table AX5-4.3.

The interplay between Pb and stress hormones is consistent with the findings of Yu et al. (1996) wherein neonatal exposure to Pb (PbB 70 μg/dL) decreased cold-water swimming endurance (a standard test for stress endurance). The enhancement of lead-induced toxicity by stress was also reported by Saxena et al. (1990) in adult male rats. Saxena et al. (1990) reported enhanced testicular injury when rats were exposed to immobilization stress in combination with Pb exposure (PbB >200 μg/dL).

5.4.7 Effects on Other Organ Systems during Development

5.4.7.1 Developmental Effects on Blood and Liver

Recent data provides evidence for lead-induced alterations in developing hematopoietic and hepatic system. The data concerning the effect of Pb exposure on the developing

hematopoietic system are limited. The 1986 Pb AQCD proposed that alterations in blood ALAD activity and erythrocyte protoporphyrin were possible biomarkers for subtle, prenatal effects of Pb on heme synthesis (Hayashi 1983a,b; Jacquet et al., 1977; Prigge and Greve, 1977; Hubermont et al., 1976). A more recent study (Iavicoli et al., 2003) of Pb effects on RBC production, HB concentration, and Hct was not able to clearly establish a dose-response relationship for these endpoints. Although limited by small group size (one litter per dose), subchronic dietary exposure to low levels of Pb (PbB 0.6 to 2 or 2 to 13 µg/dL) revealed that Pb exposure reduced red cell synthesis, hemoglobin concentration, and hematocrit at PbB 2 to 13 µg/dL and increased RBC synthesis, Hb concentration, and Hct at PbB 0.6 to 2 µg/dL. More data are needed to clarify the effect of low-dose Pb exposure on blood endpoints.

Two rodent studies provide limited suggestive evidence that Pb exposure during development produces changes in hepatic enzymes and other biomarkers of hepatic function. Pillai and Gupta (2005) reported that long-term exposure of rats (pre-mating, gestation, and lactation) to moderate levels of Pb-acetate (subcutaneous injections of 0.05 mg/kg-day; PbB not reported) resulted in reduced activities of hepatic steroid (E_2) metabolizing enzymes (17-ß-hydroxy steroid oxidoreductase and UDP glucuronyl transferase) and decreased hepatic CYP450 content. Corpas (2002) reported that exposure to Pb in drinking water exposure during gestation and lactation (pup PbB ~22 µg/dL at PND 12 and PND 21) resulted in alterations in the hepatic systems of neonates (PND 12) and pups (PND 21). The effects manifested as alterations in several biochemical indicators of hepatic toxicity: reductions in Hb, iron, alkaline and acid phosphatase levels, and hepatic glycogen, and elevated blood glucose. These data suggest that Pb may alter hepatic function during development; however, more data are needed to determine whether these effects are persistent.

5.4.7.2 Developmental Effects on Skin

Recent data provides limited evidence of altered soft tissue development resulting from Pb exposure. The literature includes one report of lead-induced abnormalities in skin development. Dey et al. (2001) reported that the pups of mice exposed orally to Pb citrate (5 µg/kg-day) throughout gestation exhibited a variety of skin anomalies, including perforations, cell deformity, and disordered collagen bundles. The PbB levels for mothers and pups were not provided. Although detailed biochemical studies are required to elucidate the mechanism for

structural abnormalities, it appears that covalent binding of Pb ions to the sulfate group of glycosaminoglycans may be involved.

5.4.7.3 Developmental Effects on the Retina

Several studies have found that Pb exposure during early postnatal development impairs retinal development in female Long-Evans hooded rats (Fox et al., 1997, 1991a,b; Fox and Rubenstein, 1989; Fox and Chu, 1988). Of these, two studies are particularly important. Fox et al. (1991a) demonstrated that lactation exposure to Long-Evans hooded rats (PbB 18.8 or 59.4 μg/dL) resulted in long-term, dose-dependent decreases retinal Na/K ATPase activity in the female offspring (only female pups were used). Fox et al. (1997) subsequently demonstrated that lactation exposure to female Long-Evans hooded rats (PbB 19 ± 3 or 59 ± 8 μg/dL) or drinking water exposure to adult females (PbB 56 ± 9 μg/dL) resulted in differential age- and dose-dependent alterations in retinal structure and function following low (PbB <20 μg/dL) and moderate (PbB <60 μg/dL) exposures during lactation or long-term (~60 days) exposure during adulthood. The mode of action for the effects of Pb on retinal development may be related to impaired Na/K ATPase activity (Fox et al., 1991a). The observation of reduced enzyme activity in the retina, but not in the kidney, suggests specificity for the retinal alpha-3 isozyme of Na/K ATPase, rather than the renal alpha-1 isozyme of Na/K ATPase. The authors suggested that this specificity may play a role in the target organ-specific toxicity of Pb (Fox et al., 1991a).

5.4.8 Conclusions

The 1986 Pb AQCD presented unequivocal evidence (derived principally from studies of rodents) for effects of Pb on reproduction and development in laboratory animals. This included evidence for lethal effects in developing organisms exposed to Pb during gestation and in the neonatal period, as well as a variety of sublethal effects on reproduction and development. Sublethal effects included changes in levels or function of reproductive hormones, effects on maturation of reproductive systems, persistent toxic effects on the gonads (both male and female), and adverse effects on the conceptus. More subtle effects on hormone metabolism and reproductive cell structure of developing organisms were also documented.

More recent studies support earlier conclusions, presented in the 1986 Pb AQCD, that Pb can produce temporary and persistent effects on male and female reproductive function and

development and that Pb disrupts endocrine function at multiple points along the hypothalamic-pituitary-gonadal axis.

Effects on Male Reproduction. Studies in experimental animals (presented in the 1986 Pb AQCD and others published subsequent to the 1986 Pb AQCD) provide convincing evidence that Pb acts as an endocrine disruptor in males. The majority of studies support the conclusion that endocrine disruption in males involves Pb acting at multiple sites along the hypothalamic-pituitary-gonadal axis. The adverse effects of Pb on male reproduction include perturbations in sexual development and maturation, changes in fertility, changes in male sex hormone levels, and alterations in gonad tissues and cell structure.

Studies conducted in male experimental animals unequivocally demonstrate that Pb exposure during early development (PbB >30 μg/dL) can delay the onset of puberty and alter reproductive function later in life. Persistent effects of Pb exposure on the male reproductive system may derive from disruption in pulsatile release of sex hormones during early development (Ronis et al., 1998c).

The 1986 Pb AQCD reported evidence that Pb exposure affects male fertility in various animal species, including rabbits (Cole and Bachhuber, 1915), guinea pigs (Weller, 1915), rats (Ivanova-Chemishanska et al., 1980), and mice (Schroeder and Mitchener, 1971). More recent studies, conducted in various animal species, have demonstrated lead-induced alteration of sperm parameters (e.g., count, motility, number of abnormal sperm) (Sokol et al., 1985; Acharya et al., 2003; Adhikari et al., 2000; Foster et al., 1998; Graca et al., 2004; McGivern et al., 1991; Mishra and Acharya, 2004; Sokol and Berman, 1991). These effects, however, have not been observed in all studies; the response may be modified by an adaptive mechanism in the hypothalamic-pituitary-gonadal axis. Lead has also been shown to alter the stability of sperm chromatin in monkeys (PbB 56 μg/dL) in the absence of gross changes in sperm parameters, a finding which may contribute to a reduction in male fertility (Foster et al., 1996a). These results are consistent with observations of reduced in vitro fertilization capacity of sperm collected from rats, rabbits, or mice previously exposed to Pb (Sokol et al., 1994; Foote, 1999; Johansson et al., 1987, respectively). Two modes of action have been proposed for lead-induced alterations in sperm capacity for fertilization: (1) Pb complexation with sulfhydryl groups in sperm, and (2) lead-induced generation of ROS in testes.

Experimental animal studies provide convincing evidence that Pb acts as an endocrine disruptor in males at various points along the hypothalamic-pituitary-gonadal axis. Although there is evidence for a common mode of action, consistent effects on circulating testosterone levels are not always observed in lead-exposed animals. The inconsistency in the reports of circulating testosterone levels complicates the derivation of a dose-response relationship for this endpoint.

The 1986 Pb AQCD reported evidence for histological changes in the testes and prostate in rats in association with relatively high doses of Pb (Chowdhury et al., 1984; Hilderbrand et al., 1973; Golubovich et al., 1968). More recent studies in animals provide additional support for testicular damage (i.e., ultrastructural changes in testes and cytotoxicity in Sertoli cells) following exposure to Pb (Foster et al., 1998; Singh et al., 1993a; Batra et al., 2001; Chowdhury et al., 1986, 1987; Corpas et al., 1995; Graca et al., 2004; Pinon- Lataillade et al., 1993; Saxena et al., 1990). Foster et al. (1998) and Singh et al. (1993a) demonstrated ultrastructural changes in testes of monkeys at PbB 35 to 40 μg/dL. Lead-induced oxygen free radical generation is the plausible mechanism of testicular injury in primates (Foster et al., 1998) and rodents (Chowdhury et al., 1984; Acharya et al., 2003; Adhikari et al., 2001; Batra et al., 2001; Bizarro et al., 2003; Chowdhury et al., 1984; Gorbel et al., 2002; Mishra and Acharya, 2004).

Effects on Female Reproduction. In females, Pb exposure has been consistently shown to disrupt the hypothalamic-pituitary-gonadal axis and to produce reproductive dysfunction. The 1986 Pb AQCD reported that Pb exposure was associated with inhibition of menstruation, ovulation, and follicular growth in monkeys (Vermande-Van Eck and Meigs, 1960) and, in rodents, delayed vaginal opening, decreased frequency of implantation, and reduced rates of pregnancy (Kimmel et al., 1980; Odenbro and Kihlström, 1977). Observations from more recent experimental animal studies support these findings. The effects of Pb on female reproduction may be classified as alterations in female sexual maturation, effects on fertility and menstrual cycle, alterations in levels of female sex hormones, and changes in morphology or histology of female reproductive organs as well as the placenta.

The 1986 Pb AQCD reported that Pb exposure (PbB 20 to 40 μg/dL) in rodents produced delays in sexual maturation. More recent studies in experimental animals (primarily rodent studies) provide convincing evidence that Pb exposure before puberty (prenatal and early postnatal PbB ~40 μg/dL) delays maturation of the female reproductive system (Dearth et al.,

2002, 2004; Iavicoli et al., 2004; McGivern et al., 1991; Ronis et al., 1998a,b,c,). Ronis et al. (1998c) suggested that lead-induced disruption of pulsatile release of sex hormones may result in delayed onset of puberty.

Numerous studies were described in the 1986 Pb AQCD that supported the conclusion that Pb was an endocrine disruptor in females. More recent studies in various mammalian species provide convincing support for endocrine-mediated alterations of the female reproductive system. The nonhuman primate studies provide dose-response information concerning the effects of Pb on female sex hormones and menstrual cycle (Foster et al., 1996b; Foster, 1992; Foster et al., 1992; Franks et al., 1989; Laughlin et al., 1987). Exposures of monkeys to Pb resulting in chronic PbB <20 μg/dL produce few effects on circulating hormone levels and do not alter the menstrual cycle. Higher exposures of monkeys to Pb (PbB >40 μg/dL) alter circulating hormone levels and the menstrual cycle, with more marked changes in these endpoints occurring at higher PbB levels. Several modes of action for lead-induced alterations in female reproduction have been proposed, including changes in hormone synthesis or metabolism (Wiebe and Barr, 1988; Wiebe et al., 1988) and changes in hormone receptor levels (Wiebe et al., 1988; Wide and D'Argy, 1986). In addition, Pb may alter sex hormone release and imprinting during early development (Ronis et al., 1998c; Tchernitchin et al., 1998a,b).

The 1986 Pb AQCD presented convincing evidence from experimental animal studies for lead-induced alterations in female fertility, including interference with implantation and pregnancy. More recent studies have confirmed that Pb exposure disturbs female fertility; however, Pb exposure does not generally produce total sterility. Studies in nonhuman primates and rodents have also demonstrated reductions in litter size, implantation dysfunction, and decreased postnatal survival following Pb exposure of gravid female experimental animals (PbB >30 μg/dL) (Lögdberg et al., 1987; al-Hakkak et al., 1988; Flora and Tandon, 1987; Piasek and Kostial, 1991; Pinon-Lataillade et al., 1995; Ronis et al., 1996; Singh et al., 1993b; Wide, 1985).

Lead-induced changes in morphology or histology in female sex organs and placenta may explain reduced fertility and impaired female reproductive success. Lögdberg et al. (1988) reported a dose-dependent reduction in placental weight and an increase in pathological lesions of the placenta in squirrel monkeys that consuming Pb-acetate in their diet during the last three-fourths or two-thirds of pregnancy (maternal PbB 37 μg/dL). Exposure to Pb in early pregnancy also produces structural changes in the epithelium of the uterus of mice (Nilsson et al., 1991;

Wide and Nilsson, 1979). These changes in uterine tissue may impair successful implantation of the blastocysts. In addition, the histological and morphological effects on the uterus and placenta may explain the reduced birth weight that has been associated with prenatal Pb exposure (possibly due to placental insufficiency).

Developmental Effect. Pre- and postnatal exposure to Pb has been demonstrated to result in fetal mortality and produce a variety of sublethal effects in the offspring. Many of these lead-induced sublethal developmental effects occur at maternal PbB that do not result in clinical (overt) toxicity in the mothers. The few studies that have reported teratogenic effects resulting from Pb exposure are confounded by maternal toxicity.

Studies conducted in rodents and primates provide convincing evidence for an association between Pb exposure and reduced birth weight and postnatal growth at doses that produce no clinical toxicity in the mothers (maternal PbB >40 μg/dL) (Dearth et al., 2002; Lögdberg et al., 1987; Berry et al., 2002; Bogden et al., 1995; Camoratto et al., 1993 Hamilton et al., 1994; Hammond et al., 1989, 1990, 1993; Minnema and Hammmond 1994; Han et al., 2000; Ronis et al., 1996, 1998a,b,c; Piasek and Kostial, 1991; Pinon-Lataillade et al., 1995; Sant'Ana et al., 2001; Singh et al., 1993b; Watson et al., 1997). The available data suggest that the mode of action for lead-induced growth suppression involves a reduction in the plasma concentration of IGF_1.

Recent experimental animal studies provide evidence for an interaction between Pb exposure during development (PbB 30 to 40 μg/dL) and stress hormones, including glucocorticoids and catecholamines (Cory-Slechta et al., 2004; Yu et al., 1996; Vyskocil et al., 1991; Saxena et al., 1990). Lead exposure during early postnatal development (PbB ~20 μg/dL) impairs retinal development in female Long-Evans hooded rats (Fox et al., 1997, 1991a,b; Fox and Rubenstein, 1989; Fox and Chu, 1988).

In addition, recent studies provide limited evidence for lead-induced alterations in developing skin, and hematopoietic and hepatic systems; however, more data are needed to clarify the effect of low-dose Pb exposure on these endpoints.

5.5 CARDIOVASCULAR EFFECTS OF LEAD

5.5.1 Introduction

Numerous large and small epidemiological studies have attempted to examine the link between Pb exposure and development of hypertension (HTN) in the general population and occupationally-exposed individuals. In addition, a number of studies have reported on other cardiovascular effects of Pb in Pb-exposed humans (U.S. Environmental Protection Agency, 1990). While several studies have demonstrated a positive correlation between blood pressure and blood Pb concentration, others have failed to show such association when controlling for confounding factors such as tobacco smoking, exercise, body weight, alcohol consumption, and socioeconomic status. Thus, the studies that have employed blood Pb level as an index of exposure have shown a relatively weak association with blood pressure. In contrast, the majority of the more recent studies employing bone Pb level have found a strong association between long-term Pb exposure and arterial pressure (Chapter 6). Since the residence time of Pb in the blood is relatively short but very long in the bone, the latter observations have provided compelling evidence for the positive relationship between Pb exposure and a subsequent rise in arterial pressure. This section reviews the published studies pertaining to the cardiovascular effects of Pb exposure in experimental animals, isolated vascular tissues, and cultured vascular cells.

5.5.2 Lead Exposure and Arterial Pressure in Experimental Animals

Numerous studies have shown that exposure to low levels of Pb for extended periods results in a delayed onset of arterial HTN that persists long after the cessation of Pb exposure in genetically normal animals (see Tables AX5-5.1 to AX5-5.5). In addition, Pb exposure during gestation has been reported to significantly raise arterial pressure in the third trimester of pregnancy in SD rats given a low calcium diet (Bogden et al., 1995). Taken together, these observations provide irrefutable evidence that extended exposure to low levels of Pb can result in the subsequent onset of HTN in experimental animals.

Many studies have been conducted to explore the mechanisms by which chronic Pb exposure may cause HTN. Most of these studies have examined various blood-pressure regulatory and vasoactive systems in animal models of Pb-induced HTN. In addition, several

studies have investigated the direct effect of Pb on vascular tone or the ability of Pb to modify the response to vasoconstrictor/vasodilator agents in isolated vascular tissues. Finally, a number of studies have explored the effect of Pb on cultured endothelial and vascular smooth muscle cells. An overview of the findings of these studies is provided below:

5.5.2.1 Effect of Lead on Production of Reactive Oxygen Species and Nitric Oxide Metabolism

Reactive oxygen species (ROS), such as, superoxide (O_2^-), hydroxyl radical (OH) and hydrogen peroxide (H_2O_2) are normally produced in the course of metabolism and are safely contained by the natural antioxidant defense system. Excess production and/or diminished containment of ROS can lead to oxidative stress in which uncontained ROS can attack and denature functional/structural molecules and, thereby, promote tissue damage, cytotoxicity, and dysfunction. In fact, oxidative stress has been implicated in the pathogenesis of HTN, atherosclerosis, neurodegenerative disorders, aging, and neoplasm among other afflictions. During the past decade, several studies have demonstrated that Pb exposure causes oxidative stress, particularly in the kidney and cardiovascular tissues, as well as in cultured endothelial and vascular smooth muscle cells (VSMC). The in vivo studies have further shown that Pb-induced oxidative stress is, at least in part, responsible for the associated HTN in experimental animals. Relevant published studies pertaining to this issue are summarized below and listed in Annex Table AX5-5.1.

Khalil-Manesh et al. (1994) were among the first to suggest that oxidative stress may be involved in the pathogenesis of Pb-induced HTN. This assumption was based on the observation that chelation therapy with dimethyl succinic acid (DMSA) rapidly ameliorated HTN and raised plasma cGMP level in rats with Pb-induced HTN. They further demonstrated that DMSA possesses strong antioxidant properties in vitro. Accordingly, they theorized (a) that Pb exposure may increase the generation of ROS, which, in turn, elevate arterial pressure by reacting with and inactivating endothelium-derived-relaxing factor (EDRF), and (b) that by scavenging ROS, DMSA rapidly lowers blood pressure prior to significantly affecting body Pb burden.

In a subsequent study, Gonick et al. (1997) showed a marked increase in renal tissue content of lipid peroxidation product malondialdehyde (MDA) coupled with significant upregulations of endothelial (eNOS) and inducible (iNOS) nitric oxide synthases. Thus, the

study provided evidence for the occurrence of oxidative stress and compensatory upregulation of NOS isotypes in the kidney of animals with Pb-induced HTN.

In another study, Ding et al. (1998) showed that infusion of NOS substrate, L-Arginine, lowers blood pressure to a much greater extent in rats with Pb-induced HTN than that seen in either control animals or DMSA-treated Pb-exposed animals. The data, therefore, provided indirect evidence for the role of depressed NO availability in the pathogenesis of Pb-induced HTN. The study further suggested that oxidative stress may be responsible for diminished NO availability in this model. It should be noted that administrating cell-impermeable native SOD did not lead to a further reduction of blood pressure beyond that seen with L-Arginine alone. As with the previous study (Khalil-Manesh 1994), oral DMSA therapy for 2 weeks significantly lowered blood pressure in the Pb-exposed animals. This was accompanied by a significant reduction of blood Pb concentration. In an attempt to explore whether the observed amelioration of Pb-induced HTN was due to the reduction of Pb burden or alleviation of oxidative stress by DMSA, Vaziri et al. (1997) carried out a study in which rats with Pb-induced HTN were treated with a lazaroid compound, a potent, non-chelating antioxidant. The study revealed marked elevation of blood pressure and oxidative stress (increased lipid peroxidation) and reduced NO availability (depressed urinary $NO_2 + NO_3$ excretion) in the untreated rats with Pb-induced HTN. Antioxidant therapy with the lazaroid compound resulted in a significant alleviation of oxidative stress, improved NO availability, and a marked attenuation of HTN without affecting blood Pb concentration. Thus, the latter study provided convincing evidence for the role of oxidative stress as a major mediator of Pb-induced HTN. The study further demonstrated that Pb-induced HTN is associated with diminished NO availability and that the latter was mediated by oxidative stress. The reduction in NO availability observed in rats with Pb-induced HTN (Pb-acetate, 100 ppm in drinking water for 12 weeks) was recently confirmed by Dursun et al. (2005) in rats treated with daily IP injection of Pb-acetate (8 mg/Kg) for 2 weeks. The authors showed that the rise in arterial pressure was accompanied by a significant reduction of urinary $NO_2 + NO_3$ excretion and a significant fall in renal blood flow (indicating increased renal vascular resistance), mimicking the effect of the NOS inhibitor LNAME.

To further explore the cause for the observed reduction of NO availability, Vaziri et al. (1999a) subsequently studied the expression of eNOS and iNOS in the kidney and cardiovascular tissues of rats with Pb-induced HTN. The study showed that the reduction in NO availability is

paradoxically associated with a significant upregulation of NOS isotypes. Moreover, in vitro incubation experiments revealed no significant change in NOS activity in the presence of lead. Interestingly, antioxidant therapy with pharmacological doses of vitamin E and ascorbic acid reversed the upregulation of NOS isotypes and paradoxically raised NO availability in the subgroup of rats with Pb-induced HTN (Vaziri et al., 1999a). These observations were subsequently confirmed by Vaziri and Ding (2001) who showed marked reduction of NO availability despite significant upregulations of eNOS, nNOS, and iNOS in the aorta, heart, kidney, and brain of rats with Pb-induced HTN and their normalization with the administration of superoxide-scavenger tempol (15 mg/Kg IP/day) for 2 weeks. It is noteworthy that tempol administration had no effect on the measured parameters in the control animals. Taken together, these observations indicated that ROS-mediated NO inactivation and, hence, depressed NO availability, results in a compensatory upregulation of NOS isotypes in animals with Pb-induced HTN. This phenomenon is consistent with other studies from this group, which have demonstrated the presence of a negative-feedback regulation of eNOS by NO (Vaziri and Wang, 1999; Vaziri et al., 2005).

The occurrence of compensatory upregulation of NOS by oxidative stress in Pb-exposed intact animals described above was subsequently replicated by Vaziri and Ding (2001) in cultured human endothelial cells incubated in media containing different concentrations of Pb-acetate (versus control media containing sodium acetate). Once again, co-incubation with tempol prevented this phenomenon. This study confirmed the ability of Pb to affect endothelium independently of its effects on humoral or hemodynamic factors, which are operative in vivo. Taken together, these observations suggest that Pb-induced reduction of biologically-active NO is not due to the reduction of NO-production capacity. Instead, it is linked to oxidative stress. In an attempt to explore this supposition, in a separate study, Vaziri et al. (1999b), tested the hypothesis that avid inactivation and sequestration of NO by ROS may be, in part, responsible for the reduction of NO availability in animals with Pb-induced HTN. To this end, they tested for the presence of immunodetectable nitrotyrosine in kidney, brain, and cardiovascular tissues harvested from untreated and antioxidant-treated (vitamin E + vitamin C) rats with Pb-induced HTN and normal control rats. Nitrotyrosine was used as a marker of NO oxidation by ROS ($NO + O_2^{\bullet} \rightarrow ONOO^-$, $ONOO^- +$ tyrosine $\rightarrow$ nitrotyrosine). The study showed an overabundance of nitrotyrosine in all plasma and tested tissues in the untreated rats with Pb-induced HTN.

Antioxidant therapy reduced nitrotyrosine abundance, attenuated HTN, and simultaneously raised NO availability in the subgroup of rats with Pb-induced HTN but had no effect on the normal control group. These observations provided compelling evidence that Pb-induced HTN causes oxidative stress, which, in turn, promotes functional NO deficiency via ROS-mediated NO inactivation. The latter, in turn, participates in the development and maintenance of HTN and cardiovascular abnormalities. In addition, the formation of the highly cytotoxic reactive nitrogen species, peroxynitrite ($ONOO^-$), from the NO-ROS interaction and the associated nitrosative stress could potentially contribute to the long-term cardiovascular, renal, and neurological consequences of Pb exposure.

In a series of subsequent studies Vaziri et al. (2003) explored the expression of NAD(P)H oxidase (which is a well-recognized source of ROS in, not only, the immune cells but also in renal, cardiovascular, and neuronal tissues) in animals with Pb-induced HTN. In addition, expression of the main antioxidant enzymes, namely Mn and CuZn-superoxide dismutases (SOD), catalase and glutathione peroxidase were investigated. The study revealed significant upregulation the $gp91^{phox}$ subunit of NAD(P)H oxidase in the brain as well as a trend for higher levels in the renal cortex and left ventricle of rats with Pb-induced HTN. This was accompanied by a significant compensatory upregulation of CuZn SOD in the kidney and brain, and of Mn SOD in the heart, of rats with Pb-induced HTN. In contrast, despite the presence of oxidative stress, catalase and glutathione peroxidase activity levels were unchanged. In a more recent study, Farmand et al. (2005), showed a significant increase in CuZn SOD activity with no change in either catalase or glutathione peroxidase activity in the aorta of rats with Pb-induced HTN compared with control animals. Since the latter enzymes are responsible for the reduction of H_2O_2 and lipoperoxides, the lack of an appropriate rise in their tissue levels may contribute to the severity of oxidative stress in Pb-exposed animals.

The contribution of oxidative stress in the pathogenesis of HTN in this model was confirmed by experiments which demonstrated normalization of arterial pressure with the infusion of superoxide-scavenger, tempol, in rats with Pb-induced HTN (but no change was observed in the blood pressure in the control rats) (Vaziri et al., 2003). As noted above, the relative reduction of tissue catalase and glutathione peroxidase, which are responsible for the reduction of H_2O_2 to water and molecular oxygen ($2H2O2 \xrightarrow[GPX]{CAT} 2H2O + O2$), can result in

accumulation of H_2O_2. H_2O_2 serves as a cellular growth signal, as well as a substrate for hydroxyl radical (·OH) generation. The former action can potentially contribute to cardiovascular remodeling, whereas the latter can promote oxidative injury. In a recent study, Ni et al. (2004) demonstrated a transient rise in O_2^- production followed by a sustained rise in H_2O_2 production by human coronary endothelial and vascular smooth muscle cells cultured in media containing Pb-acetate versus the control media containing Na-acetate. This was accompanied by, and primarily due to, upregulation of NAD(P)H oxidase and SOD together with reduced or unchanged catalase and glutathione peroxidase levels. Accordingly, the results of this in vitro study confirmed the findings of the in vivo studies and validated the anticipated accumulation of H_2O_2.

As noted above, H_2O_2 is the substrate for the Fenton and Haber-Weiss reactions, which culminate in formation of the highly cytotoxic·OH ($H_2O_2 + e^- \rightarrow OH + OH^-$). Thus, accumulation of H_2O_2 in animals with Pb-induced HTN can facilitate·OH production and, thereby, promote oxidative stress and tissue injury. This supposition was confirmed in a series of studies by Ding et al. (2001), who showed increased hydroxyl radical production in rats with Pb-induced HTN. Oxidative stress, HTN, and excess hydroxyl radical production were all reversed with IV infusion of the reputed hydroxyl radical scavenger, DMTU, in the Pb-exposed animals. Increased hydroxyl radical production observed in intact animals with Pb-induced HTN was confirmed in lead-treated cultured endothelial cells (Ding et al., 2000). The role of oxidative stress in the pathogenesis of HTN and endothelial dysfunction (depressed NO availability) has been substantiated by a number of other investigators. For instance, Attri et al. (2003), demonstrated that exposure to Pb for up to 3 months resulted in a significant rise in arterial pressure, which was substantially ameliorated by coadministration of the antioxidant vitamin ascorbic acid (20 mg/rat) in Wistar-Kyoto rats. The rise in arterial pressure in lead-treated rats was accompanied by diminished NO availability (low plasma $NO_2 + NO_3$) and biochemical evidence of oxidative stress, i.e., elevations of plasma MDA, a DNA oxidation product (8-hydroxyguanosine), and diminished ferric-reducing antioxidant power, as well as electrophoretic evidence of DNA damage. Amelioration of HTN by antioxidant therapy was accompanied by improved NO availability (plasma $NO_2 + NO_3$), marked attenuation of oxidative stress, and partial reduction of DNA damage in this model. In another study, Malvezzi et al. (2001) showed partial amelioration of HTN in Pb-exposed rats with the administration of either

DMSA or L-arginine and showed a much greater response with the combination thereof. These observations support the role of interaction of ROS and NO in the pathogenesis of Pb-induced HTN in the rat.

As cited above, Pb-induced HTN is associated with and is, at least in part, due to ROS-mediated inactivation and hence, reduced availability of biologically active NO. Many of the biological actions of NO are mediated by cGMP, which is produced from the substrate GTP by the cytosolic enzyme soluble guanylate cyclase (sGC). sGC is expressed in VSMC and several other cell types. The enzyme is activated by NO to produce cGMP, which, in turn, promotes vasorelaxation by lowering cytosolic Ca^{2+} concentrations. In an earlier study, Khalil-Manesh et al. (1993) demonstrated a significant reduction of plasma and urinary cGMP in rats with Pb-induced HTN. These observations prompted a number of studies to evaluate the effect of Pb on sGC expression and cGMP production in vascular tissues obtained from rats with Pb-induced HTN or in normal vascular tissues incubated in Pb-containing media. For instance, Marques et al. (2001) found significant reductions of acetylcholine- and Na-nitroprusside-induced vasorelaxation, despite upregulation of eNOS, in the aorta of rats with Pb-induced HTN. This was associated with marked downregulation of sGC abundance and diminished cGMP production in the aorta. In an attempt to explore the possible role of oxidative stress in Pb-induced downregulation of sGC, they included a group of rats that were co-treated with Pb and the antioxidant vitamin ascorbic acid. Antioxidant therapy ameliorated HTN, restored vasorelaxation response to acetylcholine and Na-nitroprusside, and normalized sGC expression and cGMP production. The authors, therefore, identified diminished sGC as another mechanism by which Pb exposure can promote endothelial dysfunction and HTN. They further showed that Pb-induced downregulation of sGC is mediated by oxidative stress, as evidenced by its prevention with antioxidant therapy. Downregulation of sGC protein abundance in the aorta of Wistar rats with Pb-induced HTN was recently confirmed by Farmand et al. (2005) in the Pb-exposed Sprague-Dawley rats. In another study, Courtois et al. (2003) showed that 24-h incubation of normal rat aorta in the lead-containing media resulted in a concentration-dependent downregulation of sGC (beta subunit), with the maximum effect observed at 1 ppm concentration. This was associated with increased O_2^- production and upregulation of cyclooxygenase-2 (COX-2) expression. Co-incubation with ascorbic acid reduced COX-2 expression and O_2^- production and attenuated, but did not fully prevent, the Pb-induced

downregulation of sGC. Similarly, addition of COX-2 inhibitor Rofecoxib or of protein kinase A inhibitor (H-89) partially mitigated the Pb-induced downregulation of sGC in vitro. However, the COX-2 inhibitor failed to reduce O_2^- production in Pb-exposed vascular tissues. Based on these observations, the authors concluded that Pb exposure downregulates vascular tissue sGC abundance via induction of oxidative stress and upregulation of COX-2.

Oxidative stress and altered NO metabolism can potentially trigger a cascade of events that work in concert to promote HTN and cardiovascular disease in Pb-exposed organisms. Some of these potential links are illustrated in Figure 5-5.1.

5.5.2.2 Protein Kinase C, Inflammation, NFκB Activation and Apoptosis

Protein kinase C (PKC) isoforms belong to a family of serine-threonine kinases, which serve numerous diverse cellular functions. For instance, PKC is involved in regulating vascular contractility, blood flow, permeability, and cell growth. In this regard, the activation of PKC has been shown to cause vascular contraction and Pb exposure has been found to raise PKC activity. For example, Hwang et al. (2002) found increased PKC activity in the erythrocytes of a group of Pb-exposed Korean workers, and Markovac and Goldstein (1988b) showed a significant increase in PKC activity in rat brain micro vessels following exposure to micromolar concentrations of Pb. Also, Watts et al. (1995) demonstrated that Pb-acetate (10^{-10} to 10^{-3} M) caused contraction in an isolated rabbit mesenteric artery preparation. This Pb-induced vasoconstriction was unaffected by denudation of endothelium, while it was significantly potentiated by PKC agonists and attenuated by a PKC inhibitor. Calcium channel blockade with verapamil attenuated, but did not abolish, Pb-induced vasoconstriction. These findings were considered to indicate that activation of PKC is, in part, responsible for Pb-induced vasoconstriction, independently of endothelium or extracellular influx of calcium. Taken together, these observations suggest that the activation of PKC in the vascular smooth muscle cells may, in part, contribute to the pathogenesis of Pb-induced HTN by enhancing vascular contractility. It should be noted, however, that Pb-induced contraction has been shown to be unaffected by a PKC inhibitor in the rat aorta rings (Valencia 2001). Thus, the contribution of PKC activation to the Pb-induced alteration of vascular contractility appears to be both vessel- and species-specific. It is of note, that at high concentrations, Pb can reduce PKC activity in certain cell types, including mouse macrophages and rat brain cortex (reviewed by Watts et al. [1995]).

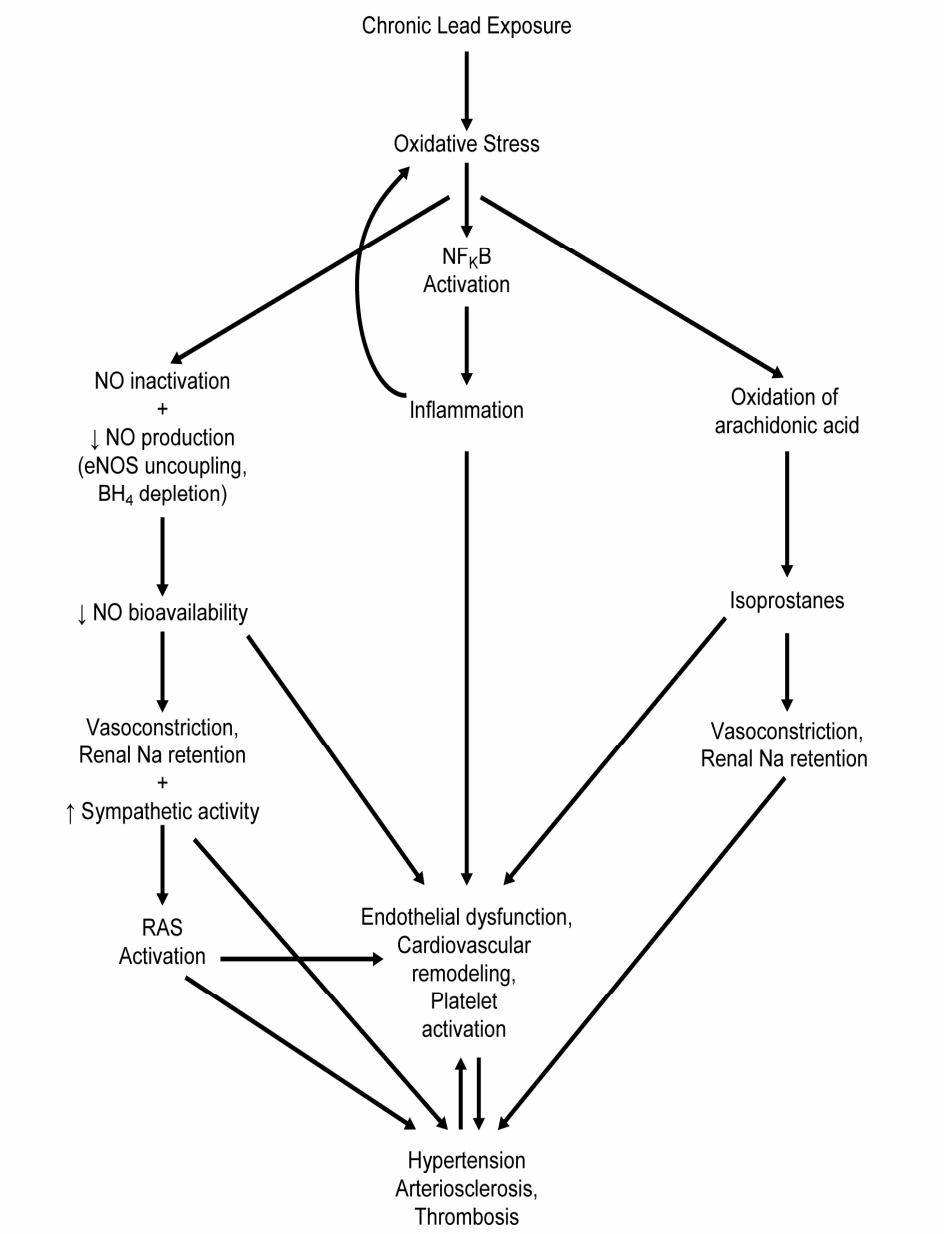


Figure 5-5-1. This illustration depicts some of the potential mechanisms by which oxidative stress may participate in the pathogenesis of Pb-induced HTN and cardiovascular complications. In the presence of oxidative stress, uncontained reactive oxygen species (ROS) inactivate nitric oxide (NO), deplete NO synthase cofactor (tetrahydrobiopterin), uncouple eNOS, promote generation of isoprostanes by oxidizing aracidonic acid, and activate the redox-sensitive transcription factor NFκB. Together, these events can cause vasoconstriction, salt retention, sympathetic system activation, renin-angiotensin system stimulation, platelet adhesion, and, thereby, endothelial dysfunction, hypertension (HTN), inflammation, arteriosclerosis, and thrombosis.

As noted earlier, Pb exposure results in oxidative stress in cultured VSMC and endothelial cells, as well as in intact animals. Oxidative stress can promote the activation of the nuclear transcription factor Kappa B (NFκB) and, thereby, trigger inflammation and apoptosis. In this context, Ramesh et al. (2001) showed that exposure to low Pb levels (50 ppm in drinking water) for 90 days activates NFκB and capsases in the rat brain. It is of note that several studies have revealed the presence of renal tubulointerstitial infiltration of activated T cells, macrophages, and angiotensin II (Ang-II) producing cells in various forms of genetic and acquired HTN in experimental animals. Moreover, the associated tubulointerstitial inflammation has been shown to contribute to the pathogenesis of HTN in these disorders (Rodriguez-Iturbe, 2004). These abnormalities are accompanied by activation of the redox-sensitive NFκB, which can account for the associated inflammation (reviewed by Rodriguez-Iturbe et al. [2004]). The NFκB activation, the accompanying inflammation, and HTN are ameliorated by antioxidant therapy in these models, pointing to the role of oxidative stress in this process. In a recent study, Rodriguez-Iturbe, et al. (2005) observed marked activation of NFκB coupled with tubulointerstitial accumulation of activated T-cells, macrophages, and Ang-II-producing cells, as well as increased apoptotic cells in the kidneys of Pb-exposed rats (100 ppm Pb-acetate in water for 3 months). This was associated with increased nitrotyrosine staining (a marker of NO/ROS interaction) in the kidney tissue. Since tubulointerstitial inflammation plays a crucial role in the pathogenesis of HTN in various other models of HTN, its presence in the Pb-exposed animals may contribute to the associated HTN. Inflammation in Pb-induced HTN is not limited to the kidney. In fact, lymphocyte infiltration is reported in the periaortic tissues in rats with Pb-induced HTN (Carmignani et al 2000). The inflammatory response to Pb exposure in the renal and vascular tissues outlined above parallels the observations reported with immune system in Section 5.9 of this chapter.

5.5.2.3 Effect of Lead Exposure on the Adrenergic System

The adrenergic system plays an important role in regulating arterial pressure, renal and systemic hemodynamics, and cardiac function in health and disease. For this reason, a number of clinical and animal studies have focused on the sympathetic system as a possible mediator of Pb-induced HTN and cardiovascular abnormalities. For instance, in a study of a group of Pb-exposed workers, Chang et al. (1996), found elevated plasma norepinephrine (NE), but normal

plasma dopamine and epinephrine, levels. The constellation of these biochemical abnormalities points to increased sympathetic nervous system activity in Pb-exposed humans. The impact of Pb exposure on the sympathetic nervous system activity has been substantiated in experimental animals. For example, Chang et al. (1997) showed that administration of Pb (Pb-acetate 0.5% in drinking H_2O) for 2 months resulted in significant rises in arterial pressure and plasma NE (but not epinephrine) in Wistar rats. This was coupled with significant reductions of the aorta β adrenergic receptor density and isoproterenol (β agonist)-stimulated cAMP production. In a subsequent study Tsao et al. (2000) reported a significant rise in plasma NE coupled with marked reductions of β receptor density as well as diminished basal and isoproterenol-stimulated cAMP productions in the aorta and heart of Wistar rats with Pb-induced HTN. In contrast to the heart and aorta, β receptor density as well as basal and β agonist-stimulated cAMP production were increased in the kidneys of Pb-exposed animals.

In another study, Carmignani et al. (2000) found significant elevations of blood pressure, plasma catecholamines, and cardiac contractility (dP/dt), together with reduced carotid blood flow in rats with Pb-induced HTN. The effect of Pb on the sympathetic nervous system activity was examined by Lai et al. (2002) who tested the rapid response to intrathecal (IT) injection of $PbCl_2$ in vivo and its addition to the thoracic cord slices in vitro in the rats. They found significant rises in arterial pressure and heart rate with IT injection of Pb-chloride. These effects of Pb were abrogated by the administration of ganglionic blockade using hexomethonium. The in vitro studies revealed a significant rise in excitatory and significant fall in inhibitory post-synaptic potentials with the addition of Pb to the bathing medium and their reversal with saline washout.

In a recent study, Chang et al. (2005) showed a gradual decline in blood, kidney, heart, and aorta Pb contents toward the control values within 7 months following cessation of exposure in rats with Pb-induced HTN. This was coupled with a parallel declines in arterial pressure, plasma NE and renal tissue β receptor density as well as parallel rises in the aorta and heart β receptors densities during the 7-month period following cessation of Pb exposure. However, while HTN and β receptor abnormalities were significantly improved, they were not completely reversed. It should be noted that bone Pb contents were not measured in this study and were most likely elevated despite normalization of blood and soft tissue levels. These findings

provided evidence for the stimulatory effect of Pb on the sympathetic nervous system and for its contribution to the cardiovascular effects of Pb exposure.

5.5.2.4 Effects of Lead on the Renin-Angiotensin-Aldosterone (RAAS) and Kininergic Systems

The available data on the effects of Pb exposure on the RAAS are contradictory. This appears to be primarily due to variability in the dosage and duration of Pb exposure, as well as the age at which exposure is initiated or the animals studied. In addition, when present, nephropathy can potentially affect the RAAS profile of Pb-exposed animals or humans. The majority of animal studies of the effects of Pb on RAAS were conducted and published in the late 1970s and 1980s. In a meta-analysis of the studies published in that period, Vander (1988) found increased plasma renin activity and renal tissue renin content in young rats after several weeks of Pb exposure sufficient to achieve blood Pb concentrations in the range of 30 to 40 μg/dL. Similar results were found in rats exposed to Pb in utero and for 1 month after birth. In contrast, plasma renin activity and renal renin contents were generally unchanged or even reduced in older rats whose Pb exposure had commenced in utero.

In a more recent study, Carmignani et al. (1999) showed a significant increase in plasma angiotensin converting enzyme (ACE) activity in the rats exposed to Pb (60 ppm Pb-acetate in water) for 10 months beginning at an early age (weaning). This was accompanied by a significant increase in plasma kininase II, kininase I, and kallikrein activities. In a subsequent study, Sharifi et al. (2004) examined plasma and tissue ACE activity in young adult rats (weighing 200 g) exposed to Pb (100 ppm Pb-acetate) for 2 to 8 weeks. They found significant rises in plasma, aorta, heart, and kidney ACE activities, peaking at 2 to 4 weeks. This was followed by a decline in plasma and tissue ACE activity to subnormal values by 8 weeks, at which point arterial pressure was markedly elevated. The authors concluded that the elevated ACE activity is involved in the induction of HTN but may not be necessary for maintaining HTN in Pb-exposed animals. Finally, in a recent study, Rodriguez-Iturbe et al. (2005) demonstrated a marked increase in the number of Ang-II positive cells in the kidneys of rats treated with lead-acetate (100 ppm in water) for 3 months. This observation points to heightened intra-renal Ang-II generation in rats with Pb-induced HTN.

Taken together, the data point to activation of the RAAS at some point in the course of Pb-induced HTN. Further studies are needed to fully elucidate the effects of Pb exposure on various other RAAS components.

5.5.3 Effects of Lead Exposure on Vasomodulators

In a study of a group of Pb workers with elevated blood Pb concentration, Cardenas et al (1993) found a significant increase in urinary excretion of the metabolite of vasoconstrictive prostaglandin, thromboxan (TXB_2), and significant reduction of the vasodilatory prostaglandin, 6-keto-PGF1, when compared with the control workers. Subsequently, Hotter et al. (1995) confirmed the elevation of urinary TXB_2 in another group of Pb-exposed workers. Based on these observations, the authors suggested that Pb can alter the balance between vasoconstrictive and vasodilatory prostaglandins in a way which may contribute to HTN and cardiovascular disease. In an attempt to examine such possible effects of Pb exposure in experimental animals, Gonick et al. (1998) measured urinary excretion of the above metabolites in the rat model of Pb-induced HTN. The study showed no significant difference in urinary excretion of the given prostaglandin metabolites between the Pb-exposed and control rats. However, in a recent in vitro study, Dorman and Freeman (2002) demonstrated that Pb promotes the release of arachidonic acid by vascular smooth cells via activation of phospholipase A_2. They further showed that, at low concentrations, Pb augments Ang-II-induced VSMC proliferation, whereas at a high concentration it reduces viability and cell count in unstimulated cells and reduces DNA synthases in Ang-II and Fetal Calf Serum (FCS)-stimulated VSMC. Thus, Pb can increase the release of arachidonic acid (the substrate for prostaglandins) via activation of phospholipase A_2.

Given the limited and contradictory nature of the published data, further in-depth studies are needed to clarify the effects of Pb on regulation of arachidonic acid metabolism and the synthesis of various classes of prostaglandins.

Endothelin

Endothelins (ET) represent a family of potent vasoconstrictive peptides that are produced by endothelium and a number of other cell types. Excess production or increased sensitivity to ET can raise arterial pressure. In an attempt to explore the possible contribution of ET to the pathogenesis of Pb-induced HTN, Khalil-Manesh et al. (1993) studied the effects of exposure to

low and high levels of Pb (100 ppm versus 5000 ppm) in the drinking water for 1 to 12 months in rats. Rats exposed to low (but not high) levels of Pb exhibited HTN and a significant increase in plasma ET-3 concentration. These findings were confirmed by these investigators in a subsequent study of rats with Pb-induced HTN (Khalil-Manesh et al., 1994). Similarly, Gonick et al. (1997) demonstrated a significant elevation of plasma concentration and urinary excretion of ET-3 in rats with Pb-induced HTN. In a recent study, Martin et al. (2005) showed that incubation in the lead-containing media resulted in the downregulation of soluble guanylate cyclase and cGMP production in the isolated artery segment of normal rats. They further found that co-incubation with an ET-A receptor antagonist can partially reverse this effect of lead. These findings suggest that the adverse effect of Pb exposure on cGMP production in the vascular tissue is, in part, mediated by its ability to raise ET activity. It, thus, appears that exposure to low-levels of Pb can raise activity or production of ET, which can, in turn, play a part in the pathogenesis of Pb-induced HTN in the rat. Further studies are required to carefully explore the effects of Pb on various components of the ET system.

Atrial Natriuretic Factor

Atrial natriuretic factor (ANF) is produced and secreted by cardiac myocytes. Plasma concentration of ANF rises with volume expansion and declines with volume contraction. ANF serves as a vasodilator and a natriuretic agent and, as such, plays a role in regulating blood volume, vascular resistance, and, hence, arterial pressure. Giridhar and Isom (1990) measured ANF in rats treated with IP injection of Pb-acetate (0.0 to 1.0 mg/kg/twice weekly for 30 days). The Pb-exposed animals exhibited fluid retention, which was coupled with a paradoxical dose-dependent decline in plasma ANF concentration. Based on these findings, they suggested that Pb may interfere with the hormonal regulation of cardiovascular system, which may, in turn, relate to the cardiovascular toxicity of this metal.

5.5.4 Effects of Lead on Vascular Reactivity

Addition of Pb-acetate to the bathing medium has been shown to elicit a cumulative concentration-dependent vasoconstriction in isolated rabbit mesenteric artery (Watts et al., 1995). This effect was reported to be partly mediated by activation of PKC. In a more recent study, Valencia et al. (2001) found a concentration-dependent vasoconstrictive response to

Pb-acetate (0.1 to 3.1 mM) in Wistar rat thoracic aorta rings. The contractile response was observed in both intact and endothelium-denuded rings. Likewise, Pb-induced vasoconstriction was preserved in calcium-free medium and was unaffected by either α-1 blockade (prazosin), PKC inhibition (Calphostin) or L-type calcium channel blockade (verapamil). However, Pb-induced vasoconstriction was inhibited by lanthanum, which is a general calcium-channel blocker. These observations suggest that Pb can promote an endothelium-independent vasoconstriction by a direct effect on the vascular smooth muscle cells. The data further suggests that the effect of Pb is Ca-independent and may depend on the entry of Pb to the cell via a lanthanum-blockable channel. In contrast to the latter studies, addition of Pb-acetate did not cause vasoconstriction in the rat aorta rings used in a study reported by Shelkovnikov and Gonick (2001). Moreover, Pb-acetate at either high (10^{-4}m) or low (10^{-8}m) concentrations did not modify the response to NE, phorbol ester, or isoproterenol. However, at 10^{-4}M, Pb-acetate augmented the contractile response to submaximal concentrations of calcium. Thus, the rapid action of Pb on vascular reactivity in vitro seems to vary depending on the type of the vessel used, the Pb concentration employed, and the animal species being studied.

A number of studies have endeavored to discern possible differences in vascular reactivity to various agonists between animals with Pb-induced HTN and control animals. For instance, Purdy et al. (1997) found no significant difference in vasoconstrictive response to NE and phenylephrine or vasodilatory response to acetylcholine or nitroprusside in the aorta rings obtained from Sprague-Dawley rats with Pb-induced HTN. In contrast, Marques et al. (2001) showed a significant reduction of vasodilatory response to both acetylcholine and nitroprusside in Wistar rats with Pb-induced HTN. It should be noted that the Wistar rats employed in the latter study had been treated with 5 ppm Pb-acetate in the drinking water for 1 month, whereas those reported by Purdy et al. (1997) had been given a higher dosage (100 ppm) for a longer period (3 months). Therefore, the magnitude and duration of exposure may account for the differences observed between the two reports. Also, the effect of Pb on vascular reactivity may vary from one tissue to the next, as clearly exemplified by studies (Oishi et al., 1996) that showed significant endothelium-dependent vasorelaxation of mesenteric artery response to acetylcholine in the presence of the NOS inhibitor L-NAME in tissues from rats exposed to Pb-acetate for 3 months. These observations suggest that chronic Pb exposure may impair

endothelium-dependent hyperpolarization in the rat mesenteric artery. However, no such effect was noted in the aorta obtained from the same animals.

5.5.5 Lead-Calcium Interactions in Vascular Tissue

Changes in cytosolic Ca^{2+} concentrations are intimately involved in regulating vascular tone and vascular smooth muscle contraction. Consequently, several studies have focused on the interaction of Pb with cellular Ca^{2+} and Ca^{2+}-dependent signaling pathways as a means to gain insight into the pathogenesis of Pb-induced HTN (Piccini et al 1977; Favalli et al 1977; Webb et al 1981; Goldstein 1993; Watts et al 1995). Lead can potentially compete with Ca^{2+} in transport systems (i.e., channels and pumps) involved in physiological movements of ions, particularly Ca^{2+}, into and out of the cell (Simons 1993a,b). Moreover, Pb can alter the intracellular distribution of Ca^{2+} between cytoplasm, endoplasmic reticulum, and mitochondria, which normally regulates cytosolic Ca^{2+} concentration, (Simons 1993a,b). In addition, Pb can serve as a substitute for calcium in Ca^{2+}-dependent signaling pathways by interacting with calmodulin, PKC, and calcium-dependent potassium channels (Haberman, 1983; Richardt, 1986; Chai and Webb, 1988; Simons, 1993a,b; Watts, 1995). Thus, interactions of Pb with cellular Ca^{2+} via these complex mechanisms in the vascular cells may contribute to alterations of vascular resistance and HTN. For example, Piccini et al. (1997) and Favalli et al. (1977) showed that Pb exposure increases calcium content in the tail artery in rats. The authors attributed this phenomenon to a possible Pb-induced inhibition of Ca^{2+} extrusion from the vascular cells. Using rabbit mesenteric artery preparations, Watts et al. (1995), showed that blockade of either PKC or voltage-gated Ca channels by verapamil substantially attenuated Pb-induced vasoconstriction in both intact and endothelium-denuded preparations. Based on these observations, the authors suggested that Pb promotes a vasoconstrictive response in rabbit mesenteric artery via a Ca^{2+}-dependent activation of PKC. In contrast, Valencia et al. (2001) using rat aorta rings reported a vasoconstrictive response to Pb-acetate in rat aorta rings bathed in either Ca^{2+}-free or Ca^{2+}-containing media and in the presence or absence of the L-type calcium-channel blocker verapamil or of the PKC inhibitor calphostin. Moreover, depletion of intracellular Ca^{2+} stores by preincubation of rings in EGTA, while diminishing the intensity, did not abrogate Pb-induced vasoconstriction in this system. In contrast, Pb-induced vasoconstriction was prevented by lanthanum (a general blocker of calcium channels) in both Ca^{2+}-containing and Ca^{2+}-free media.

Based on these observations, the authors concluded that Pb can elicit a PKC-independent contractile response in the rat aorta by entering VSMC via a non-voltage-gated Ca^{2+} channel and mimicking the action of Ca^{2+}. It, thus, appears that Pb exerts its effect by mechanisms that are species- and vessel-specific.

5.5.6 Cardiotoxicity and Atherogenesis

Acute Pb exposure has been reported to affect cardiac function, and chronic exposure has been linked to atherosclerosis and increased cardiovascular mortality by some, but not by all investigators, in humans (See Chapter 6). In an attempt to assess the cardiotoxicity of lead, Prentice and Kopp (1985) carried out the in vitro perfusion of isolated rat heart preparations with a perfusate containing 0.3 and 30 μM Pb-acetate for up to 60 min. At 30 μM concentration, Pb prolonged the AV node and His bundle conduction times, reduced coronary blood flow and heart rate, and altered cardiac energy metabolism. Milder, and statistically insignificant, changes were also observed at 0.3 μM Pb concentration in this model. These observations illustrate the direct cardiotoxicity of Pb independently of its systemic and neuroendocrine actions in acute intoxication. In an attempt to determine whether chronic exposure to Pb or cadmium can cause atherosclerosis, Revis et al. (1981), studied male white pigeons that were exposed to Pb (0.8 ppm in drinking water) for extended periods. Long-term low-level Pb exposure in this model resulted in a significant rise in arterial pressure and a near doubling of the number of atheromatous plaques in the aorta. These observations demonstrate the proatherogenic effects of chronic exposure to low levels of Pb in pigeons.

5.5.7 Effects of Lead on Endothelial Cells

Endothelium is an important constituent of the blood vessel wall and regulates macromolecular permeability, vascular smooth muscle tone, tissue perfusion, and blood fluidity. Endothelial damage or dysfunction results in atherosclerosis, thrombosis, and tissue injury. Chronic Pb exposure has been shown to promote atherosclerosis in experimental animals (Revis et al., 1981). Given the central role of endothelial injury/dysfunction in the pathogenesis of atherosclerosis, numerous studies have explored the effect of Pb on cultured endothelial cells. These studies have searched for evidence of Pb-mediated endothelial cell injury and the effects of Pb on endothelial cell proliferation, tube formation (angiogenesis), monolayer wound repair,

and production of heparansulfate proteoglycans, plasminogen activator (tPA), and plasminogen activator inhibitor-1 (PAI-1).

Using cultured bovine aorta endothelial cells, Kaji et al. (1995a) showed that incubation with Pb-nitrate at concentrations equal to or below 50 μM for 24 h, results in mild de-endothelialization of endothelial monolayers in vitro. They further showed that adding Pb at 10 μM concentration markedly increased cadmium-induced endothelial injury.

Proliferation of endothelial cells is a critical step for the repair of injured endothelium. Failure of the repair process can result in thrombosis, VSM cell migration and proliferation, and atherosclerosis. In this regard, Pb (Pb-nitrate 0.5 to 5 μM) has been shown to significantly reduce DNA synthesis and cell proliferation in growing cultured bovine aorta endothelial cells (Kaji, 1995a). Similarly, the proliferative response to βFGF and αFGF is significantly attenuated by Pb in this system (Kaji, 1995b). The reported inhibition of endothelial cell proliferation by Pb can potentially diminish the repair process in response to endothelial injury. This supposition has been confirmed by Fujiwara et al. (1998) who showed that at 5 to 10 μM concentrations, Pb markedly inhibited the repair of the wounded endothelial monolayer in vitro. Moreover, Pb severely mitigated the zinc-stimulated endothelial cell proliferation and repopulation of the denuded sections in this system.

Endothelial cell proliferation is the primary step in angiogenesis, a phenomenon that is essential for numerous physiological functions such as growth, development, wound repair, and menstrual cycle as well as certain pathological events including diabetic retinopathy and tumor growth. In view of the demonstrated inhibition of endothelial cell growth by lead, it has been postulated that Pb may impair angiogenesis. This assumption has been confirmed by a number of studies testing the effect of Pb by angiogenesis assay (tube formation) in endothelial cells cultured on matrigel (a laminin-rich basement membrane product) matrix in vitro. For instance, Ueda et al. (1997) and Kishimoto et al. (1995) have shown that Pb-acetate (1 to 100 μM) results in a concentration- and time-dependent inhibition of tube formation by human umbilical vein endothelial cells cultured on a matrigel matrix.

Endothelial cell migration and proliferation are critical for angiogenesis and repair of the damaged endothelium. βFGF is a powerful mitogen for endothelial cells as well as several other cell types. Endothelial cells synthesize βFGF, which is released following injury or spontaneous death of endothelial cells and acts in an autocrine fashion to facilitate the repair process by

promoting endothelial cell migration and proliferation. Binding of βFGF to its receptor on the endothelial cell is facilitated by heparan sulfate proteoglycans (HSPGS) that are normally produced and released by the endothelial cells for attachment to the cell surface as well as incorporation in the extracellular matrix. As noted above, Pb significantly attenuates βFGF and αFGF-mediated DNA synthesis and proliferation in cultured endothelial cells (Kaji et al., 1995b). In this regard, Pb has been shown to reduce βFGF binding to the cell surface HSPGs without changing the biosynthesis or intracellular abundance of βFGF in cultured bovine endothelial cells (Fujiwara and Kaji, 1999a). Moreover, Pb has been shown to significantly reduce the synthesis of glycosamino-glycans (GAG, measured by sulfate incorporation into heparan sulfate) in the growing endothelial cells.

The above observations suggest that Pb-induced reduction of βFGF-mediated proliferative response in cultured endothelial cells is largely due to impaired production of HSPGs. This supposition is further supported by observations that DNA synthesis can be restored by adding heparin in lead-treated growing endothelial cells (Fujiwara et al., 1995). The reduction in the production of GAGs by Pb in the growing endothelial cells (Fujiwara et al., 1995) is also seen in confluent (quiescent) cells. For instance, Kaji et al. (1991) demonstrated a marked reduction of GAG production following incubation with 10 μM Pb nitrate in confluent endothelial cells in vitro. The Pb-induced reduction of heparan sulfate production was more severe than that of the other GAGs. Moreover, the reduction in the cell surface-associated GAGs was more severe than that of the newly synthesized GAG found in the incubation media. GAGs combine with a series of specific core proteins to form anionic macromolecular complexes known as proteoglycans, which are widely distributed in the extracellular matrix of the mammalian tissues. Endothelial cells produce two types of HSPGs, i.e., the high-molecular weight and low-molecular weight classes. Perlecan is a high-molecular weight heparan-sulfate proteoglycan which is a component of the basement membrane. Syndecan, glypican, ryudocan, and fibroglygan are among the low-molecular weight subclass and are primarily associated with the cell surface. Proteoglycans play an important role in regulating vascular function and structure. For instance, by providing a negative electrostatic charge, these molecules constitute a major barrier against extravasations of negatively-charged plasma proteins. In addition, by interacting with antihthrombin-III and tPA, these molecules serve as important endogenous anticoagulants. Moreover, perlecans facilitate βFGF binding to its receptor on endothelial cells and, thus, contributes to the endothelial growth

and repair processes. In contrast, these molecules tend to inhibit migration and growth of vascular smooth muscle cells and, thereby, help to prevent athero- and arteriosclerosis. Another important function of HSPGs is their role in stabilizing and anchoring lipoprotein lipase and VLDL receptors on the endothelial surface. Consequently, they play an important indirect part in the clearance of VLDL and chylomicrons from the circulation, a process which has major implications for energy metabolism and cardiovascular protection.

In a study of cultured bovine endothelial cells, Kaji et al. (1997) found that Pb-chloride, at 10 μM concentration, markedly lowers incorporation of precursors (glycosamine and sulfate) into HSPG in confluent bovine aorta endothelial cells. The effect of Pb was more severe on low-molecular than high-molecular weight HSPGs. However, Pb did not change the length of heparan sulfate chains. It is of note that Pb slightly increased the abundance of the HSPG core proteins. This observation excluded a reduction in core protein synthesis as a cause of diminished HSPGs in the lead-treated confluent endothelial cells. In a subsequent study, Fujiwara and Kaji (1999) investigated the effect of Pb-nitrate on production of high- and low-molecular weight subclasses of HSPGs in growing bovine aorta endothelial cells. In contrast to the quiescent cells, lead-treated growing cells exhibited a marked reduction in the high-molecular weight with no change in production of low molecular weight (~50KD) HSPGs. They further showed a significant reduction of the core protein of perlecan, which is a high-molecular weight (400 KD) HSPG. Thus, Pb appears to affect productions of subclasses of HSPGs differently depending on the cells' growth cycle. Accordingly, in the growing endothelial cells (a condition which simulates the response to injury), Pb downregulates perlecan, which is involved in βFGF-mediated migration and proliferation of endothelial cells and inhibition of migration and proliferation of VSMC. This phenomenon may adversely affect endothelial repair and promote athero- and arteriosclerosis. On the other hand, Pb-induced reduction of the cell surface-associated low-molecular weight HSPGs (which are predominantly involved with lipolytic, anticoagulant, and other functions of confluent endothelial cells (simulating intact endothelium) can contribute to hyperlipidemia and thromboembolism, among other disorders.

One of the major properties of normal endothelium is its ability to prevent coagulation. Several factors contribute to the thromboresistance of the endothelial lining. These include the surface coating of HSPG (which confers heparin-like properties), nitric oxide (which inhibits platelet adhesion and activation), and tPA (which promotes thrombolysis), thrombomodulin, and

prostacycline. As noted earlier, Pb exposure reduces HSPG-production (Kaji et al., 1995b, 1997) and diminishes nitric oxide availability via ROS-mediated NO inactivation (Vaziri 1999). In addition, Kaji et al. (1992) showed that incubation of confluent human umbilical vein endothelial cells with Pb nitrate, at 0.01 to 1.0 μM concentrations, significantly reduced basal and thrombin-stimulated tPA release. It thus, appears that Pb exposure may confer a thrombophilic diathesis.

5.5.8 Effects of Lead on Vascular Smooth Muscle Cells

Lead has been shown to stimulate proliferation of bovine aorta VSMCs in a concentration-dependent manner (Fujiwara et al., 1995). Moreover, the combination of Pb and βFGF results in an additive effect on VSMC proliferation. As with bovine aorta VSMCs, cultured rat aorta VSMCs exhibit hyperplasia in response to a low concentration of (100 μg/L) of Pb-citrate (Carsia, 1995). The reported hyperplasia is accompanied by phenotypical transformation of cells from the spindle or ribbon shape to cobblestone shape, simulating the neointimal cell morphology. This was accompanied by a significant reduction in Ang-II receptor but no change in α, β, or ANP receptor densities. It is of note that, in contrast to the low concentration, a high concentration (500 μM/L) of Pb resulted in growth arrest in this system. Thus, the effect of low concentration of Pb on VSMC proliferation is opposite of its action on the endothelial cells.

Under normal conditions, intact endothelial lining shields the cells residing in the subendothelial tissue, i.e., fibroblasts and VSMCs, from coming into contact with the circulating blood. However, this barrier is lost when the endothelium is injured, an event which can lead to platelet adhesion and fibrin thrombosis formation. Propagation of fibrin thrombus is limited by activation of the fibrinolytic system, which, in turn, depends on the balance between tPA and plasminogen activator inhibitor-1 (PAI-1). In addition to endothelial cells, VSMCs and fibroblasts express tPA and PAI-1. Using cultured human aorta VSMCs and fetal lung fibroblasts, Yamamoto et al. (1997) investigated the effect of Pb chloride on the release of tPA and PAI-1 in vitro. The authors found that Pb causes a significant inhibition of tPA release and a significant increase in PAI-1 release in cultured fibroblasts in a dose-dependent manner. The lead-treated VSMC exhibited a significant dose-dependent decline in tPA release and to a lesser extent of PAI-1 release. Taken together, exposure to Pb appears to evoke a negative effect on fibrinolytic process by the cellular constituents of the subendothelial tissue.

5.5.9 Summary/Conclusion

In vivo and in vitro studies published during the past 15 years have considerably expanded our knowledge of the effects of Pb exposure on the cardiovascular system. However, many questions remain unanswered and await further investigation.

A number of in vivo and in vitro studies conducted during the review period have provided compelling evidence for the role of oxidative stress in the pathogenesis of Pb-induced HTN. Moreover, the effect of oxidative stress on blood pressure has been shown to be, in part, mediated by avid inactivation of NO and downregulation of sGC. In addition, a limited number of in vitro studies have provided indirect evidence that, via activations of PKC and NFκB, Pb may raise vascular tone and promote inflammation.

The adrenergic system plays a major role in regulating cardiovascular function and structure and, as such, has been the focus of several studies during the review period. Based on these studies, chronic low level lead exposure appears to increase central sympathetic activity, reduce cardiac and vascular and raise kidney β adrenergic receptor density. These events can, in turn, increase peripheral vascular resistance and renal renin release/production and, thereby, arterial pressure. Since sympathetic outflow is inhibited by NO, inactivation of NO by oxidative stress may be, in part, responsible for the increased sympathetic activity in Pb-exposed animals.

The renin-angiotensin-aldosterone system (RAAS) plays an important role in regulating blood pressure and cardiovascular function and structure. The available data published during the review period suggest that Pb exposure can raise plasma ACE and kininase activities at different points in the course of Pb-induced HTN in experimental animals. This can, in turn, contribute to the genesis and/or maintenance of HTN. Since renin release (which is responsible for production of ACE substrate, i.e., Ang-1) is, in part, driven by β adrenergic activation, upregulation of renal β adrenergic activity may, in part, account for increased RAAS activity in the Pb-exposed animals.

The balance in production of vasodilator and vasoconstrictor prostaglandins plays an important role in regulation of blood pressure and cardiovascular function. Studies of the Pb exposed humans have revealed an imbalance in production of prostaglandins favoring a rise in arterial pressure. However, the animal and in vitro studies published during the review period have been limited and inconsistent. Further studies are needed to address this issue.

Based on the available studies, Pb exposure appears to increase endothelin production in experimental animals. This phenomenon can, in part, contribute to the rise in blood pressure in the Pb-exposed animals. A number of studies have explored the effect of Pb on vascular tone as well as vascular response to vasoconstrictor and vasodilator agents. For instance, Pb has been shown to cause vasoconstriction and to attenuate acetylcholine- and NO-mediated vasodilatation in some, but not all vascular tissues and in some, but not all, studies. These effects have been variably attributed to lead-mediated activation of PKC and Ca^{2+}-mimetic action of Pb, among other possibilities.

Finally, a number of studies have explored the effects of endothelial and vascular smooth muscle cells to explore the possible atherogenic effect of Pb exposure. In this context, Pb has been found to inhibit proliferation of the growing (non-confluent) endothelial cells (mimicking in vivo response to injury), impair tube formation (angiogenesis), and the repair of wounded endothelial monolayer in vitro. Likewise, Pb exposure was shown to reduce production of HSPGs and tPA by confluent endothelial monolayers, events that may favor thrombosis and hyperlipidemia. Lead exposure has been also shown to promote vascular smooth muscle cell and fibroblast proliferation and phenotypic transformation in ways that seem to favor arteriosclerosis and vascular remodeling.

Among many questions awaiting clarification, a few are of particular interest. For instance, it is not clear as to why low, but not high, levels of Pb exposure cause HTN in experimental animals. Similarly, it is uncertain as to why HTN occurs long after the onset of Pb exposure in the intact animals, whereas the effects on cultured cells and isolated tissues are manifested within short periods of time.

5.6 GENOTOXIC AND CARCINOGENIC EFFECTS OF LEAD

5.6.1 Introduction

The 1986 Pb AQCD (U.S. Environmental Protection Agency, 1986) and its 1990 Supplement (U.S. Environmental Protection Agency, 1990) concluded that, at relatively high concentrations, Pb may be carcinogenic to laboratory animals, particularly the rat. Cell culture studies were considered to be supportive of these observations, but also indicated that Pb was not

particularly potent. Human data were considered to be of concern, but not definitive, and given the animal data, the prudent choice was to consider Pb to be a possible human carcinogen.

This section reviews reports of Pb-induced carcinogenesis and DNA damage published since 1986. More than 200 publications were read and considered and those that reported any effect related to carcinogenesis or genotoxicity that was attributable to Pb are presented below.

This report follows the same format as the previous one (1986) and the explanations for the relative importance of the various types of studies (e.g. epidemiology, animal and cell culture) can be found in the original report and are not repeated here. Carcinogenesis studies are presented first, followed by genotoxicity studies. Each of these sections is further subdivided into human studies (considering adults and then children), animal studies, and then cell culture studies (considering human, mammalian, and then nonmammalian). When appropriate, these sections are followed by a section describing acellular (cell-free) model studies.

There are some differences with this new report. For one, each section is more distinctly broken out. The epidemiology has been reviewed in more detail in Chapter 6 (Section 6.7) in this document and, so, only a brief summary is presented here. Because of more recent concerns about effects on childhood development, this issue was specifically considered in a separate section. Following advances in hypotheses and technology, much more specific sections about the possible epigenetic effects of Pb have also been added.

5.6.2 Carcinogenesis Studies

5.6.2.1 Human Studies

The human carcinogenesis studies are only briefly reviewed in this section; for a more detailed review, see Chapter 6 (Section 6.7) in this document.

Adults

The assessment of the carcinogenicity of Pb through human epidemiological studies remains ambiguous. Several reports state that occupational exposure to Pb increases the risk of lung, kidney, brain, stomach, and liver cancer (Fu and Boffetta, 1995; Kauppinen et al., 1992; Gerhardsson et al., 1995a; Ades and Kazantzis, 1988; Wicklund et al., 1988; Steenland et al., 1992; Englyst et al., 2001; Gerhardsson et al., 1986; Antitila et al., 1995, 1996; Cocco et al., 1998; Shukla et al., 1998). However, a full interpretation of the data in these studies is

complicated by the fact that the study participants also incurred coexposure to other known carcinogens, such as arsenic, cadmium, and hexavalent chromium. Thus, it is difficult to determine if the excess cancers observed were due to exposure to Pb, one of these other carcinogens, or some combination of the various chemicals. In addition, other reports indicate that occupational or environmental exposure to Pb did not alter cancer risk (Cocco et al., 1996; Fanning, 1988; Jemai et al., 2002). Consequently a definitive assessment of the carcinogenicity of Pb from human studies cannot be made at this time.

Children

There have been no recent studies of Pb-induced cancers in children. This lack of data is not unexpected and is largely because Pb has not been considered a likely cause of childhood cancers. There have, however, been studies of cancers in children resulting from paternal exposure. Here again, the same confounding problems encountered are as seen in the adult population studies, and it is difficult to draw any definitive conclusions. For example, two studies reported elevated childhood tumors (Wilm's tumor and acute nonlymphocytic leukemia) in children whose fathers worked in Pb-related industries, such as welding, painting, and auto repair (Buckley et al, 1989; Olshan et al., 1990). However, workers in these occupations also experienced coexposure to arsenic, cadmium, and hexavalent chromium, and so the cancers observed cannot be solely linked to Pb exposure. In addition, a report from the printing industry in Norway found no link between paternal exposure and childhood cancers and, perhaps, even found a possible reduction in the incidence of childhood cancers with paternal Pb exposure (Kristensen and Andersen, 1992).

The possible interaction of paternal occupation and childhood cancer is an important area of concern. However, a definitive assessment of paternal exposure to Pb cannot be made at this time and more research is needed.

5.6.2.2 Laboratory Animal Studies

Lead is a well-established animal carcinogen, as noted in the 1986 Lead AQCD. Consequently, limited tumorigenesis studies have been conducted in animal models and the focus has been more on the mechanism of neoplasia (e.g., the roles of calcium and

metallothionein) and possible immunomodulatory effects of Pb in the promotion of cancer. These studies are summarized in Table AX5-6.1.

All of the studies exposed animals to Pb-acetate except one, which focused on Pb-chromate. One study investigated the carcinogenicity of a series of chromate compounds, i.e., Pb-chromate and several Pb-chromate-based compounds were included as part of the group of chromate compounds. The Pb-chromate was administered by implantation into the lung after being embedded within a cholesterol pellet. The authors indicated that in this design, Pb-chromate was not carcinogenic, but that 4 of the Pb chromate compounds did induce a very rare tumor in the mice. Thus, there is some ambiguity about the carcinogenicity of Pb-chromate in the study, as the statistics calculated an expected tumor level based on any tumor and were not based on the occurrence of this very rare (for rats) tumor. It is likely that had the expected value been adjusted for the rare tumor, a conclusion would have been reached that either Pb-chromate was tumorigenic or that the study lacked the power to make any determination. The previous EPA report had concluded that Pb-chromate is tumorigenic. Thus, it is difficult to draw a firm conclusion from this study.

The remaining five studies focused on Pb-acetate (Schrauzer, 1987; Blakley, 1987; Teraki and Uchiumi, 1990; Bogden et al., 1991; Waalkes et al., 2004). In most studies, this compound was administered in drinking water at concentrations from 0.5 to 4000 ppm, but one study considered effects from a subcutaneous (SC) injection both in mice and in rats. Consistent with the findings in the 1986 Pb AQCD, Pb not only induced renal tumors, but also induced other tumors, although the possible effect on mammary tumors is difficult to interpret, as important study details were omitted, as discussed below. In a surprising development, during one lifetime exposure study, Pb suppressed liver tumors (Waalkes et al., 2004).

The key study in this group of studies was a lifetime exposure study that investigated mice exposed to drinking water concentrations of 1,000 to 4,000 ppm Pb and also considered the role of metallothionein. In wild-type mice, Pb-acetate induced a low frequency of renal tumors, but hyperplasia was common and exhibited overexpression of cyclin D1. Lead inclusion bodies were also common. Lead also suppressed liver tumors in this study.

By contrast, in metallothionein-deficient mice, Pb-acetate induced a high frequency of kidney tumors and severe inflammation. Both the tumors and the regions of inflammation exhibited cyclin D1 overexpression. Lead also suppressed liver tumors in these animals. In

contrast to the wild-type mice, Pb inclusion bodies were not seen in these animals. Thus, the data convincingly indicate that metallothionein binds Pb as part of an inclusion body and prevents the formation of tumors.

Another study focused on the ability of Pb to induce tumors in rats after SC injection of Pb-acetate (Teraki and Uchiumi, 1990). Tumors formed at the site of injection, and Pb accumulated in the tumors, indicating that Pb is tumorigenic. However, full interpretation of the data is complicated by the absence of data on control animals and the fact that only a single dose was considered.

Three studies investigated compounds that might reduce or prevent Pb-induced cancers, specifically selenium and calcium compounds (Schrauzer, 1987; Bogden et al., 1991). The first study used a rather complex approach to study the possibly protective effects of selenium (Shrauzer, 1987). In this study, mice were infected with the murine mammary tumor virus, because they are known to develop mammary adenocarcinomas when maintained on a low-selenium diet. The data indicated that Pb can induce tumors in these mice even when they are maintained on a high-selenium diet. However, the data are difficult to interpret and the impact of the study is uncertain, as the methods are incomplete, the data on control animals are not provided, and the experimental results are stated but not presented in tables or figures.

The second study investigated the effect of calcium (Bogden et al., 1991). The main focus of this study appeared to be blood pressure, but tumorigenesis was also considered. It might be anticipated that calcium might reduce Pb tumorigenesis by competing for its binding sites or blocking its uptake. However, in this study, calcium did not affect Pb levels in tissue and actually exacerbated Pb-induced carcinogenesis. The full impact of this study is also difficult to assess, as the calcium-treated animals incurred profound nephrocalcinosis.

The remaining study considered Pb-induced immunosuppression as a possible factor contributing to the tumorigenesis induced by other agents, including viruses or chemicals (Blakley, 1987). The results indicated that Pb may suppress humoral immunity but not cellular immunity. However, this is the only study of its kind and the results need to be repeated in other settings. In addition, it is difficult to determine if these data are specific to the agents used (e.g., murine lymphocytic leukemia virus) or if they represent a class of agents (e.g., viruses in general).

Overall, the above studies confirm that Pb is an animal carcinogen and extends our understanding of mechanisms involved to include a role for metallothionein. Specifically, the recent data show that metallothionein may participate in Pb inclusion bodies and, thus, serves to prevent or reduce Pb-induced tumorigenesis. Much more work is needed to determine the potential exacerbating or ameliorating roles of calcium and selenium and to determine what role Pb-induced immunomodulation may play in the promotion of tumors.

5.6.2.3 Cell Culture Studies

Carcinogenesis is measured in cell culture systems through studies of neoplastic transformation, where morphologically transformed cells are injected into athymic mice to see if the cells can form a tumor in the host animal. Morphological transformation refers to cells that incur a change in morphology, such as formation of a focus (or foci) of cell growth. In addition, for faster study results and as a screening tool, the ability of cells to grow in agar without a surface to attach to (anchorage independence) is often used as a short-term substitute measure for transformation.

Human Cell Cultures

Since the 1986 Pb AQCD, only four studies have used human cell culture systems to study the carcinogenesis of Pb compounds. One found that Pb-acetate induced anchorage independence in primary human foreskin fibroblasts (HFF) (Hwua and Yang, 1998). The full impact of these data is uncertain, as previous studies of known metal carcinogens in primary HFF found that these carcinogens induced anchorage independence, but those anchorage-independent cells ultimately senesced. These studies are summarized in Table AX5-6.2. Further study is needed to confirm that Pb can induce anchorage independence and to see if these cells can progress to full neoplastic transformation.

In an effort to explore the importance of oxidative metabolism in inducing anchorage independence, Hwua and Yang (1998) also co-treated some cells with 3-aminotriazole, a known catalase inhibitor. This co-treatment had no effect on Pb-acetate-induced anchorage independence, suggesting that catalase was not involved in this effect. It would be premature to conclude that oxidative metabolism is not involved in anchorage independence, as these are the

only data available and are limited to catalase only. More data are needed to elucidate whether oxidative metabolism is involved in this lead effect.

The remaining three studies focused on Pb-chromate (Beiderman and Landolph, 1987, 1990; Sidhu et al., 1991). Two used similar HFF cells and found that Pb-chromate induced anchorage independence (Beiderman and Landolph, 1987, 1990). However, these anchorage-independent cells ultimately underwent senescence, suggesting that anchorage independence may not be a suitable short-term marker for neoplastic transformation in primary HFF. It should be noted that these studies were focused on the chromate component of this compound and the potential contribution of Pb was not investigated or discussed. By contrast, Sidhu et al. (1991) found that Pb-chromate did not induce anchorage independence in a human osteosarcoma cell line, while it did induce full neoplastic transformation of these cells and the transformed cells did grow in agar. It should be noted that this study was also focused on the chromate component of this compound and that the potential contribution of Pb was not investigated or discussed.

The 1986 Pb AQCD did not include any studies of transformation in human cells. Given that other chromate compounds have been shown to induce anchorage independence, it seems quite possible that the data from Pb-chromate exposures may represent effects from chromate and not from Pb. Thus, the data currently seem to indicate that Pb can induce anchorage independence in human cells, but its ability to induce neoplastic transformation of human cells is uncertain. Further study of different Pb compounds and the full assessment of their neoplastic potential (i.e., including studies of the ability of treated cells to form tumors in experimental animal models) are needed before definitive conclusions can be drawn.

Animal Cell Cultures

The 1986 Pb AQCD presented several studies demonstrating that Pb compounds could induce anchorage independence and morphological and neoplastic transformation in rodent cell culture systems. Since that report, six studies have further considered the ability of Pb compounds to induce these effects. Three focused on Pb-chromate and three on Pb compounds without the confounding factor of chromate; and these studies are summarized in Table AX5-6.3.

Four studies considered Pb-acetate, Pb-chloride, or Pb-nitrate in Syrian hamster embryo and C3H10T1/2 mouse embryo cells (Zelikoff et al., 1988; Patierno et al., 1988; Patierno and Landolph, 1989; Elias et al., 1991). Three found that Pb compounds did not induce

transformation (Patierno et al., 1988; Patierno and Landolph, 1989; Elias et al., 1991); but the third study (Zelikoff et al., 1988) indicated that Pb was weakly positive, though no statistics were performed to validate this conclusion. Zelikoff et al. (1988) indicated that the observations were repeated several times, but only showed data from one experimental run. It is unclear why the studies were not averaged together, as multiple repeats would likely have provided the power to detect whether the observed weak increase was significant.

Five studies considered Pb-chromate, which induced neoplastic and morphological transformation of Syrian hamster and mouse C3H10T1/2 embryo cells, as well as enhancing viral transformation (Patierno et al., 1988; Patierno and Landolph, 1989; Schectman et al., 1986; Elias et al., 1989, 1991). The focus on Pb-chromate was based largely on concern about chromate; but these studies found that Pb-chromate was more potent than other chromate compounds, suggesting that Pb may enhance or contribute to the carcinogenicity. Indeed, one study found that combining Pb-nitrate with soluble chromate was as potent as Pb-chromate and greater than soluble chromate alone (Elias et al., 1991).

Thus, all together, these studies suggest that Pb ions alone cannot transform rodent cells; however, they may be co-carcinogenic or promote the carcinogenicity of other compounds. These data are in contrast to findings described in the1986 Pb AQCD that included a positive study. One possible factor may be exposure duration; the study in question indicated that the Pb-transformed cells were exposed for 9 days. The studies discussed here all exposed cells for 7 days or less. Further careful study of a time course of exposure is necessary to determine whether Pb actually induces transformation in cultured rodent cells.

Nonmammalian Cell Cultures

No carcinogenesis studies were located that used nonmammalian cell culture models.

5.6.2.4 Organ-Specific Studies

No organ-specific or organ culture studies concerning Pb carcinogenesis were located.

5.6.2.5 Carcinogenesis Summary

It still remains difficult to conclude whether Pb is a human carcinogen. The assessment of the carcinogenicity of Pb through human epidemiological studies remains ambiguous.

By contrast, the studies confirm that Pb is an animal carcinogen and further extend our understanding of the mechanism to include a role for metallothionein. The cell culture data suggest that Pb can induce anchorage independence, but whether it can induce full neoplastic transformation of human cells is uncertain.

5.6.3 Genotoxicity Studies

The human genotoxicity studies are only briefly reviewed in this section. For a more detailed review, see Chapter 6 (Section 6.7) in this document.

5.6.3.1 Human Studies

Adults

A number of studies investigating the potential genotoxicity of Pb have been conducted in human populations. Endpoints considered include chromosome aberrations, sister chromatid exchanges (SCE), micronuclei formation, DNA strand breaks, and hypoxanthine guanine phosphoribosyl transferase (HPRT) mutations. In general, these studies were much more specific than the carcinogenesis studies, as correlations with blood-Pb levels could be made, other confounders could be ruled out, and the endpoints were more short-term.

The chromosome damage studies are ambiguous and contained some methodological flaws. Four studies were positive (Xupei et al., 1988; De at al., 1995; Bilban, 1998; Pinto et al., 2000), while two were negative (Anwar and Kamal, 1988; Rajah and Ahuja, 1996). Moreover, the four positive studies included two that could not rule out potential contributions from other genotoxic metals and one that found a correlation only at very high blood Pb levels (>52 μg/dL).

By contrast, the studies of micronucleus formation (Bilban, 1998; Vaglenov et al., 1998; Pinto et al., 2000; Palus et al., 2003; Minozzo et al., 2004), SCE (Xupei et al., 1988; Bilban, 1998; Pinto et al., 2000; Duydu et al., 2001; Palus et al., 2003), DNA strand breaks (Restrepo et al., 2000; Fracasso et al., 2002; Hengstler et al., 2003; Danadevi et al., 2003; Palus et al., 2003) all consistently found clear correlations between Pb and genotoxicity. It should be noted that there were two negative studies for SCE (Rajah and Ahuja, 1995, 1996), but both were by the same group and considered the same very small population of workers (only 5 Pb-exposed workers) and, thus, may not have had enough power to detect potential differences.

It is notable that one study found an interesting correlation of HPRT mutation rates and blood Pb levels from environmental Pb exposure in Belgian women (Van Larebeke et al., 2004). This study is the first and only one to consider Pb-induced mutations. Further research is needed to assess the validity of these data.

Thus, it appears from these studies that Pb is genotoxic to humans, although it may not induce substantial amounts of chromosome damage. This conclusion is consistent with the laboratory studies discussed below. For more in-depth consideration of the epidemiology studies see Chapter 6, Section 6.7.

Children

Two recent studies of Pb-induced genotoxicity in children have been published. One study of children living in a high Pb contamination area of Czechoslovakia found no increase in chromosome damage in white blood cells compared with children living in an area with lower Pb contamination (Smejkalova, 1990). Comparisons were not done with children living in an area with little or no Pb contamination. Measurements of blood Pb levels indicated a statistical difference in blood levels between the two groups but not necessarily a substantial, or biologically significant, difference between them. (Typically the control group levels were in the high 20's compared to the low 30's μg/dL in the exposed group). Thus, the possibility that each group was exposed to a Pb level that could induce a baseline level of damage cannot be ruled out and, thus, it cannot be conclusively stated that Pb was not clastogenic in this study.

The other study found an increase in Pb-induced strand breaks in white blood cells from children living in an area of Mexico with high Pb contamination compared to children living in an area with lower Pb contamination (Yanez et al., 2003). Blood Pb levels confirmed a difference in exposure to Pb, but urinary arsenic levels confirmed that these children were exposed to higher levels of arsenic, too; and, thus, it cannot be determined which chemical was responsible for the damage.

The possible genotoxicity of Pb for children is an important concern. However, there are simply too few data to draw definitive conclusions, and more research is needed. See Chapter 6 (Section 6.7) for more in-depth discussion of the epidemiology of Pb in human populations.

5.6.3.2 Laboratory Animal Studies

Fourteen studies evaluated the genotoxicity of Pb compounds in animal models. The majority of these studies focused on mice, and the Pb was administered by intraperitoneal (IP) or intravenous (IV) injection. Several endpoints were considered including chromosome aberrations, SCE, micronucleus formation, and DNA strand breaks. Overall, the results are ambiguous, due in part to study design and the various endpoints considered. These studies are summarized in Table AX5-6.4.

Lead compounds appear to be able to damage chromosomes, if only weakly. Two studies with well-performed analyses were positive (Fahmy, 1999; Aboul-Ela, 2002). The other positive studies observed that Pb could induce karyotypic arrangements, indicating a possible clastogenic response; however, these studies did not analyze very many cells (Chakraborty et al., 1987; Nayak et al., 1989a,b; Dhir et al., 1990, 1992a,b; Nehez et al., 2000). Some found chromosome damage, but it did not increase with dose (Chakraborty et al., 1987; Nayak et al., 1989a,b; Dhir et al., 1990). Altogether, the data do suggest some role for Pb in inducing chromosome damage, but it may be a weak effect.

Similarly, the data for micronuclei and DNA damage are ambiguous. One study found that Pb induced micronucleus formation in a dose-associated manner, but only considered two doses (Roy et al., 1992). The other study found that Pb induced micronucleus formation but not in a dose-dependent manner (Jagetia and Aruna, 1998). This difference may reflect the somewhat shorter exposure time in the second study.

One DNA damage study found that Pb nitrate could induce DNA strand breaks in the white blood cells of mice (Devi et al., 2000); however, the damage was not dose-dependent. Another found DNA damage in a number of organs, but only one dose was considered and the authors described the effect as weak (Valverde et al., 2002). In both studies, the highest doses caused less damage than the moderate- to low-doses. These data again suggest that Pb is only weakly causing damage.

By contrast, the results for SCE are consistently positive. The three studies that were positive found that SCEs were induced in a dose-dependent manner (Fahmy, 1999; Nayak et al., 1989a; Dhir et al., 1993).

The route of administration complicates the interpretation of all of these genetic studies. All of the studies, except for three chromosome damage studies, used injection-based exposures.

It is unknown if exposures that reflect more realistic scenarios (e.g., from drinking water) would cause any of these effects. Only one study of DNA strand breaks used a physiologically relevant exposure (inhalation).

Four studies exposed animals by gavage, which is still a somewhat artificial exposure. One was a DNA damage study that found weak activity (Devi et al., 2000). The other three considered chromosome damage (Aboul-Ela, 2002; Dhir et al., 1992b; Nehez et al., 2000). Two found a dose-response for a 24 h-exposure to Pb nitrate-induced chromosome aberrations in mice (Aboul-Ela, 2002; Dhir et al., 1992b). The other found that a 4-week exposure to Pb-acetate induced aneuploidy, but not chromosome aberrations, in rats (Nehez et al., 2000). It is difficult to reconcile these two studies, as they use different exposure times, chemicals, and species. More work is needed using relevant doses and exposure conditions to Pb compounds in multiple species to determine if Pb induces chromosome aberrations.

Some studies also tried to offset the effects of Pb with a variety of compounds. Potential modulators included fruit extract from *Phyllanthus emblica*, ascorbic acid, calcium, and iron (Aboul-Ela, 2002; Dhir et al., 1990, 1992a, 1993; Roy et al., 1992). Other studies sought to determine if coexposure to other toxicants would potentiate the effects of Pb (Dhir et al., 1992b; Nehez et al., 2000) and considered both zirconium and cypermethrin. The data indicated that the fruit extract could block the toxic effects of Pb, an effect which may, in part, be attributable to ascorbic acid, but that other components must also be involved, because ascorbic acid alone produced variable results. Iron also had an effect, but only if given just before, or with, the Pb compound; post treatments with iron had no effect. Calcium had a strong effect.

The effects with zirconium and cypermethrin are less clear. Both were reported to exacerbate the effects of Pb, but the effects for both are complicated by experimental design problems. For example, zirconium only exacerbated Pb's effects when given simultaneously and not when given 2 h before, or after, Pb. This seems rather unusual as the total exposure to each was 24 h and, thus, simultaneous exposure occurred in every circumstance. Thus, the data would seem to suggest that a 22-h coexposure had no effect, but that a 24-h exposure did. Alternatively, there may have been some interaction of the two chemicals in the gut during coexposure, creating a more toxic species.

Interpretation of the cypermethrin study is complicated by its design and the results. Only 20 metaphases were analyzed for each animal, instead of the recommended 100. In addition, the

statistical analyses were done relative to untreated controls and not to animals treated with Pb or cypermethrin alone. Careful inspection of the tables reveals that actual exposure to Pb plus cypermethrin induced less damage than that induced by Pb alone. Thus, the effects of them together appear to be less than additive. More work is needed to explore the meaning of these data and the importance of Pb mixtures.

The previous report found a similar amount of ambiguity; some animal studies were positive for chromosome damage and others were negative. Other endpoints were not described after Pb exposure in experimental animals. These data suggest that Pb can induce SCE but that it can induce chromosome damage, DNA damage, or micronuclei either weakly or not at all.

5.6.3.3 Cell Culture Studies

Few cell culture studies were reported in the 1986 Pb AQCD. Since 1986, a great deal of theoretical and technological progress has allowed for a large number of cell culture studies to be performed, as discussed below.

Human Cell Culture

Mutagenicity

Two studies considered Pb-acetate-induced mutagenesis in human cells. Both considered mutations at the HPRT locus, with one using keratinocytes and the other skin fibroblasts (Ye, 1993; Hwua and Yang, 1998). These studies are summarized in Table AX5-6.5.

One study reported no lead-induced mutagenesis (Hwua and Yang, 1998) but sought to explore the importance of oxidative metabolism in lead-induced mutagenesis by co-treatment with 3-aminotriazole, a known catalase inhibitor. This co-treatment did not increase Pb-acetate-induced mutagenesis, suggesting that either catalase was not involved in this effect or that Pb is truly not mutagenic. It would be premature to conclude that oxidative metabolism is not involved in anchorage independence, as these are the only data and are limited to catalase. Further data is needed to elucidate whether oxidative metabolism is involved in this effect of Pb as well as further studies of lead-induced mutagenesis.

The other study reported that Pb-acetate induced mutagenesis (Ye, 1993). However, interpretation of this study is hampered by its methodology. The study did not actually measure HPRT mutations or colony formation, but rather it attempted a quicker methodology that

measured tritium incorporation. Although a shorter assay is highly desirable, the study did not verify the observed effects with standard methods, and, thus, it is uncertain if the tritium incorporation actually reflected lead-induced mutations.

One study considered Pb-chromate and found that it was not mutagenic (Biedermann and Landolph, 1990).

There are insufficient data at this point to conclude whether Pb is mutagenic in human cells, although the few data that exist are largely negative.

Clastogenicity

Ten studies investigated the ability of Pb compounds to induce chromosome damage in cultured human cells. All but one were essentially from the same research group, and all but two considered Pb-chromate. All were done using normal, or nearly normal, human cells. These studies are summarized in Table AX5-6.6.

Only two of those studies focused on the clastogenicity of Pb itself (Wise et al., 2004b, 2005), the remainder used Pb compounds but focused on either chromate or radioactive particles as the clastogenic species. These studies found that Pb-glutamate was not clastogenic.

All of the Pb-chromate studies found that Pb-chromate induced chromosome damage in a concentration-dependent manner. However, the effects were either attributed or demonstrated to be caused by chromate ions. Lead ions were produced by Pb-chromate, but they were not clastogenic.

There was one study of radioactive Pb (Martins et al., 1993). The focus was on the clastogenic activity of alpha particles, and the identity of the specific Pb salt was not provided. The alpha particles were able to induce chromosome damage.

Overall, the data appear to indicate that Pb does not induce chromosome damage in human cells, although more investigation of different compounds is needed.

DNA Damage

Studies of DNA damage in cultured human cells have considered DNA strand breaks, Pb-DNA adducts, and DNA-protein crosslinks for a variety of Pb compounds. The only clear positive damage induced by Pb was Pb-DNA adducts following Pb-chromate exposure, although the authors referred to them as Pb associated with DNA (Singh et al., 1999). It is uncertain if

these represent actual adducts or some weaker association. Two studies found no DNA strand breaks induced by Pb (Hartwig et al., 1990; Snyder and Lachmann, 1989), and one study involving several laboratories found no DNA-protein crosslinks after Pb exposure (Costa et al., 1996). The other study found DNA double-strand breaks, but these were attributed to chromate and not Pb (Xie et al., 2005). These studies are summarized in Table AX5-6.7.

One other study was positive (Wozniak and Blasiak, 2003), but the results were unusual and their impact uncertain. Specifically, this study found that Pb-acetate induced DNA single-strand breaks but that the amount of damage decreased with concentration, and ultimately the highest concentration had less damage than the control. DNA double-strand breaks were observed, but were lowest at the highest concentration. DNA-protein crosslinks were seen only at the highest concentration, and the authors attempted to explain the decrease in strand breaks with this effect. This explanation may partially correct, but it does not entirely explain the decreased amount of damage at the middle concentration. These data need to be repeated by an independent group before they can be fully assessed.

Together, these data suggest that Pb likely does not induce DNA damage; however, the data are still too limited to allow any definitive conclusions.

Human Cell Genotoxicity Summary

The cumulative data suggest that Pb is not mutagenic and does not induce chromosome aberrations or DNA damage in cultured human cells. It is interesting to note that Pb-induced SCEs have not been considered in human cells.

5.6.3.4 Animal Cell Cultures

Mutagenicity

The potential mutagenicity of Pb compounds in rodent cells was considered in six studies. In particular, three mutagenesis systems were considered: mutagenesis at the HPRT locus, the gpt locus, and mutations in sodium-potassium ATPase. The results are highly variable and may be specific to the Pb compound considered in each case. In particular, Pb-chromate and Pb-acetate appear to be nonmutagenic. Lead acetate was positive but only at highly cytotoxic concentrations. By contrast, Pb-chloride and Pb-sulfate appeared to be mutagenic at relatively nontoxic concentrations. These studies are summarized in Table AX5-6.8.

Insufficient data exist at this point to conclude whether or not Pb is mutagenic in animal cells.

Clastogenicity

Seven studies investigated the ability of Pb compounds to induce chromosome aberrations in cultured mammalian cells (Table AX5-6.9). Four of these studies considered Pb-chromate and further investigation revealed that chromate was responsible for the clastogenic effect (Wise et al., 1992, 1993; Blankenship et al., 1997). Three of these studies considered other lead-containing compounds (Wise et al., 1994; Lin et al., 1994; Cai and Arenaz, 1998). All but one were negative and that one only found a small response at a single high dose (Wise et al., 1994). Lower doses had no effect. Considered together, the studies indicate that Pb does not induce chromosomal aberrations in cultured mammalian cells.

Only two studies considered Pb-induced micronuclei in cultured mammalian cells. One was negative (Lin et al., 1994) and the other positive (Bonacker et al., 2005).

Four studies considered Pb-induced SCE in cultured mammalian cells. The results were predominately negative (three studies [Hartwig et al, 1990; Lin et al., 1994; Zelikoff et al., 1988]). Interpreting these studies, however, is complicated by the fact that too few metaphase cells (less than 30 per concentration) were analyzed in each study. The one positive study considered 100 metaphases per concentration, making those data more reliable (Cai and Arenaz, 1998).

DNA Damage

Several measures of DNA damage in cultured human cells have been investigated, including DNA single-strand breaks and DNA-protein crosslinks. Most Pb compounds did not induce DNA single-strand breaks. The exception was Pb-chromate, which did induce DNA strand breaks, but this effect was likely a result of the chromate ion. These studies are summarized in Table AX5-6.10.

Both Pb-chromate and Pb-nitrate induced DNA-protein crosslinks in cultured mammalian cells. These data suggest that Pb is genotoxic in this manner; however, it is thought that the Pb-chromate-induced DNA-protein crosslinks result from the chromate and that the method used for

Pb-nitrate is not sufficiently rigorous. Thus, while the data are certainly suggestive, they are insufficient to make any definitive conclusion.

Nonmammalian Cell Cultures

Only one study was located considering Pb in a nonmammalian model (Table AX5-6.11). This study found that Pb-chromate was not mutagenic in a bacterial assay. The compound was studied because of its chromate content and, given that it is the lone study, no definitive conclusions can be reached.

5.6.3.5 Cell-Free Studies

No cell-free studies concerning Pb carcinogenesis or genotoxicity were located.

5.6.3.6 Organ-Specific Studies

One study (Valverde et al., 2002) considered organ-specific effects (see Table AX5-6.4). That study found a different pattern of DNA strand breaks in mice after inhalational exposure to Pb-acetate. DNA in the brain and lung were damaged the most, kidney and liver next, then nasal epithelia and leukocytes, with no damage in testicle DNA. These data are intriguing, as they suggest organ-specific responses after a physiologically relevant exposure (inhalation). More research is needed, however, to fully assess the impact of these findings. Moreover, while the damage was statistically significant, the authors described the effects as weak.

5.6.3.7 Genotoxicity Section Summary

There is some ambiguity in the genotoxicity results, as some endpoints were positive while most were negative. Consistent with the animal study data, Pb can induce SCE in rodent cells, but it is unknown if it can do so in human cells because this has not been tested. Lead also seems to induce DNA-protein crosslinks in rodent cells.

5.6.4 Genotoxicity as it Pertains to Potential Developmental Effects

The human genotoxicity studies are only briefly reviewed in this section. For a more detailed review, see Chapter 6 (Section 6.7). Only limited animal data and no cell culture studies focused on this issue as a concern. The available data are described below.

Adults

One study was located that considered the effects of Pb on sperm quality and quantity. This study considered Pb, cadmium, and selenium levels in 56 nonsmoking volunteers (Xu et al., 2003). No effects on sperm quality were correlated with Pb exposure up to 10 μg/L.

Two studies were located on the effects of Pb on sperm morphology in animals (Fahmy, 1999; Aboul-Ela, 2002). Both were positive, indicating that Pb may have an effect on sperm. They also found that Pb induced DNA damage in the sperm (See Table AX5-6.4). These studies are summarized in Table AX5-6.12.

Children

No studies were analyzed that considered the genotoxic effects of Pb in children as a developmental hazard. There are two studies that considered the genotoxic effects of Pb in children. They were discussed in Section 5.6.3.1.

Three studies were located on the fetal effects of Pb-nitrate on the fetus (Kristensen et al., 1993; Nayak et al., 1989a,b). Lead induced an increase in resorptions and there were hints of possible fetal chromosome damage, but the methods were poorly described and much more work is needed before conclusions can be drawn. These studies are summarized in Table AX5-6.13.

5.6.5 Epigenetic Effects and Mixture Interactions

Lead has been proposed to be a co-mutagen or possibly a promoter. Thus a number of epigenetic mechanisms have been proposed. Epigenetic effects occur when a compound such as Pb induces changes in cellular processes that do not result from changes in DNA sequence. In other words, Pb has been proposed to alter cells in ways that may change the cell without breaking or mutating DNA. There are three possible mechanisms: (1) alterations of gene expression that can stimulate cells to grow (mitogenesis) and/or can interfere with DNA repair; (this possibility has been investigated in several studies); (2) interaction with other metals; and (3) alteration of oxidative metabolism. Neither of the latter two have been extensively investigated.

5.6.5.1 Gene Expression

It has been argued that Pb may induce or co-induce carcinogenesis by altering cellular metabolism or by altering the metabolism of another chemical. Both whole animal and cell culture studies have been conducted to address this question and are described below.

Animal

Animal studies indicate that Pb can induce the expression of some phase I metabolizing enzymes, such as cytochrome P4501A1, and phase II metabolizing enzymes, such as glutathione and glutathione-S-transferase. These studies are summarized in Table AX5-6.14.

Thus, it is plausible that through this mechanism, Pb may act as a co-carcinogen by affecting the metabolism of other chemicals or possibly as a direct carcinogen by enhancing endogenously-induced damage. However, no studies have directly shown that such Pb effects are linked to cancer or alter the potency of another chemical; and, thus, it remains only a plausible hypothesis.

Human Cell Culture Studies

A few human cell culture studies have been done, and these generally confirm the animal studies. These studies are summarized in Table AX5-6.15.

Lead has been shown to affect the induction of some phase I metabolizing enzymes (such as cytochrome P4501A1) and phase II metabolizing enzymes (such as glutathione and glutathione-S-transferase and NAPDH oxidase). These experiments also indicate that Pb can affect the metabolism of other carcinogenic compounds, although they do not show that the genotoxic or carcinogenic effects change as a result of these effects; and, thus, more work remains to make this more than just a plausible explanation.

Animal Cell Culture Studies

No animal cell culture studies concerning the effects of Pb on the expression of metabolic genes were located.

5.6.5.2 DNA Repair

It has been argued that Pb may induce or co-induce carcinogenesis by altering the repair of DNA lesions induced by another agent. The greatest focus has been on damage induced by ultraviolet (UV) light. Only cell culture and cell-free studies have been conducted to address this question and are described below.

Human

Only one study considered Pb-induced effects on DNA repair in cultured human cells (see Table AX5-6.16). This study found that coexposure to Pb caused persistence of strand breaks induced by UV light. This persistence suggests that Pb interfered with the repair of these lesions, but direct evidence of that interference was not provided. These are the only data in human cells and, thus, it cannot be determined if Pb inhibits DNA repair in human cells.

Mammalian Cell Culture Models

Two studies considered Pb-induced effects on DNA repair in cultured mammalian cells. These studies are summarized in Table AX5-6.17. Both found that Pb-acetate increased UV-induced DNA damage including SCE, mutagenesis, and cytotoxicity. Lead did not affect strand breaks induced by UV. These data suggest that Pb may indeed inhibit repair, although direct interactions with repair proteins were not demonstrated.

Cell Free Systems

One study considered the effects of Pb on DNA repair proteins (McNeill et al., 2004). That study found that Pb can inhibit APE nuclease in cell-free systems.

5.6.5.3 Mitogenesis

It has been argued that Pb may induce or co-induce carcinogenesis by inducing cells to grow when they should not. Both animal and cell culture studies have been conducted to address this question and are described below.

5.6.5.3.1 Animal

Several studies have considered Pb-induced mitogenesis in animal models. These studies

are summarized in Table AX5-6.18. These studies found that Pb can stimulate cell growth, but primarily in the liver. One study did consider TNF-α expression in brain cells, but it was not demonstrated whether these effects were mitogenic. The interpretation of many of the studies is complicated by the exposure method (IV injection), which does not reflect human exposure. In general, the data indicate that Pb is mitogenic to the liver.

Human Cell Culture Studies

A number of studies have considered the potential growth-stimulatory effects of Pb in cultured human cells (Table AX5-6.19). These studies all found that Pb did not stimulate cell growth. Thus, mitogenesis is not a likely epigenetic effect for Pb in human cells.

Mammalian Cell Culture Studies

A number of studies have considered the potential growth-stimulatory effects of Pb in cultured mammalian cells other than the kidney. These studies all found that Pb did not stimulate cell growth. Thus, mitogenesis is not a likely epigenetic effect of Pb in human cells. One study found an increased mitotic index; however, it did not consider possible cell cycle arrest (Lin et al., 1994). Indeed, another study found that Pb increased the mitotic index, because it induced M-phase arrest (Wise et al., 2005).

Other

Lead-induced oxidative damage has been investigated as a potential cause of genotoxic or carcinogenic effects. Generally, the results suggest that Pb only produces low levels of reactive oxygen species, but that it may inhibit some enzymes involved in oxidative metabolism (Table AX5-6.20). Thus, Pb may affect oxidative metabolism, but more work is needed to draw meaningful conclusions.

5.6.5.4 Epigenetic Mechanisms Summary

The collective data support the hypothesis that Pb can induce an epigenetic effect. Lead can alter the expression of metabolic genes in cultured cells and may alter DNA repair, although much more study is needed. Lead may also affect oxidative metabolism or interact with other

metals, but again more study is needed. By contrast, it is unclear if Pb is mitogenic. It is mitogenic to the liver in animals, but it is not mitogenic in cultured cells. More study is needed to determine if this difference reflects differences between in vivo and cell culture models or if this property is specific to only certain organs, e.g., the liver.

5.6.6 Overall Conclusions

The overall conclusions have not changed much from the 1986 Pb AQCD. Lead remains an ambiguous carcinogen in humans and a clear carcinogen in animals. Cell culture studies support both of these conclusions, as effects in rodent cells were not seen in human cells. Lead does appear to be genotoxic in human epidemiology studies. By contrast, the laboratory studies are more ambiguous in both animal and cell culture studies. In these systems, the genotoxicity in culture is limited to SCE and, perhaps, to DNA-protein crosslinks. For other endpoints, it is only weakly active, if at all. Lead has not been evaluated sufficiently as a potential genotoxic hazard, but this probably stems from the fact it appears to be weakly genotoxic. The available data suggest that Pb can damage sperm and affect fetuses. More work is urgently needed on this topic. Cell culture studies do support a possible epigenetic mechanism or co-mutagenic effects.

5.7 LEAD AND THE KIDNEY

5.7.1 Review of Earlier Work

This section summarizes key finding from the 1986 Pb AQCD on the effects of Pb on the kidney in animals. Human studies published since 1986 are then reviewed in Section 6.4.

Both in vivo and in vitro studies on several different animal species revealed that renal accumulation of Pb is an efficient process that occurs in both proximal and distal portions of the nephron and at both luminal and basolateral membranes (Victery et al., 1979a; Vander et al., 1977). The transmembrane movement of Pb appears to be mediated by an uptake process that is subject to inhibition by several metabolic inhibitors and the acid-base status of the organism. Alkalosis increases Pb entry into tubule cells via both the luminal and basolateral membranes (Victery et al., 1979b).

Goyer et al. (1970a) were principally responsible for defining the role of renal proximal tubular nuclear inclusion bodies in the response to Pb intoxication. In addition to the early

reports of nuclear inclusion bodies appearing in the proximal tubule following Pb exposure (Goyer et al., 1970b), biochemical studies on the protein components of isolated rat kidney intranuclear inclusion bodies have shown that the main component has an approximate molecular weight of 27 kDa (Moore et al., 1973) or 32 kDa (Shelton and Egle, 1982) and is rich in glutamate and aspartate. Goyer et al. (1970c) suggested that the intranuclear inclusion body sequesters Pb, to some degree, away from sensitive renal organelles and metabolic pathways. Goyer et al. (1975, 1978) also showed that single or repeated administration of $CaNa_2EDTA$ leads to the disruption of the nuclear inclusion bodies and their removal from the nuclei. Rats treated for 24 weeks with both Pb and $CaNa_2EDTA$ had no inclusion bodies, but showed early interstitial nephropathy. As an extension of this study, Cramer et al. (1974) examined renal biopsies from 5 Pb workers with 0.5 to 20 years of exposure. The two workers with normal GFRs, and shortest exposure duration, showed intranuclear inclusion bodies, whereas the remaining three workers had no intranuclear inclusions but showed peritubular fibrosis.

Formation of intranuclear inclusion bodies was a common pathognomic feature for all species examined. In addition, proximal tubular cytomegaly and swollen mitochondria with increased numbers of cytosomes were also observed (Fowler et al., 1980; Spit et al., 1981). The morphological changes were principally localized in the straight (S3) segments of the proximal tubule. Goyer (1968) and Goyer et al. (1968) had demonstrated earlier that, after lead exposure, mitochondria were not only swollen but had decreased respiratory control ratios (RCRs) and inhibited state-3 respiration.

Aminoaciduria has been reported in several studies (Studnitz and Haeger-Aronson, 1962; Goyer et al., 1970b; Wapnir et al., 1979). Other studies have reported increased urinary excretion of electrolytes (e.g., sodium, potassium, calcium, water) following Pb administration (Mouw et al., 1978). Victery et al. (1981, 1982a,b, 1983) found that zinc excretion was increased following injection of lead.

Wapnir et al. (1979) observed that Pb-acetate administration caused a reduction in renal alkaline phosphatase activity and an increase in Mg-ATPase activity, but no significant changes in NaK-ATPase activity. On the other hand, Suketa et al. (1979) found marked a decrease in renal NaK-ATPase activity following a single oral administration of Pb-acetate at a dose of 200 mg/kg, but no change in Mg-ATPase.

Renal ALAD was found to be inhibited by Pb in both acute and chronic experiments (Silbergeld et al., 1982). Renal ALAD was similar to control levels when GSH was present but was significantly reduced in the absence of GSH (Gibson and Goldberg, 1970). Accumulation of both ALA and porphobilinogen was also observed in kidney tissue of Pb-treated rabbits, compared to controls. Other studies have not shown a reduction in renal ALAD following Pb exposure (e.g., Fowler et al., 1980). Higher levels of Pb may be required to cause the reduction in ALAD reported by Silbergeld et al. (1982), and it may possibly involve Pb-binding proteins in the kidney.

5.7.2 Markers of Renal Toxicity

The establishment and validation of new screening tests for nephrotoxic effects have been principally due to the efforts of the Belgian group (Price et al., 1996; Price, 2000; Lauwerys et al., 1992). They proposed the following battery of tests be used to screen both environmentally exposed and occupationally exposed individuals: (1) measures of glomerular integrity, i.e., urinary high-molecular weight proteins (albumin, IgG, transferrin); (2) measures of tubular absorption and secretion, i.e., low-molecular weight proteins (retinol binding protein, α-1-microglobulin; (3) measures of tubular integrity, i.e., enzymes, lysosomal N-acetyl β-D-glucosaminidase (NAG), brush border alanine aminopeptidase, brush border intestinal alkaline phosphatase, nonspecific alkaline phosphatase, α-glutathione-S-transferase (GST), and brush border antigens (BB50, BBA, HF5); (4) measures of glomerular and distal tubular function, i.e., prostanoids (thromboxane B2, prostaglandin F2 alpha, 6-keto prostaglandin F1alpha) ; (5) measures of glomerular structural proteins (fibronectin and laminin fragments); and (6) measures of distal tubular function, i.e., Tamm-Horsfall protein and π-GST. Other useful markers include urinary β_2-microglobulin, as a marker of proximal tubular integrity; PGE_2 and PGF_2, distal nephron markers; kallikrein, a marker of the distal tubule; lysozyme, ribonuclease, and γ-glutamyl transferrase, enzymes reflecting proximal tubule integrity; and sialic acid, an extracellular matrix marker (Fels et al., 1994; Pergande et al., 1994; Taylor et al., 1997). One or several of these urinary markers have been used in screening tests for human Pb workers and in animal studies of renal nephrotoxicity.

Questions have been raised about the usefulness of urinary NAG due to the absence of light or electron microscopic changes in low-dose Pb-treated animals who showed substantial

increases in NAG (vide infra) (Khalil-Maesh et al., 1993). Furthermore, Chia et al. (1994) found that urinary NAG in workers exposed to Pb correlated best with recent blood lead changes, suggesting that the increased urinary NAG activity reflected an acute response to a sharp increase in the renal Pb burden rather than to exocytosis. Questions have also been raised about the value of measuring the vasoconstricting prostariod cytokine thromboxane B2 (TXB_2) and the vasodilating prostanoid 6-keto prostaglandin F1 alpha (PGF1 alpha). Conflicting results have been reported in human Pb-exposed workers. Cardenas et al. (1993) reported an elevation in TXB_2 and a diminution in PGF1 alpha in 41 Pb-exposed workers in contrast to 41 controls. Hotter et al. (1995), on the other hand, reported that both substances were increased in 69 Pb-exposed workers in contrast to 62 controls. Blood Pb levels in the two worker groups were comparable, i.e., 48 µg/dL in the first group and 43 µg/dL in the second. In animal experiments (Gonick et al., 1998), the excretion of both prostanoids was equal in low-Pb (100 ppm)-fed rats as contrasted to normal controls after 3 months, despite an elevation in blood pressure in the Pb-fed rats. Blood Pb in the Pb-fed rats averaged 12.4 µg/dL compared to 1 µg/dL in the controls. Thus, measurements of these prostanoids remain of questionable value.

Attempts to validate nephrotoxic markers were conducted by Pergande et al. (1994), utilizing Pb-exposed workers as contrasted to normal controls. They found that about 30% of the Pb workers showed an increased excretion of α_1-microglobulin, NAG, ribonuclease, and/or Tamm-Horsfall protein, with positive correlations between these tubular indicators and blood Pb concentration.

5.7.3 Biochemical Mechanisms of Lead Toxicity

Nolan and Shaikh (1992) summarized what was known about biochemical mechanisms underlying Pb-induced toxicity at that time. A more detailed description based on recent animal studies follows in the next section.

The initial accumulation of absorbed Pb occurs primarily in the kidneys. This takes place mainly through glomerular filtration and subsequent reabsorption, and, to a small extent, through direct absorption from the blood. Lead may be taken up by the renal tubular epithelial cells from the basolateral side by active transport of the free ion. Smaller amounts can also cotransport with low molecular weight organic anions. The uptake of Pb through the renal brush border does not appear to occur via any specific carriers. Instead, the process may involve binding of Pb to

nonspecific surface sites on the brush border membrane, followed by internalization via endocytosis. Acute kidney damage due to Pb manifests primarily in the proximal tubules. The ultrastructural changes observed in acute experimental Pb nephropathy include both specific and nonspecific effects on the proximal tubular epithelium, e.g., dilation of the endoplasmic epithelium, blebbing of the nuclear membrane, enlargement of the autophagosomes, changes in mitochondrial structure, formation of inclusion bodies. Chronic exposure to Pb affects glomerular filtration, renal clearance, and tubular reabsorption and can lead to renal failure from interstitial nephritis.

Kidneys of chronically exposed individuals often show fewer or no nuclear inclusion bodies compared to kidneys of acutely exposed individuals. The specific ultrastructural changes associated with Pb nephropathy are the formation of cytoplasmic and nuclear Pb inclusion bodies (discussed at greater length below). These inclusion bodies are not limited to the proximal tubular epithelium, and have also been observed in peritoneum, astrocytes, neuroblastoma cells, and osteoclasts upon Pb exposure. The inclusion bodies are roughly spherical and typically consist of an electron-dense core, with a fibrillary network at the periphery. Research has revealed that the formation of the nuclear inclusion bodies is preceded by the synthesis of cytoplasmic inclusion bodies with a very similar structure. A protein unique to these structures is rich in acidic amino acids and has an isoelectric point of 6.3 and a molecular weight of 32 kDa. Two additional proteins with apparent molecular weights of 11.5 kDa and 63 kDa have been identified in kidney extracts. Both of these proteins have a high affinity, but little capacity, for binding lead. A Pb-binding protein of 12 kDa molecular weight was identified in the supernatant of brain homogenate from Pb-treated rats. A Pb binding protein of 10 kDa has also been isolated from the erythrocytes of Pb-exposed workers.

Mitochondrial function, in addition to structure, is very sensitive to lead. Changes include the uncoupling of oxidative phosphorylation, decreased substrate oxidation, and modification of ion transport processes. Other effects of Pb on cellular energetics include chelation of ATP and inhibition of microsomal NaK-ATPase. These changes may account for the proximal tubular dysfunction seen with acute Pb poisoning in children.

A new area of investigation of the mechanism of Pb toxicity was initially proposed by Quinlan et al. (1988) and Hermes-Lima et al. (1991). Both investigators proposed that free radicals, or ROS, stimulated by lead, may accelerate iron-dependent lipid peroxidation, causing

tissue injury. Hermes-Lima et al. (1991) stated further that ALA, which is formed in large amounts in Pb toxicity, may undergo enolization and autoxidation, yielding ROS. Autoxidation of ALA, in the presence or absence of iron complexes, yields superoxide, peroxide, and hydroxyl radicals. Gurer and Ercal (2000), based on several animal studies to be discussed below, have proposed that antioxidant supplementation following Pb exposure may provide a partial remedy by restoring the cell's antioxidant capacity.

5.7.4 Animal Studies

Two excellent review articles have been written about the effects of heavy metals on, and their handling by, the kidney (Barbier et al., 2005) as well as the mechanisms of kidney cell injury from metals (Fowler, 1992). The interested reader is directed to these reviews, although individual effects and mechanisms will be discussed subsequently.

5.7.4.1 Lead Toxicokinetics

deVries et al. (1998) published a model for Pb toxicokinetics to be used in planning treatment. The model is a four-compartment model with first-order kinetics. The four compartments of this model are blood, bone, liver, and kidney. Soft tissues are represented by the kidney and liver compartments. In addition, intake and excretion are included in the model. Excretion of Pb is mainly via the kidneys (70 to 80%), via bile and feces (15%), via nails, hair, and sweat (8%). The blood makes up the central compartment from which Pb is distributed after uptake in the body. The blood compartment contains about 4% of the total body burden of lead, and within this compartment, the Pb is mainly taken up by erythrocytes. The half-life of Pb in blood is about 30 days. From the blood, Pb is distributed relatively quickly to the soft tissues and bone. The distribution constant from blood to bone is much higher than the one from bone to blood, resulting in the accumulation of Pb in bone. The half-life in the soft tissues is about 30 to 40 days. Most of the body burden of Pb can be found in the bone compartment (~94%), where the half-life of Pb is several decades. Because of the vast amount of Pb in bone, a rebound in blood Pb usually occurs after chelation therapy. This model can be compared with a toxicokinetic model developed by Marcus (1985a,b,c) and further explored by Hogan et al. (1998), as discussed in Chapter 4 of this document.

Dieter et al. (1993) examined the effect of the nature of the Pb salt on the oral intake of Pb in male F344 rats. For 30 days, they administered doses of 0, 10, 30, and 100 ppm Pb in the form of soluble Pb-oxide, Pb-acetate, Pb-sulfide, and Pb-ore. At 100 ppm of Pb-acetate or soluble Pb-oxide, the rats developed ~80 µg/dL of blood and ~200 µg/g of bone Pb levels, whereas rats fed Pb-sulfide or Pb ore developed ~10 µg/dL of blood Pb and 10 µg/g of bone lead. In rats fed Pb-acetate or soluble Pb-oxide, blood Pb progressively increased with increasing dose, while in the other two groups measurable levels of Pb were observed only at the highest dose (100 ppm).

5.7.4.2 Pathology, Ultrastructural, and Functional Studies

Two important series of studies contrast the pathological and functional changes in the kidney after prolonged exposure to lead, with and without chelation therapy (i.e., DMSA or $CaNa_2EDTA$). In the first series of 3 long-term studies, Khalil-Manesh et al. (1992a,b, 1993a) described the effects of Pb-acetate on renal function and morphology in male Sprague-Dawley rats fed a low-calcium diet. Lead acetate was used in concentrations of 0.5% (high dose) and 0.01% (low dose) in drinking water for periods from 1 to 12 months, and then Pb-exposed animals were compared to pair-fed controls (12 rats in each group). In all studies GFR was measured as ^{125}I-iothalamate clearance by a single injection technique. Urinary markers included NAG, GST, and brush border antigens (BB50, HF5, and CG9) and were expressed as units/g creatinine. Blood and urine Pb were measured prior to sacrifice in each group of animals. Wet and dry weights of kidneys were determined, then the kidneys were processed for light, electron, and immunofluorescent microscopy.

In the first study (Khalil-Manesh et al., 1992a), animals treated with continuous high-dose Pb for 12 months reached a maximum blood Pb of 125.4 ± 10.1 µg/dL after 6 months, at which time the dose of Pb was reduced from 0.5% to 0.1%. Blood Pb at the end of 12 months averaged 55 µg/dL. Urine Pb remained above 100 µg/g creatinine at all times, but it was highest at 3 months, averaging 340 µg/g creatinine. In the Pb-treated animals, GFR was increased above controls at 3 months (1.00 ± 0.14 vs. 0.83 ± 0.26 mL/min/ 100 g body wt, $p = 0.05$), then declined after 6 months to 0.78 ± 0.16 vs. 0.96 ± 0.08 mL/min/100 g body wt in controls (Figures 5-7.1 and 5-7.2). As indicated by the ratio of kidney dry/wet weight, increased kidney tissue mass was observed during the first 3 months of Pb exposure, but decreased tissue mass

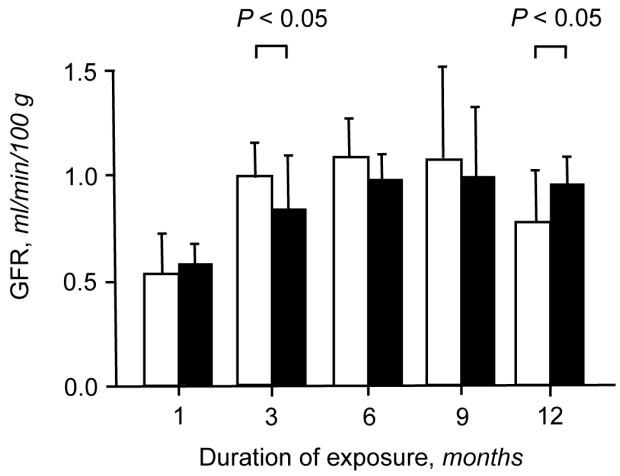


Figure 5-7.1. Changes in GFR of experimental high-dose lead and control animals with duration of exposure to lead. Open and closed bars represent GFR in experimental and control rats, respectively.

Source: Khalil-Manesh et al. (1992a), with permission.

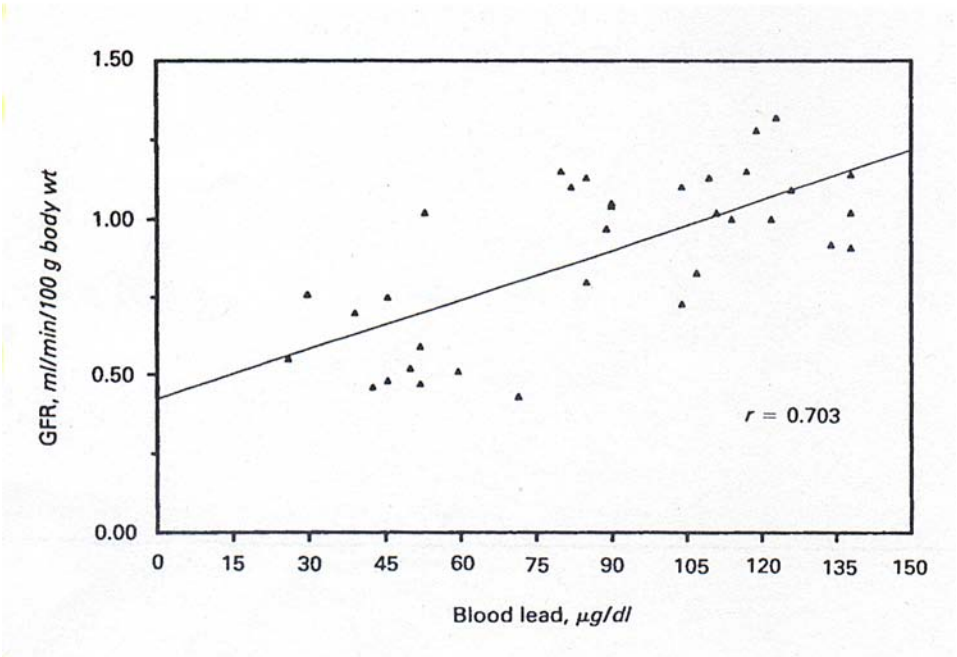


Figure 5-7.2. Correlation between GFR and blood lead during the first 6 months of high-dose lead exposure.

Source: Khalil-Manesh et al. (1992a), with permission.

was observed by 12 months. With regard to urinary markers, NAG was elevated above control levels at 3, 6, and 9 months of Pb exposure; GST was elevated at 3, 6, and 12 months of Pb exposure; and no significant differences were observed in the brush border antigens. Proximal tubular nuclear inclusion bodies were present at all time periods in Pb-treated animals. Enlargement of proximal tubular cells and nuclei were seen beginning at 3 months. At 6 months, focal tubular atrophy and interstitial fibrosis appeared, increasing in extent up to 12 months. Mitochondrial alterations, consisting of rounding and elongation, appeared by 1 month and were persistent. Glomeruli were normal through 9 months, but, at 12 months, they showed focal and segmental sclerosis. There were no electron-dense deposits and immunofluorescent studies were negative. Renal arteries and arterioles were normal at all time point examined.

The second study (Khalil-Manesh et al., 1992b) consisted of the discontinuation of both the high- and low-dose Pb exposure after 6 months, then treatment with three courses of DMSA or discontinuation of high-dose Pb alone after 1, 6, and 9 months of Pb feeding. Controls were pair-fed, exposed to Pb for 6 months, then removed from exposure for 6 months without receiving DMSA. Low-dose Pb-treated rats showed no significant pathologically with or without DMSA treatment but exhibited a significant increase in GFR after DMSA treatment (1.09 ± 0.19 vs. 0.88 ± 0.22 mL/min/100 g body weight; $P < 0.03$) (Figure 5-7.3). Urinary markers remained unchanged, and there were no structural alterations by light or electron microscopy. High-dose Pb-treated animals showed no functional or pathologic changes when Pb exposure was discontinued after 1 month. However, when the duration of exposure was 6 or 9 months, GFR was decreased and serum creatinine and urea nitrogen were increased compared to controls. Tubulointerstitial disease was severe. Administration of DMSA resulted in an improvement in GFR (Figure 5-7.3) and a decrease in albuminuria, together with a reduction in size and number of nuclear inclusion bodies in proximal tubules. However, tubulointerstitial scarring was only minimally reduced. In conclusion, except for a brief initial exposure, discontinuation of high-dose Pb exposure failed to reverse Pb-induced renal damage. Treatment with the chelator, DMSA, improved renal function but had less effect on pathologic alterations. Because GFR improved after DMSA treatment in both low- and high-dose Pb-treated animals, irrespective of the degree of pathologic alterations, it may be concluded that the DMSA effect is most likely mediated by hemodynamic changes.

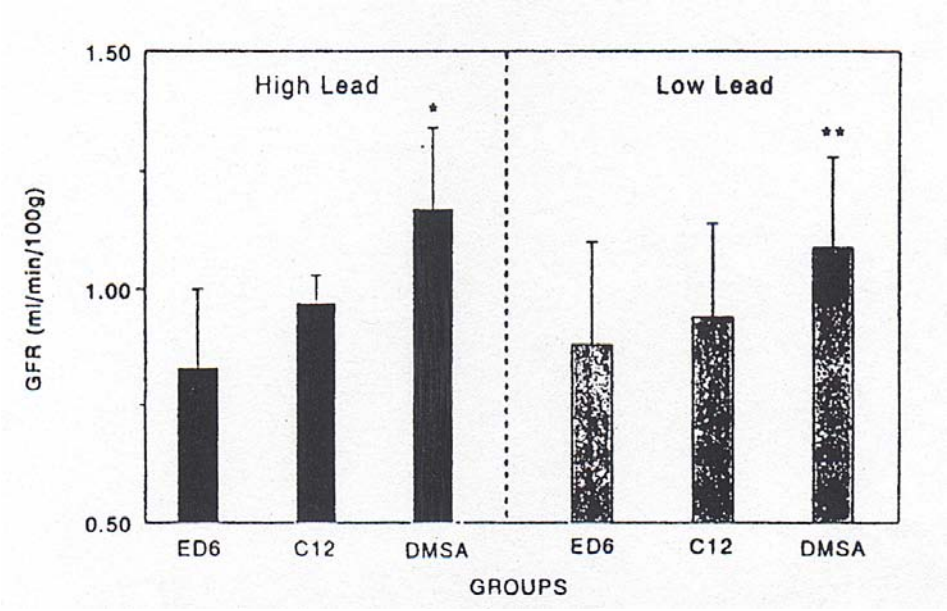


Figure 5-7.3. GFR in high-lead and low-lead experimental discontinuous (ED6) and DMSA-treated rats (DMSA) as compared to controls (C12). All rats were studied at 12 months.

*$p < 0.01$ when compared to ED6 and C12.
**$p < 0.05$ when compared to ED6.

Source: Khalil-Manesh et al. (1992b), with permission.

The third study (Khalil-Manesh et al., 1993a) examined the course of events over 12 months in continuous low level Pb-exposed animals. Maximum blood Pb levels in experimental animals were reached at 3 months, averaging 29.4 ± 4.1 µg/dL. GFR was found to be significantly increased above pair-fed controls at 1 and 3 months, but it was normal at other time periods (1 month experimental, 1.18 ± 0.12 vs. control, 0.76 ± 0.15mL/min/100 g; $p < 0.001$; 3 month experimental, 1.12 ± 0.16 , vs. control, 0.86 ± 0.10 mL/min/100 g; $p < 0.001$) (Figure 5-7.4). Levels of urinary NAG in Pb-exposed rats exceeded control levels at all time periods, except at 12 months, when the normal increase with aging obscured differences between experimental animals and controls (Figure 5-7.5). In contrast, urinary GST, a more specific marker of metal-associated proximal tubular injury, was normal at all time periods. Proximal tubular nuclear inclusion bodies were sparse and were observed only at 1 and 3 months.

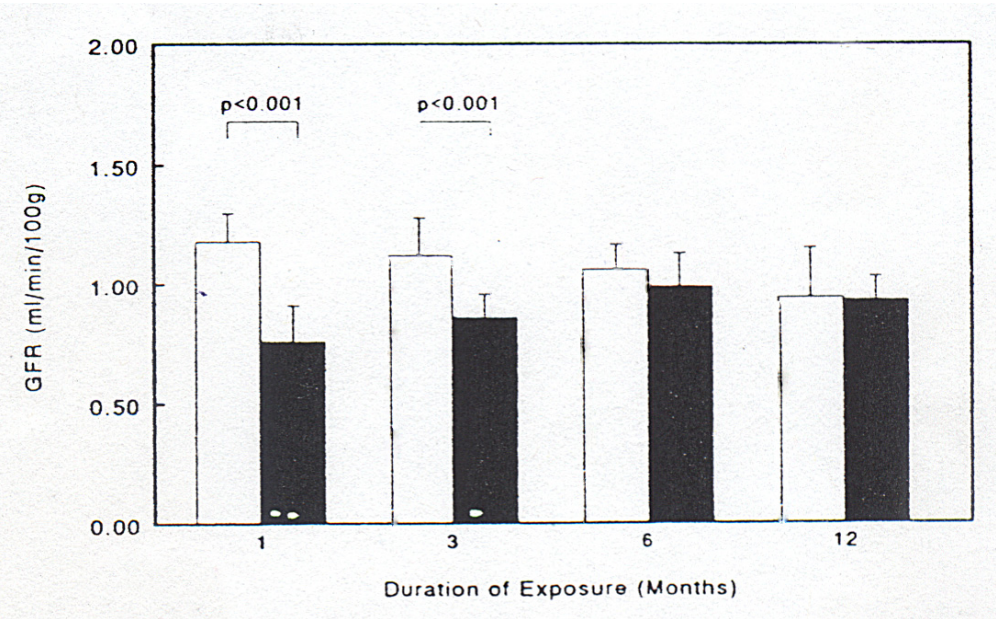


Figure 5-7.4. Changes in GFR in experimental and control rats, at various time periods.

Source: Khalil-Manesh et al. (1993a).

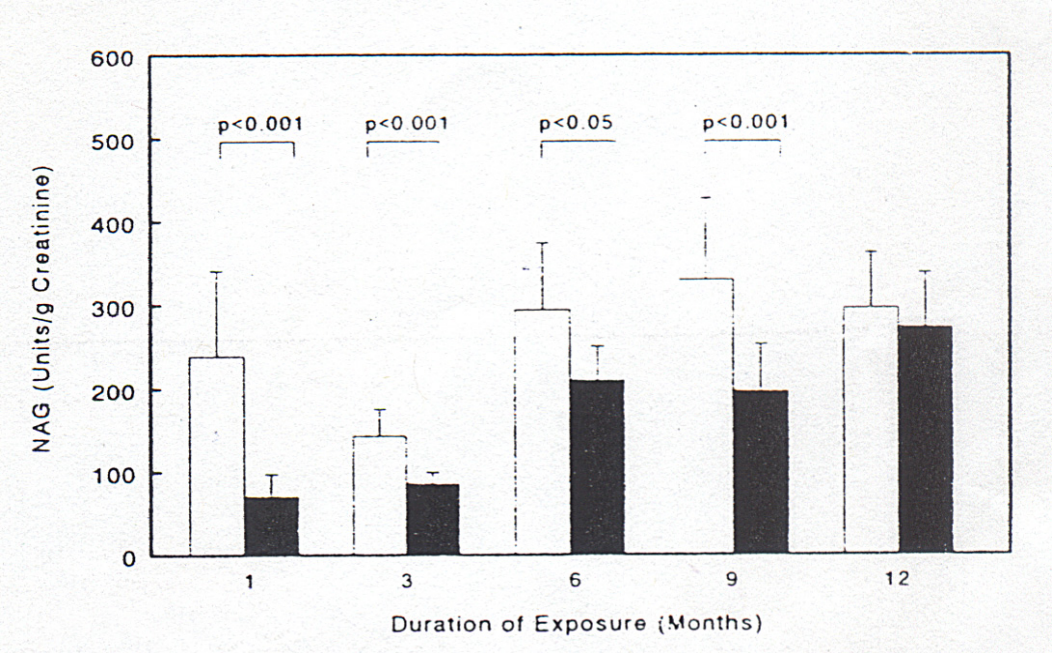


Figure 5-7.5. Urinary NAG concentration in experimental and control rats at various time periods.

Source: Khalil-Manesh et al. (1993a).

No other pathologic alterations were found in the kidneys until 12 months of exposure, when mild tubular atrophy and interstitial fibrosis were seen. The absence of changes in urinary GST accorded with the relative absence of morphologic changes, whereas the observed increases in urinary NAG suggest that this enzyme may be an overly sensitive indicator of tubular injury, more probably reflecting upregulation of the enzyme even in the absence of tubular injury. It should be noted that both low-dose Pb-treated animals and high-dose Pb-treated animals showed a "hyperfiltration" phenomenon during the first 3 months of Pb exposure. This observation could be invoked as a partial explanation for the late changes of glomerulosclerosis in the high-dose animals, but it cannot explain the lack of glomerular changes in the low-dose animals. Thus, these studies join those of Roels et al. (1994) and Hu (1991) in humans that indicate that Pb nephropathy should be added to diabetic nephropathy as diseases that lead to early hyperfiltration.

The second series of studies were performed by Sanchez-Fructuoso et al. (2002a,b). Sanchez-Fructuoso et al. (2002a,b) evaluated the effect of $CaNa_2EDTA$ on tissue mobilization of Pb in Wistar rats initially treated with 500 ppm Pb-acetate for 90 days, followed by treatment with three courses of $CaNa_2EDTA$ 50 mg/kg/day for 5 days, separated by 9 days, or placebo. Lead levels were measured in blood, urine, kidney, liver, brain, and femur. There was no change in bone Pb after $CaNa_2EDTA$ compared to placebo, but Pb levels were significantly reduced in all other tissues (Figure 5-7.6). The authors emphasized that there was no redistribution to brain. Cory-Slechta et al. (1987) had originally reported that with $CaNa_2EDTA$ chelation in rats Pb is preferentially mobilized from bone and then redistributed to other organs, including brain. The Sanchez-Fructuoso et al. (2002a,b) findings stand in contrast, explained by the authors as due to a 3-fold higher level of $CaNa_2EDTA$ used by Cory-Slechta et al. (1987).

Sanchez-Fructuoso et al. (2002b) also evaluated pathologic changes, as well as the response of ALAD activity before and after $CaNa_2EDTA$ treatment in the same rats. In the 90-day Pb-treated animals, the main findings were hypertrophy and vacuolization of medium and small arteries (Figure 5-7.7); mucoid edema and muscular hypertrophy in arterioles; loss of cell brush borders, cell loss, and intranuclear inclusion bodies in the proximal tubule; and fibrosis and the presence of infiltrates in the interstitial component. Treatment with $CaNa_2EDTA$ slowed the progression of most alterations (Figure 5-7.8) and resulted in a diminution in nuclear inclusion

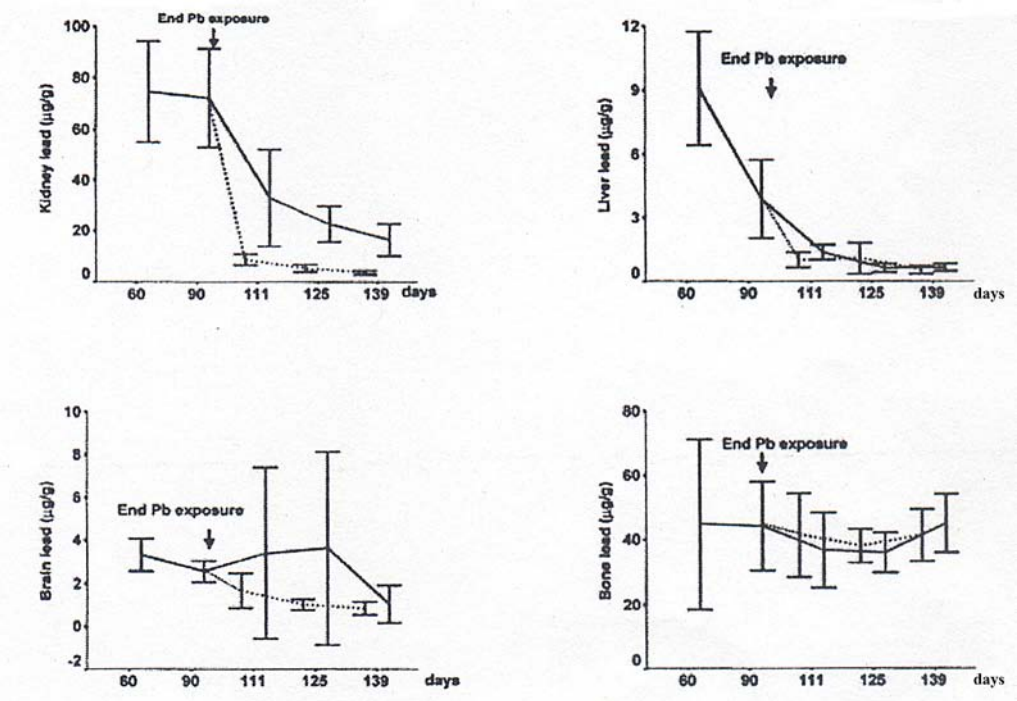


Figure 5-7.6. Kidney, liver, brain, and bone Pb levels in 56 Pb-exposed rats. After 90 days of poisoning, animals were administered serum saline (solid line) or calcium disodium EDTA (broken line).

Source: Sanchez-Fructuoso et al. (2002a), with permission.

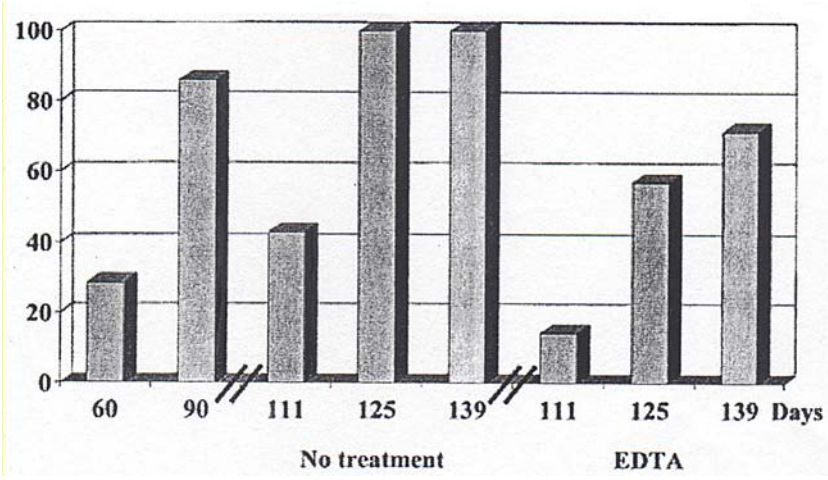


Figure 5-7.7. Percentage of moderate and severe hypertrophy and vacuolization lesions in small and medium sized arteries in the kidney of lead-exposed rats.

Source: Sanchez-Fructuoso et al. (2002b), with permission.

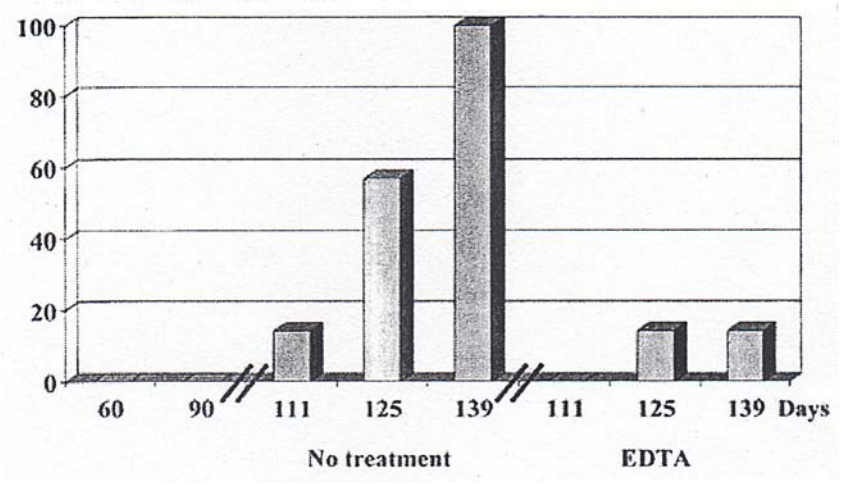


Figure 5-7.8. Percentage of moderate and severe muscular hypertrophy lesions in arterioles of the kidney in lead-exposed rats.

Source: Sanchez-Fructuoso et al. (2002b), with permission.

bodies. ALAD activity was reduced from 3.18 ± 0.52 U/mL in controls, to 0.82 ± 0.16 U/mL in the Pb-exposed rats. In the rats treated with $CaNa_2EDTA$, ALAD returned to near control levels (2.98 ± 0.41 U/mL) at 137 days. It is surprising that such remarkable vascular changes were noted in this study, while none were noted in Khalil-Manesh et al. (1992a), even with high-dose Pb for longer periods of time. The kidney content of Pb (mean 74.6 μg/g) was also lower than the mean kidney content at 12 months (294 μg/g) in the Khalil-Manesh et al. (1992a) study. The only explanation for these striking differences that can be offered is that different strains of rats were employed, i.e., Wistar in the Sanchez-Fructuoso (2002b) study and Sprague-Dawley in the Khalil-Manesh et al. (1992a) study. The presence or absence of hypertension cannot be invoked as an explanation, because in another Khalil-Manesh et al. (1993b) study the low-dose Pb animals became hypertensive while the high-dose animals did not. These and other related studies are summarized in Table AX5-7.1.

5.7.4.3 Biochemical Mechanisms of Lead Toxicity

Role of Free Radicals (Reactive Oxygen Species)

Since the early 1990s, it has been appreciated that free radicals, now known as reactive oxygen species (ROS), are involved in the manifestations of Pb poisoning, presumably via their

adverse effects on tissue integrity and/or their vasoconstrictive effects on vascular endothelium. Wolin (2000) produced an extensive review of individual ROS, and their interactions with NO, the major endogenous vasodilator, which acts via a second messenger, cGMP. The production of ROS often begins with a one-electron reduction of molecular oxygen to superoxide anion (O_2^-) by various oxidases. NAD(P)H oxidases are the principal enzymes involved. Superoxide anion is a negatively charged free radical that can be broken down to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) or can interact with NO to form the highly reactive peroxynitrite ion ($ONOO^-$), which, because of its extremely short half-life, is measured as its reaction product, tissue nitrotyrosine. Catalase and glutathione (GSH) peroxidase (GSHRx) metabolize H_2O_2 to Compound I and oxidized glutathione (GSSG), respectively, while myeloperoxidase metabolizes H_2O_2 to hypochlorous acid (HOCl). The reaction of H_2O_2 with ferrous ion results in the formation of hydroxyl ion ($^{\bullet}OH$). ROS can be scavenged by endogenous thiols (e.g., GSH) or exogenous thiol, e.g., N-acetylcysteine (NAC). ROS can be measured as the concentration of the lipid peroxidation product, malondialdehyde-thiobarbituric acid (MDA-TBA) or by the more recently introduced F-2 isoprostanes.

Kumar and Das (1993) explored the involvement of ROS in the pathobiology of human essential hypertension. They found that plasma levels of lipid peroxides were higher in subjects with uncontrolled essential hypertension compared to normal controls. Angiotensin II, a potent vasoconstrictor, was found to stimulate free radical generation in normal leukocytes, which was thought to inactivate NO, and possibly prostacyclin, which can lead to increased peripheral vascular resistance and hypertension.

Hermes-Lima et al. (1991) also explored the involvement of ROS in Pb poisoning. They described the process of autoxidation of ALA in the presence or absence of iron complexes, which yields free radicals. Free radicals are also produced by Pb-stimulated iron-dependent lipid peroxidation, as determined by quantification of thiobarbituric acid-reactive species (TBARS). Pereira et al. (1992) demonstrated that chronically ALA-treated rats (40 mg/kg body weight every 2 days for 15 days) under swimming training reached fatigue significantly earlier than the control group, as well as demonstrating decreased mitochondrial enzymatic activities. In vivo prooxidant properties of ALA were also suggested by the observed increase of CuZnSOD in brain, muscle, and liver of untrained rats submitted to chronic treatment with ALA.

Ercal et al. (1996) contrasted the effects of treatment with DMSA or NAC in Pb-exposed C57BL/6 mice. Five weeks of Pb exposure was found to deplete GSH levels, increase GSSG, and promote MDA production in both liver and brain samples. Glutathione levels increased and GSSG and MDA levels decreased in groups of Pb-exposed mice that received 1 mmol/kg DMSA or 5.5 mM/kg NAC for 7 days prior to sacrifice. Treatment with DMSA caused reduction in blood, liver, and brain Pb levels consistent with its function as a chelating agent, while treatment with NAC did not reduce these Pb levels. However, NAC treatment reduced indices of oxidative stress in both brain and liver samples. Concentrations of blood Pb in controls were 0.5 ± 0.5 μg/dL; in Pb-treated mice, were 36.5 ± 2.4 μg/dL; in Pb + DMSA-treated mice, were 13.7 ± 1.3 μg/dL; and in Pb + NAC-treated mice, were 36.0 ± 3.5 μg/dL. Thus both DMSA and NAC acted as antioxidants, presumably via their thiol groups, but only DMSA reduced the concentration of lead.

Vaziri and co-workers (Gonick et al., 1997; Ding et al., 1998, 2000, 2001; Vaziri et al., 1997, 1999a,b, 2000, 2001a,b, 2003; Zhou et al., 2002; Ni et al., 2004) have published a number of articles relating to the production of ROS and alterations in enzymatic activities in Pb-induced hypertension. These were discussed in detail in Section 5.5 but are described briefly here. In the majority of studies, Pb-induced hypertension was produced by the administration of Pb-acetate, 100 ppm in drinking water, for 3 months to male Sprague-Dawley rats. Early studies (Gonick et al., 1997) revealed that hypertension could occur in the absence of changes in NO or cGMP but with an attendant rise in plasma and kidney MDA-TBA, indicating an increase in ROS. In a second study, Ding et al. (1998) showed that infusion of arginine, the precursor of NO, or DMSA, a thiol Pb chelator and antioxidant, reduced blood pressure to or towards normal, while simultaneously increasing depressed urinary NO and decreasing an elevated MDA-TBA. Ding et al. (2000, 2001) further showed that the ROS species, $^{\bullet}OH$, measured as salicylate-trapped 2,3 dihydroxybutyric acid, was increased in plasma and cultured rat aortic endothelial cells after exposure to lead, and that dimethylthiourea, a reputed scavenger of $^{\bullet}OH$, returned blood pressure, MDA-TBA, $^{\bullet}OH$, and nitrotyrosine to or towards normal. Ni et al., in 2004, demonstrated in both human coronary endothelial (EC) and vascular smooth muscle cells (VSMC) that Pb-acetate also increased superoxide (demonstrated by flow cytometry using hydroethidine) and H_2O_2 (demonstrated with dihydrorhodamine) production. After long-term (60-h) exposure, detectable superoxide levels fell to near normal while H_2O_2 production remained high.

Vaziri et al. (1997) showed that lazaroids, a class of non-thiol antioxidant, also restored blood pressure, NO, and MDA-TBA to normal. Vaziri et al. (1999a) studied rats treated for 12 weeks with either Pb-acetate alone or Pb-acetate + vitamin E-fortified food (5000 units/kg rat chow). They measured urinary excretions of stable NO metabolites (NO_x) and plasma and tissue abundance of nitrotyrosine, the footprint of NO oxidation by ROS. The Pb-treated group showed a marked rise in blood pressure; a significant increase in plasma and kidney, heart, liver, and brain nitrotyrosine abundance; and a substantial fall in urinary NO_x excretion. Concomitant administration of high-dose vitamin E ameliorated hypertension and normalized both urinary NO_x excretion and tissue nitrotyrosine without altering tissue Pb content. Vaziri et al. (1999b) also measured eNOS and iNOS in the aorta and kidney of Pb-treated and Pb + vitamin E-treated rats. Lead treatment increased both isotypes in aorta and kidney, signifying increased NO production, while Pb + vitamin E lowered aortic, but not kidney, expression of eNOS and iNOS. Vaziri and Ding (2001) tested the effect of lead, 1 ppm, on cultured human EC cells. Lead was tested alone or with either the SOD-mimetic agent, tempol, or a potent antioxidant lazaroid compound (both at 10^{-8} or 10^{-7}mol/L) on eNOS expression and NO production. Lead-treated cells showed a significant upregulation of endothelial eNOS, increase in protein abundance, and increase in the production of NO metabolites. Treatment with either tempol or lazaroids abrogated the Pb-induced upregulation of eNOS protein and NO_x production. Vaziri et al. (2001) also studied increases in NOS isoforms in vivo in Pb-induced hypertension and reversal by tempol. Both eNOS and iNOS were increased in kidney, aorta, and heart, while NOS was increased in cerebral cortex and brain stem, of Pb-treated rats; blood pressure and NOS isoforms were returned to normal by tempol. Vaziri et al. (2003) determined whether the oxidative stress in animals with Pb-induced hypertension is associated with dysregulation of the main antioxidant enzymes (i.e., SOD, catalase, and GSHPx), or increases in the superoxide-producing enzyme NAD(P)H oxidase. At the conclusion of the experiment, immunodetectable CuZnSOD, MnSOD, catalase, GSHPx, and the gp^{91}phox subunit of NAD(P)H oxidase were measured by Western analysis in the kidney, brain, and left ventricle of control and Pb-exposed rats. Lead exposure resulted in a significant increase in kidney and brain CuZnSOD with a significant increase in brain, and insignificant increase in kidney and heart, gp^{91}phox. In contrast, MnSOD, catalase, and GSHPx in the kidney, brain, and left ventricle were unchanged. Incubation with Pb-acetate did not alter SOD activity in vitro. Thus, animals with Pb-induced hypertension

exhibited oxidative stress, which was associated with mild upregulation of the superoxide-generating enzyme NAD(P)H oxidase, with no evidence of quantitative SOD, catalase, or GSHPx deficiencies.

Vaziri et al. (2000) demonstrated that induction of oxidative stress in normal animals (by feeding the GSH synthase inhibitor, buthionine sulfoximine, 30 mmol/L in drinking water for 2 weeks) led to an increase in blood pressure, a reduction of urinary NO_x, a 3-fold decrease in liver GSH, and an increase in nitrotyrosine in kidney, aorta, heart, liver and plasma. Administration of vitamin E + ascorbic acid ameliorated hypertension and mitigated nitrotyrosine accumulation despite persistent GSH depletion. This experiment demonstrated the importance of GSH in protecting against the adverse effects of ROS accumulation in normal animals. Majority of the studies reported by Vaziri and co-workers indicated that low Pb exposure induced hypertension to be primarily mediated by ROS-induced depletion of NO. NO production, on the other hand, is stimulated, as shown by the increase in eNOS and iNOS. Enzymatic control of ROS levels by low Pb is achieved by upregulation of NAD(P)H oxidase with no decrease in SOD, catalase, or GSHPx, i.e., the enzymes that breakdown ROS. Scavengers of ROS ameliorate the elevated blood pressure, while the depletion of the endogenous methyl scavenger, GSH, increases blood pressure in normal animals. No studies have been done to date to address the question of why high-dose Pb administration does not lead to hypertension.

Farmand et al. (2005) pursued enzymatic studies by activity measurements and measures of protein abundance in the rat kidney and aorta following the protocol of Gonick et al. (1997) whereby rats are fed Pb-acetate 100 ppm for 12 weeks. They demonstrated that the activities of CuZnSOD and catalase were increased by Pb administration in renal cortex and medulla, whereas GSHPx was unchanged. In the thoracic aorta, Pb exposure resulted in significant upregulation of CuZnSOD activity, while catalase and GSHPx activities were unchanged, CuZnSOD, MnSOD, and catalase protein abundance were likewise unchanged. However, guanylate cyclase protein abundance in the thoracic aorta was decreased. The authors suggested that the Pb-induced compensatory upregulation of CuZnSOD and catalase and the decrease in aortic guanylate cyclase may be related to Pb-induced hypertension.

Gurer et al. (1999a) evaluated whether captopril, an ACE inhibitor, acted as an antioxidant in Pb-exposed F344 rats. Lead acetate was given in drinking water for 6 weeks.

Group I were the controls; group II received 1100 ppm Pb for 5 weeks and plain water during the week 6; group III received 1100 ppm Pb for 5 weeks and, during the week 6, received water containing captopril (10 mg/day). Blood Pb concentrations in the control group measured 0.8 µg/dL; in the Pb treated group, 24.6 ± 20 µg/dL; in the Pb + captopril group, 23.8 ± 1.6 µg/dL. MDA concentrations in liver, brain, and kidney were increased by Pb administration and reduced to or towards normal by the Pb + captopril treatment. GSH concentrations were decreased by Pb administration and restored by Pb + captopril treatment, whereas GSSG concentrations were increased by Pb administration and reduced by Pb + captopril treatment. Thus, this study showed that captopril was capable of augmenting the reducing capacity of the cells by increasing GSH/GSSG ratios without affecting blood Pb concentrations.

McGowan and Donaldson (1987) examined total nonprotein sulfhydryl and GSH concentrations in liver and kidney as well as GSH-related free amino acid concentrations in liver, kidney, and plasma in 3-week-old Pb-treated (2000 ppm dietary lead) chicks. Cysteine, converted from methionine, is the rate-limiting amino acid in GSH formation. The availability of glutamate, cysteine, and glycine becomes important in the restoration of depleted GSH. GSH, nonprotein sulfhydryl groups, glycine, and methionine were increased versus controls in the liver, but only nonprotein sulfhydryl, glycine, cysteine, and cystathionine increased in the kidney. Plasma levels of cysteine, taurine, and cystathione were reduced. Thus, Pb, for short periods of time, increases GSH turnover. These and other studies are summarized in Table AX5-7.2.

Effect of Lead on Selective Renal Enzyme Levels

Effects of Lead on Renal NAG

Dehpour et al. (1999) studied NAG release by the rat kidney perfused with Pb-acetate at 10, 20, and 50 µg/dL for 120 min, or Pb + arginine (the substrate for NO), or Pb + L-NAME (an inhibitor of NOS). Lead acetate caused a time and concentration-dependent increase in enzymuria. Addition of arginine decreased, while addition of L-NAME increased, Pb-induced NAG release. Histologic studies showed damage to some of the proximal tubule epithelial cells in rats treated with 50 µg/dL Pb-acetate, damage that which was increased further by the addition of L-NAME.

Effect of Lead on Renal GST

Two studies (Moser et al., 1995; Oberley et al., 1995) reported the effects of Pb administration on GST isoforms in developing rat kidney. In the first study (Moser et al., 1995), rats were treated either acutely (14- and 50-day old rats given three daily injections of Pb-acetate, 114mg/kg) or chronically (Pb levels of 0, 50, 250, and 500 ppm in drinking water for 1, 2, 3, 4, and 7 weeks postnatal). Chronic treatment rats were also given a 0.66% low calcium diet or standard rat chow. Essentially all kidney cytosolic GSTs (Yb1, Yb2, Yp, Yc1, Yl, Yb3, Ya1, Ya2, Yk) increased in the acute experiment (1.1- to 6.0-fold). In the chronic experiment, all but one isoform (Yb3) increased, and these results were markedly exacerbated by placing the rats on a low-calcium diet (Yb1 and Yp increased >25-fold). In the second study (Oberley et al., 1995), pregnant rats were given 250 ppm Pb from conception until weaning, then pups received 500 ppm from weaning until termination at either 3 or 7 weeks of age. By 7 weeks, proximal tubular cells showed intranuclear inclusions, tubular injury, and interstitial fibrosis. Creatinine clearances were reduced (0.55 + 0.05 versus 1.05 + 0.07 mL/min/100g; $P < 0.001$). Treatment with Pb also caused large increases in the immunoreactive protein of Yc, Yk, Yb1, and Yp GST subunits in proximal tubules but did not increase in the antioxidant enzymes CuZnSOD, catalase, and GSHPx.

Another experiment that examined the effect of an acute dose of Pb as Pb-nitrate (100 µmol/kg IV) on GST levels in rat liver and kidney was reported by Planas-Bohne and Elizade (1992). Seventy hours after injection, there was a marked increase in GST activity in both organs, accompanied by induction of the isoenzyme GST 7-7 in the liver.

The relationship between GST induction by acute exposure to Pb-acetate and oxidative stress was explored by Daggett et al. (1998). Rats in the 72-h and 7-day experimental groups received three consecutive daily injections of 114 mg/kg body weight of Pb-acetate. The level of kidney GST was increased at 3, 6, 12, and 24 h after injection, but MDA levels remained unchanged. Immunohistochemical markers of oxidative stress and NO production (MnSOD, eNOS, iNOS, and 4-hydroxy-2-nonenal) also did not change. The authors concluded that the GST changes were not the result of oxidative stress.

Witzman et al. (1998) and Kanitz et al. (1999) utilized two-dimensional (2-D) gel electrophoresis to explore protein markers of Pb exposure. Witzman et al. (1998) gave three consecutive IP injections of Pb-acetate (114 mg/kg) to Sprague-Dawley rats, sacrificed them on

the fourth day, and subjected the cytosolic fraction of kidney homogenate to 2-D gel electrophoresis. Lead exposure caused detectable inductions in both GSTP1 and GSTM1 and caused quantifiable charge modifications in GSTP1. Kanitz et al. (1999) examined kidney protein expression in male rabbits injected with Pb-acetate (260, 360, or 100 μg/kg) designed to produce blood levels of 20, 40, or 80 μg/dL. Injections were given during weeks 6 to 10, followed by maintenance doses during study weeks 11 to 20. Kidney homogenates were subjected to 2-D electrophoresis. Significant quantitative changes occurred in 12 proteins in a dose-related manner. Four proteins cross-reacted with anti-rat GSTp1 (π-GST). Thus, both studies confirmed GST induction by lead.

Daggett et al. (1997) examined the effects of triethyl Pb administration on the expression on GST isoenzymes and quinone reductase in rat kidney and liver. Fischer 344 rats were given one IP injection of triethyl Pb chloride (10 mg/kg body weight) and subsequent changes in enzyme expression were measured. There was a significant increase in GST activity in kidney; all GST subunits were significantly elevated, the largest increase being a 3.2-fold increase in GST Yb1. In the liver, injection of triethyl Pb-chloride resulted in decreased GST activity. The largest decrease in subunits was a 40% reduction in GST Ya1. The activity of quinone reductase was elevated 1.5-fold in kidney and 2.7-fold in liver within 14 days after the injection of triethyl Pb chloride.

Effects of Lead on Renal Heme Enzymes

Vij et al. (1998) explored Pb-induced alterations in male rats in the heme synthesizing enzymes, ALAD, and uroporphyrinogen I synthetase, and the effect of ascorbic acid supplementation in reversing these alterations. Lead-treated rats were injected IP with 20 mg/kg of Pb-acetate for 3 consecutive days and sacrificed 4 days later. A separate group of animals were administered 100 mg/kg ascorbic acid PO for 3 days following Pb administration. Blood Pb concentration was 4.67 ± 1.49 μg/dL in control rats, 16.59 ± 4.65 μg/dL in Pb-treated rats, and 7.83 ± 2.03 μg/dL in the Pb + ascorbic acid treated rats. Lead content of liver and kidney followed the same pattern. Blood ALAD activity was diminished in the Pb-treated rats but was restored in the Pb + ascorbic acid-treated rats. Uroporphyrinogen I synthetase activity followed the same pattern in blood but was not restored by ascorbic acid in liver. Total and nonprotein

sulfhydryl concentrations in blood were depressed by Pb administration and were not restored by ascorbic acid. However, levels in liver and kidney were restored by ascorbic acid.

ALAD levels following administration of Pb were also investigated by Rodrigues et al. (1996) and Peixoto et al. (2004). The study by Rodrigues et al. (1996) examined rats from Pb-exposed mothers that were maintained after weaning on either 0.5 or 4.0 mM Pb-acetate in drinking water for 21 days or 6 months. At sacrifice, ALAD activity was measured in kidney, forebrain, and cerebellum. Both 6-month-old Pb-exposed groups showed an increase in the kidney-to-body weight ratio, suggesting Pb-induced cell proliferation in the kidney. Blood Pb increased from 6.53 to 7.61 µg/dL in the 21-day-old exposed rats compared to 6-month-old controls. In the 0.5 mM Pb-treated group, blood Pb was 9.77 µg/dL in the 21-day-old and 41.63 µg/dL in 6-month-old rats, while in the 4.0 mM group, blood Pb was 44.35 µg/dL in the 21-day-old and 116.91 µg/dL in the 6-month-old group. ALAD activity was reduced at 6 months in the forebrain of the 4.0 mM Pb-treated group, and in the kidneys at 6 months in both the 0.5 mM and 4.0 mM Pb-treated groups. The study by Peixoto et al. (2004) examined the in vitro sensitivity (IC_{50}) to Pb of ALAD activity of brain, kidneys, and liver from suckling rats aged between 1 and 5, 8 and 13, or 17 and 21 days. The metal concentrations ranged from 0 to 50 µM for Pb-acetate. Rats in the first age group showed the greatest sensitivity in all three organs. Liver was the least sensitive to ALAD inhibition by lead, while brain was the most sensitive.

Effects of Lead on NaK-ATPase

Fox et al. (1991) explored the effect of in vivo Pb exposure on adult rat retinal and kidney NaK-ATPase. Pups, exposed to Pb through the milk of dams consuming 0, 0.02, or 0.2% Pb solutions, had mean blood Pb concentrations of 1.2, 18.8, and 59.4 µg/dL at weaning, respectively, and 5 to 7 µg/dL as 90 to 100-day-old adults. Prior Pb exposure produced significant dose-dependent decreases in isolated retinal NaK-ATPase activity (−11%; −26%), whereas activity in the kidney was unchanged. In contrast, NaK-ATPase from both isolated control tissues was inhibited by Pb in vitro. The half-maximal inhibitory dose of Pb for retinal and renal NaK-ATPase was 5.21×10^{-7} and 1.25×10^{-5} M, respectively. Retinal and renal NaK-ATPase were 20-fold and 1.1-fold more sensitive to inhibition by Pb than calcium. The

increased sensitivity of retinal, compared to renal, NaK-ATPase to inhibition following in vivo or in vitro Pb exposure may be related to their different α subunit composition.

Kramer et al. (1986) had also explored the half-maximal inhibitory dose for Pb-chloride on renal cortical homogenate NaK-ATPase, and found it to be 7×10^{-5} M. There was a competitive inhibition with regard to the substrate, ATP. Of several metals tested, Pb was second only to Hg in potency as a NaK-ATPase inhibitor.

Weiler et al. (1990) studied the effect of Pb on the kinetics of purified (from hog cerebral cortex) NaK-ATPase and potassium-stimulated p-nitrophenylphosphatase (K-pNPPase), which is referred to as the E2 configuration of the NaK-ATPase system. IC_{50} for Pb was found to be 8.0×10^{-5} M for NaK-ATPase and 5.0×10^{-6} M for K-pNPPase. Inhibition of NaK-ATPase by Pb was found to be noncompetitive with respect to K, but competitive with respect to Na and MgATP. Inhibition of K-pNPPase by Pb was competitive with respect to K.

Effects of Lead on Cardiovascular Hormones

Effects of Lead on Endothelin

Khalil-Manesh et al. (1993a) examined the role of endothelial factors in Pb-induced hypertension. They found that low Pb administration (0.01%), but not high Pb administration, (0.5%) resulted in increased blood pressure in rats treated for 12 months. In the low-Pb-treated rats, measurement of plasma endothelins-1 and -3 revealed that endothelin-3 concentration increased significantly after both 3 months (lead, 92.1 ± 9.7 vs. control, 46.7 ± 12.0 pmol/ml; $p < 0.001$) and 12 months (lead, 105.0 ± 9.3 vs. control, 94.1 ± 5.0 pmol/ml; $p < 0.01$), while endothelin-1 was unaffected. Plasma and urinary cyclic GMP concentrations, as a reflection of endothelium-derived relaxing factor (EDRF), decreased significantly at 3 months (plasma lead, 1.8 ± 0.9 vs. control, 4.2 ± 1.6 pmol/ml; $p < 0.001$) and 12 months (plasma Pb 2.2 ± 0.7 vs.control, 4.2 ± 0.9 pmol/ml; $p < 0.001$). High levels of Pb exposure did not result in hypertension, perhaps related to the fact that plasma concentrations of endothelin-1, endothelin-3, and cyclic GMP were unaltered at 3 months, while their concentrations were significantly decreased at 12 months (plasma cyclic GMP at 12 months, 2.2 ± 0.7, lead, vs. 4.2 ± 0.9 pmol/ml, control; $p < 0.001$). Thus, the path to development of hypertension in low-Pb rats was thought to be through an increase in the concentration of the vasoconstrictor, endothelin-3, and a decrease in the vasodilator hormone, endothelium-derived relaxing factor or NO.

Novak and Banks (1995) studied the effects of Pb on the actions of endothelin. They measured renal clearances and mean arterial pressure in rats in which endothelin-1 was infused at 110 ng/kg/min for 30 min. Lead was infused as Pb-acetate throughout the experiment at 0.48, 4.8, and 24 nmoles/min. At the two higher doses, Pb significantly attenuated the endothelin-induced increase in mean arterial pressure; Pb infused as 0.48 nmoles/min had no effect. An endothelin-induced decrease in GFR in control rats was completely blocked at the higher doses of lead. In additional experiments, calcium chloride was infused at 500 nmoles/min for 105 min, and then calcium + Pb (4.8 nmoles/min) were infused for another 105 min. In these experiments, there was no Pb-induced inhibition of the mean arterial pressure response to endothelin. However, the GFR response to the peptide remained blocked. These data illustrate that Pb inhibits the cardiorenal actions of endothelin and that a calcium-related process is involved in the systemic, but not the renal, component of this inhibition.

Effects of Lead on the Catecholamine System

Carmignani et al. (2000) studied the effects of low Pb exposure (60 ppm of Pb-acetate), given for 10 months, on catecholamine and monoaminoxidase (MAO) levels. Plasma catecholamines were measured by HPLC and MAO in aorta, liver, heart, kidney, and brain by a histochemical technique. Plasma norepinephrine (NE) was increased by 104% and adrenaline by 81% with no changes noted in L-DOPA and dopamine levels. MAO activity was increased in all organs. These workers ascribed the low Pb-induced hypertension in part to raised catecholamines levels.

Tsao et al. (2000) and Chang et al. (2005) measured changes in the β-adrenergic system in Wistar rats during and following Pb exposure. In Tsao et al. (2000), rats were chronically fed with 0.01, 0.05, 0.1, 0.5, 1.0, and 2.0% Pb-acetate for 2 months. Plasma catecholamine levels were measured by HPLC; cAMP levels in heart, kidney, and aorta by radioimmunoassay; and β-adrenergic receptors in heart, kidney, and aorta membranes by a radio ligand binding assay. Blood Pb increased from 0.05 ± 0.05 μg/dL in controls to 85.8 ± 4.1 μg/dL in the 2.0% Pb-treated group. Plasma NE, but not E, levels increased with increasing Pb dosage. β-Adrenoreceptor density of heart and kidney decreased progressively with increasing Pb dosage, whereas kidney β-adrenoreceptor density increased up to the 0.5% Pb group and then remained constant. Unstimulated cAMP was constant in all tissues, but cAMP stimulated by

isoprotorenol was lowered progressively in aorta and heart and increased in kidney. Chang et al. (2005) continued these measurements in rats fed 2% Pb-acetate for 2 months then withdrawn from Pb for periods of 1, 2, 3, 4, 5, 6, and 7 months. Blood Pb levels, systolic and diastolic blood pressure levels, and plasma NE were reduced after cessation of Pb exposure. This occurred in conjunction with an increase in β-adrenoreceptor density in heart and aorta and a decrease in β-adrenoreceptor density in kidney. (See Table AX5-5.5 for experimental details on these studies).

Effects of Chelators (Single or Combined) on Lead Mobilization

Effects of DMSA Alone

Cory-Slechta (1988) studied the mobilization of Pb by DMSA, following a 3- to 4-month exposure to 50 ppm of Pb-acetate in rats. These rats received an IP injection of saline or 25 or 50 mg/kg of DMSA once daily for either 1, 2, 3, 4, or 5 days. Tissue analyses indicated that DMSA mobilized Pb from blood, brain, kidney, and liver with no loss noted from femur.

Pappas et al. (1995) reported on Sprague-Dawley rats exposed to 550 or 1100 ppm Pb-acetate for 35 days and treated either with Pb + DMSA or DMSA alone at varying dosage for 21 days. Animals showed a dose-related reduction in Pb content of blood, brain, femur, kidney, and liver whether they received DMSA alone or Pb + DMSA.

Smith and Flegal (1992) studied the influence of DMSA on the mobilization and redistribution of Pb in skeletal and soft tissue compartments of low-Pb-exposed female rats, using stable Pb isotope tracer techniques. Rats reared on a low-Pb diet received ^{206}Pb-enriched drinking water for 1.5 days and then were chelated with a single IP injection of 0.11 mmol/kg dose of DMSA. Blood, kidney, brain, tibia, urine, and feces were collected 24 h after chelation and analyzed for Pb concentrations and for Pb isotope compositions. DMSA chelation significantly increased the diuresis of labile soft tissue Pb but not skeletal Pb. DMSA also appeared to cause the redistribution and input of a comparable amount of Pb to the skeleton and smaller relative amounts of Pb to the soft tissues of the chelated animals.

Varnai et al. (2001) determined whether ongoing Pb exposure influenced the mobilization of Pb in suckling rats. Six-day-old Wistar rats were given Pb-acetate in a dose of 2 mg/kg/day for 8 consecutive days. A treated group received a daily dose of 0.5 mmol/kg of DMSA PO six times on days 1 to 3 and 6 to 8. DMSA efficiently reduced Pb concentration in carcass, liver,

kidneys, and brain by approximately 50% versus with untreated controls. The results indicate that DMSA is an efficient oral chelator, even when challenged with ongoing Pb exposure.

Effects of Combined Chelators

Flora et al. (1994) compared the combined use of $CaNa_2EDTA$ with DMSA on the distribution of Pb and Pb-related biochemical effects with the influence of each chelator used alone. Wistar rats were given 1000 ppm Pb as Pb-acetate in drinking water for 4 months. They were then treated for 5 days with either saline, DMSA, 25 mg/kg PO twice daily; $CaNa_2EDTA$, 75 mg/kg once daily; or DMSA, 25 mg/kg twice daily, all followed by a single daily IP injection of 75 mg/kg of $CaNa_2EDTA$. Blood ALAD was reduced from 6.54 ± 0.18 nmol/min/ml in controls to 0.84 ± 0.10 in Pb-treated animals, with restoration to 3.03 ± 0.29 after combined treatment. Lead content in blood, liver, kidney, brain, and femur followed the same pattern: controls had 2.11 ± 0.23 μg/dL; Pb-treated, 46.0 ± 4.1 μg/dL; combined chelator-treated, 12.8 ± 0.3 μg/dL. Treatment with either DMSA or $CaNa_2EDTA$ alone produced intermediate results. Tandon et al. (1994) reported similar results.

Jones et al. (1994) compared the effects of DMSA, $CaNa_2EDTA$, $ZnNa_2EDTA$, and $ZnNa_3DTPA$ on Pb mobilization in mice. Mice were given 10 IP injections of Pb-acetate, 5.0 mg/kg per injection. Three days after the final Pb injection, mice received one of the chelators. Injections were given at a dose of 1 mmol/kg/day IP for either 4 days or 8 days. At 8 days, DMSA was the most effective chelator in removing Pb from kidney and bone. $CaNa_2EDTA$ was more effective in removing brain lead. When animals were loaded with 100 mg of Pb per kg body weight, DMSA remained more effective in removing Pb from kidney and bone while $CaNa_2EDTA$ was more effective in brain.

Kostial et al. (1999) evaluated the efficacy of three chelating agents, administered either as monotherapy or as combined treatments, in suckling rats. Lead acetate (5 mg Pb/kg IP) was administered to 7-day-old rat pups on experimental day 1, and chelating agents was administered on experimental days 2 and 3. The pups were divided into untreated control, EDTA-treated, meso-DMSA-treated, racemic DMSA-treated, EDTA plus meso-DMSA-treated, and EDTA + plus racemic DMSA-treated. Rats were killed on experimental day 5 and tissue analyses were done for lead, zinc, and copper. Treatment with EDTA did not affect tissue lead, but it reduced zinc in the carcass and liver. Meso-DMSA reduced Pb in the kidneys and brain and did not

affect organ essential elements. Racemic DMSA most efficiently reduced Pb concentrations in the carcass, kidneys, and brain, but it also reduced zinc and copper in the liver and zinc in the kidneys. Combined treatments with EDTA did not improve the efficiency of either DMSA isoform in decreasing tissue lead, but they did reduce tissue zinc concentrations. The results suggest that meso-DMSA may be the treatment of choice in acute Pb poisoning in infants, reducing Pb without affecting trace elements.

Malvezzi et al. (2001) evaluated the effects of DMSA, L-arginine (a precursor of NO), and the association of L-arginine and DMSA on tissue Pb mobilization and blood pressure levels in Pb-intoxicated rats. Tissue Pb levels and blood pressure evolution were evaluated in rats exposed to Pb (750 ppm in drinking water for 70 days), Pb + water for 30 more days , Pb + DMSA (50 mg/kg day, PO), L-arginine (0.6% in drinking water), the combination of L-arginine + DMSA for 30 more days, and their respective matching controls. Lead exposure increased Pb levels in the blood, liver, femur, kidney, and aorta. Lead levels in tissue decreased after cessation of Pb administration, except in the aorta. Blood Pb decreased from 67.8 µg/dL to 11.2 µg/dL in those subsequently treated with water, to 13.8 µg/dL in animals treated with Pb + DMSA, to 11.6 µg/dL in animals treated with Pb + L-arginine, and to 6.1 µg/dL in animals treated with Pb + L-arginine + DMSA. Lead mobilization from the aorta was only effective with the L-arginine/DMSA treatment. Lead administration increased blood pressure starting from the week 5, while L-arginine and DMSA treatments and the combination of L-arginine + DMSA decreased blood pressure levels of intoxicated rats; but these levels did not reach those of nonintoxicated rats. Treatment with L-arginine + DMSA was more effective than individual treatments in mobilizing Pb from tissues and in reducing the blood pressure of intoxicated rats. This paper lacks measurements of NO, which would have allowed the reader to more properly judge the mechanism of the effects of L-arginine administration. Furthermore, the dose of Pb was higher than in earlier studies that showed that DMSA was effective in lowering blood pressure. These and other studies are summarized in Tables AX5-7.3 and AX5-7.4.

Effects of Other Metals on Lead Distribution

Lead and Calcium

Fullmer (1992) published a review of intestinal interactions of Pb and calcium. High affinity Pb binding to intracellular calcium receptors and transport proteins, as well as the

involvement of Pb in calcium-activated and calcium-regulating processes, are thought to provide a partial molecular basis for the cellular and systemic effects of lead.

Maldonado-Vega et al. (1996) examined the intestinal absorption of Pb and bone mobilization during lactation. All experiments were started with 3-week-old female Wistar rats. Rats were impregnated at 16 weeks and were fed a 100 ppm solution of Pb-acetate for 158 or 144 days (mid-lactation or before lactation). Rats were also exposed for only 14 days, from 144 to 158 days (i.e., only during lactation). Nonpregnant rats from the same litter were exposed to Pb for periods equivalent to each of these groups. In the nonpregnant rats, blood Pb increased to 27.3 μg/dL from 5.2 μg/dL in controls. Similarly, kidney Pb increased to 13.2 nmol/g from 0.5 nmol/g, and bone Pb increased to 88.9 nmol/g from 0.9 nmol/g. ALAD activity decreased to 410 nmol/h/ml from 1004 nmol/h/ml. Compared to nonpregnant rats, there was a moderate increase in blood Pb in the lactating animals whether the Pb was given to mid-lactation or up to the period before lactation. Similarly, when Pb was administered only during lactation, there was a much higher increase in blood Pb in the pregnant rats than in the nonpregnant rats. Bone Pb concentration increased when Pb was given only during lactation, whereas bone Pb decreased (compared to Pb-treated nonpregnant rats) when the Pb was given either before lactation or before and during lactation. The authors considered that resorption of Pb from bone was the main additional source of Pb during lactation. The data indicate that Pb stored in bone as a result of prior maternal exposure should be considered as a major source of self intoxication and of Pb in milk available to suckling pups.

Lead and Cadmium

Skoczynska et al. (1994) compared the effects of the combined exposure to Pb and cadmium to each metal singly on tissue composition of trace metals. Experiments were performed on 5- to 6-week-old male Buffalo rats given Pb-acetate (70 mg lead/kg body weight twice a week) and cadmium chlorate (20 mg Cd/kg body weight once a week) intragastrically for 7 weeks either singly or in combination. Blood Pb in the control group was 5.1 μg/dL, compared to 29.6 μg/dL in the Pb-treated group. In contrast, the Pb + cadmium group showed a blood Pb of 37.4 μg/dL. After combined exposure to Pb and cadmium, the level of these metals in the liver and kidney was lower than after the single administration of Pb or cadmium. Exposure of the rats to cadmium resulted in an increase of kidney zinc and copper and liver zinc

concentrations; combined exposure to Pb + cadmium did not produce more extensive changes in tissue zinc and copper concentrations.

Lead and Selenium

Othman and Missiry (1998) examined the effect of selenium against Pb toxicity in male rats. Male albino rats were given a single dose of Pb-acetate (100 µmol/kg body weight) and sacrificed 3 or 24 h later. Another group of animals was pretreated with sodium selenite (10 µmol/kg body weight) 2 h before receiving Pb-acetate and sacrificed 24 h later. Selenium is well known as an antioxidant and cofactor for GSHPx. In this experiment, GSH content, GSHPx, SOD activities, and the products of lipid peroxidation (i.e., TBARS) were determined. It was found that lipid peroxidation was prevented and the reduction in GSH caused by Pb in liver and kidney was diminished by selenium. Lead-induced diminution in SOD activity and GSHPx activity was also returned to normal by selenium.

Tandon et al. (1992) studied the effect of selenium supplementation during chelation of Pb with $CaNa_2EDTA$. Rats were given Pb-acetate 10 mg/kg/day by gastric gavage for 6 weeks. This was followed by a 5-day treatment course of $CaNa_2EDTA$, 0.3 mmol/kg IP or of $CaNa_2EDTA$ + sodium selenite, 0.5 mg/kg PO. Selenium had marginal effects on Pb removal by $CaNa_2EDTA$ in blood, liver, and kidney and similar effects on ALAD activity.

Lead and Zinc

Flora et al. (1989) examined the role of thiamine, zinc, or their combination in the prevention or therapy of Pb intoxication. Albino rats received the following treatments daily through gastric gavage for 6 days each week over a six-week period, 10 mg/kg of Pb as Pb-acetate; or the same dose of Pb-acetate + thiamine (25 mg/kg) zinc sulfate (25 mg/kg) or Pb + thiamine and zinc. Rats that had been exposed to Pb only were additionally divided into four groups treated by gastric gavage daily for 6 days as follows: group I, water only; group II, thiamine only; group III, zinc only; and group IV, combined zinc + thiamine. The activities of blood ALAD, blood ZPP, blood lead, and urine ALA were determined. Blood Pb concentrations increased from 6.2 to 120.9 µg/dL, contrasting normal controls with Pb-treated animals. There was a slight reduction in blood Pb in animals treated with either thiamine or zinc and a greater reduction in animals treated with thiamine + zinc. In the post-Pb-exposure treatment group,

thiamine + zinc was also the most effective treatment. Liver and kidney Pb levels followed the same course but brain Pb was not reduced by treatment. Blood ALAD activity was decreased from a normal level of 7.63 µmol ALA/min/L to 0.69 in Pb-treated animals and restored to 7.52 in Pb + thiamine + zinc-treated rats. ZPP was increased from 1.78 µg/g hemoglobin to 4.22 in Pb-treated animals and reduced to 2.50 in Pb + thiamine + zinc-treated animals. Urine ALA was increased from 0.07 to 0.24 mg/dL in Pb-treated animals and decreased to 0.17 in Pb + thiamine + zinc-treated rats. Prevention was more effective than post-Pb-exposure treatment. This was thought to be due mainly to the decrease in the absorption of Pb in the GI tract in the presence of thiamine and/or zinc.

Flora et al. (1994) explored the dose-dependent effects of zinc supplementation during chelation of Pb in rats. The chelator employed was $CaNa_2EDTA$, whose toxic effects are known to be mainly due to the depletion of endogenous zinc and, possibly, copper and manganese. In this experiment, male Wistar rats were started on exposure to Pb-acetate, 10 mg/kg, administered through gastric gavage once daily for 56 days. Twenty-four hours later, the Pb-exposed animals were treated daily for 5 days as indicated: group I, saline ; group II, $CaNa_2EDTA$ 0.3 mmol/kg, IP, once daily for 5 days; group III, $CaNa_2EDTA$ + zinc sulfate, 10 mg/kg, PO once daily for 5 days; and group IV, $CaNa_2EDTA$ + zinc sulfate, 50 mg/kg, PO once daily for 5 days. Blood ALAD decreased from 6.30 to 1.44 nmol/min/mL erythrocyte in Pb-exposed animals, with no change after $CaNa_2EDTA$ treatment and partial restoration after the $CaNa_2EDTA$ + zinc, 10 mg/kg treatment. There was no improvement following zinc, 50 mg/kg. Lead concentration in blood increased from 4.6 µg/dL to 43.0 µg/dL in Pb exposed animals, decreasing to 22.5 µg/dL in $CaNa_2EDTA$-treated animals and decreasing further to 16.5 µg/dL in $CaNa_2EDTA$ plus zinc-treated animals. Zinc at 50 mg/kg led to an increase in blood Pb to 56.1 µg/dL. Changes in the liver follow the same pattern, while in the kidney, zinc increased the Pb levels further, and in the femur, zinc had no influence on Pb content. Blood zinc decreased from 6.1 to 5.7 µg/ml in Pb-exposed rats and further to 5.0 µg/ml in $CaNa_2EDTA$-treated animals. There was an increase to levels of 6.6 µg/ml on the 10 mg/kg supplement of zinc and a further increase to 8.1 µg/ml on the 50 mg/kg zinc supplement.

Lead and Iron

Hashmi et al. (1989) examined the influence of dietary iron deficiency, Pb exposure, or the combination of the two on the accumulation of Pb in vital organs of rats. Animals fed an iron deficient diet for 2 weeks were also subjected to orbital plexus puncturing twice a week to allow a Hb levels to decrease to 7 to 8 g/dL. Animals were thereafter treated for the next 6 weeks with iron deficient diets or iron-deficient diets + 0.1% Pb-acetate in drinking water. At the end of 3 and 6 weeks, animals from each group were sacrificed. Feeding of an iron-deficient diet during Pb exposure enhanced the accumulation of Pb in soft tissues and flat bones. For example, liver Pb content was 0.75 µg/g in control animals, 8.43 in Pb treated animals, and 12.93 in iron-deficient and Pb-treated animals. The sequence of events was similar in kidney, spleen, and femur except that the Pb content in femur was reduced in the iron deficient and Pb-treated group.

Singh et al. (1991) conducted a study to ascertain the role of iron deficiency during pregnancy in inducing fetal nephrotoxicity in mothers exposed to lead. Rats were fed either a normal iron diet or an iron free synthetic diet for 15 days, followed by a diet containing half of the daily required iron (47 mg/100 g ferrous ammonium sulfate) for a further 15 days. Female animals were mated with healthy adult males. Lead doses of 250, 500, 1000, and 2000 ppm were given in drinking water during pregnancy and lactation. Fetuses were removed by Caesarean section on the 21st day. Maternal blood Pb levels in rats on an iron deficient diet were higher than those in rats on a normal iron diet at all levels of Pb dosing. Similarly, placental Pb levels were higher in animals on an iron-deficient diet as compared to a normal diet. Lead content in the fetuses were higher on the iron-deficient diet. Lead administration resulted in dose-dependent hydropic degeneration of renal proximal tubular cells in the fetuses. At a dose of 2000 ppm Pb with iron deficiency, more Pb accumulated in maternal blood, placenta, and fetuses and maximum pathological changes were seen in the fetal kidney as compared to other doses.

Lead and Aluminum

Shakoor et al. (2000) reported beneficial effects of aluminum on the progression of Pb-induced nephropathy in rats. Male albino rats were treated with water only or Pb-acetate (125 mg/kg) and/or aluminum chloride (50 mg/kg or 100 mg/kg) for a period of 90 days. Aluminum was found to prevent the Pb-induced increase in relative kidney weight in a dose-

dependent manner. Aluminum also prevented Pb-induced increases in plasma creatinine levels of Pb- treated animals. The net deposition of Pb in kidneys was lower in animals that were given both Pb-acetate and aluminum chloride simultaneously. By day 90, plasma creatinine was 1.26 mg/dL in control animals, 1.88 mg/dL in Pb-treated animals, and 1.34 and 1.44 mg/dL in Pb and aluminum-treated animals. Similarly, kidney Pb increased from 5.4 µg/g in control animals to 220.0 µg/g in Pb-treated animals and decreased to 138.5 and 98.9 µg/g in Pb and aluminum treated animals. These and other studies are summarized in Table AX5-7-5.

5.7.4.4 Effect of Age on Lead Toxicity

Han et al. (1997) examined the hypothesis that the high rate of bone remodeling during childhood and the consequent high calcium and Pb turnover would result in a substantial reduction in bone Pb stores, so that much of the Pb incorporated in bone during childhood does not persist into adulthood. They treated female Sprague-Dawley rats with 250 ppm of Pb in drinking water for 5 weeks beginning at 5, 10, or 15 weeks of age. Organ harvesting occurred 4 weeks after the end of Pb exposure for all groups, as well as 8 and 20 weeks after cessation of Pb ingestion in the rats exposed beginning at 5 weeks of age. Organs examined were brain, kidney, liver, femur, and spinal column bone. Blood and organ Pb concentrations were significantly higher in the rats exposed beginning at 5 weeks of age than in those exposed beginning at 10 or 15 weeks of age. The results of this experiment rejected the hypothesis and suggested instead that a younger age at Pb exposure is associated with greater Pb retention and toxicity, even in the absence of continued Pb exposure.

Garcia and Corredor (2004) examined biochemical changes in the kidneys after perinatal intoxication with Pb and/or cadmium. Lead acetate (300 ppm) and/or cadmium acetate (10 ppm) were administered in drinking water to pregnant Wistar rats from day 1 of pregnancy to parturition (day 0) or until weaning (day 21). The following kidney enzyme activities were determined: alkaline and acid phosphatases, Mg-ATPase, and NaK-ATPase. Blood Pb was measured in control pups as well as in pups exposed to lead at parturition and at weaning. Control pups showed 1.43 µg/dL of blood Pb compared to 31.5 µg/dL at day 0 and 22.8 µg/dL at day 21 in pups exposed to lead. In those rats receiving both cadmium and Pb, the blood Pb concentration was 23.2 µg/dL at day 0 and 13.2 µg/dL at day 21. Lead caused a significant inhibition of kidney alkaline phosphatase and kidney acid phosphatase. At parturition, Pb

intoxication produced a strong inhibition of NaK-ATPase (~80%) as well as of Mg-ATPase activities (~24%); whereas, when Pb was given in combination with cadmium, these inhibitory effects were attenuated. At weaning, Pb continued to produce a significant inhibition of Mg-ATPase but had no effect on NaK-ATPase. Thus, simultaneous perinatal administration of both Pb and cadmium seemed to protect against the toxicity produced by Pb separately.

Cory-Slechta (1990a,b) published two articles on the effects of old age on the disposition of lead. In the first study (1990a) male F344 rats, at the ages of 8 months (adult) and 16 months (old) were exposed to concentrations of 0, 250, or 500 ppm Pb-acetate in drinking water for 7 months. At these Pb doses, prior studies had indicated that blood Pb levels ranged from 60 to 90 µg/dL. Blood lead, ZPP, and urinary ALA levels were determined after both 3 and 7 months of exposure. Organ weights, tissue Pb concentrations, and urinary excretion of lead, calcium, copper, and zinc were examined after 7 months of exposure. Tissue Pb distribution was markedly altered in old rats: in bone and kidney, Pb levels were reduced while liver Pb was substantially increased. Blood Pb levels in adult and old rats were comparable at both measurement intervals, as was urinary Pb excretion at 7 months. Lead-induced elevation of ZPP exhibited differential changes between 3 and 7 months; values in adults declined while levels in old rats increased or remained unchanged. In the adult group, Pb exposure increased calcium excretion primarily at the 500 ppm exposure level. In contrast, Pb exposure decreased urinary calcium excretion in old animals at the higher exposure level. No effects of either age or Pb exposure were detected in the comparison of adult versus old urinary excretion of zinc or copper.

In the second study, Cory-Slechta (1990b), young (21 days old), adult (8 months old), and (16 months old) rats exposed to 0, 2, or 10 mg of Pb-acetate/kg per day for a period of 9.5 months were evaluated. Differences in the tissue distribution of Pb with age included lower bone levels, but increased concentrations in brain, liver, and kidney. Differences in blood Pb levels over the course of exposure were not remarkable. Thus, these effects did not appear to reflect an enhanced Pb absorption from the GI tract with age. Instead, the bone changes may reflect enhanced bone resorption with a concurrent decline in bone apposition with age, combined with altered patterns of urinary Pb excretion over time, i.e., elevated urinary Pb at 3 and 6 months, but comparable Pb excretion at 9.5 months, as compared to young and adult rats.

5.7.5 Summary

Highlights of the previous 1986 Pb AQCD and of studies done between 1986 and the present are outlined in this section.

1986 Document

- In animal studies, nuclear inclusion bodies were found in proximal tubules, identified as 27 kDa or 32 kDa proteins in combination with lead. Subsequently, a 63 kDa Pb-binding cytosolic protein was described in kidney.

- Swollen mitochondria, with diminished mitochondrial function, were found in the proximal tubules.

- Renal ALAD was the same in Pb-treated animals as in controls when GSH was present, but was reduced when GSH was absent.

Newer studies

- Hyperfiltration, when compared to age- and sex-matched normal controls, was found in adults who had suffered from childhood Pb poisoning, in young occupationally exposed Pb workers in Korea, and in both low-Pb-treated rats and high-Pb-treated rats up to 3 months of exposure. This is paralleled in animal experiments by an increase in kidney weight.

- Various new urinary markers for Pb toxicity have been described. These include NAG, β2-microglobulin, α1-microglobulin, retinol binding protein, GST, lysozyme, γ-glutamyl transferase, alanine aminopeptidase, prostanoids, and brush border antigens. The literature on these markers is voluminous, but, on review, only GST and α1-microglobulin seemed to be appropriate urinary markers. NAG, which has been most extensively investigated, appears in detailed-animal studies to be overly sensitive, increasing in low-Pb-treated animals, despite an absence of pathological changes on ultrastructural study. β2-Microglobulin, and possibly retinol binding protein, which are low-molecular weight proteins reabsorbed by the proximal tubule, appeared to be elevated only with high levels of blood Pb (>80 μg/dL).

- Animal studies have implicated free radicals in the pathogenesis of Pb-induced hypertension and renal disease. A sequence of free radicals can be demonstrated in Pb-induced disease, as evidenced by an increase in superoxide radicals, hydroxyl radicals, hydrogen peroxide, and peroxynitrite, together with a diminution in GSH in liver, brain, and aorta. Nitric oxide is most commonly decreased (by free radicals) as is urinary cyclic GMP. Aortic guanylate cyclase is decreased. The enzyme responsible for an increase in the production of free radicals, NAD(P)H oxidase, is increased by Pb, whereas eNOS and iNOS, the enzymes involved in the production of nitric oxide, are also increased, attesting to the importance of free radical destruction of nitric oxide. Antioxidants reverse these changes and diminish blood pressure.

- Norepinephrine and epinephrine are increased by Pb administration, whereas β-adrenoreceptor density of heart and kidney are decreased. In a second study, norepinephrine, but not epinephrine, was increased by Pb.

- Various antioxidants have been used in conjunction with chelators, to both remove Pb from tissue and to diminish free radicals. Taurine, lipoic acid, arginine, ascorbic acid, vitamin E, thiamine, tempol, and lazaroids have been used in conjunction with DMSA, all improving free radical diminution.

- Metal combinations have also been employed to reduce tissue Pb and/or affect free radicals. Cadmium increases Pb in blood when both are given, but diminishes Pb in liver and kidney. Selenium, an antioxidant, improves both parameters, as does thiamine or L-lysine plus zinc. Iron deficiency increases intestinal absorption of Pb and the Pb content of soft tissues and bone. Aluminum decreases kidney Pb content and serum creatinine in Pb-intoxicated animals.

- Age also has an effect on Pb retention. There is higher Pb retention at a very young age and lower bone and kidney Pb at old age, attributed in part to increased bone resorption and decreased bone accretion.

5.8 EFFECTS ON BONE AND TEETH

5.8.1 Biology of Bone and Bone Cells

By weight, bone is composed of 28% collagen fibers (predominantly type I collagen) and 5% noncollagenous proteins (osteocalcin, osteonectin, and other proteoglycans), with crystals of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] making up the remaining 67%. In addition to providing mechanical support for the body and protection of vital organs, the skeletal system also functions in a metabolic capacity. Historically, bones have been classified as either long or flat based on their appearance, with long bones including limb bones, e.g., the femur and humerus, and flat bones including the bones of the skull, sternum, pelvis, and scapula. Long and flat bones originate by distinct methods of formation, endochondral and intramembranous, respectively, with long bones eventually using both processes. In endochondral bone formation, a mineralized, cartilaginous matrix precedes the transition into true bone, while in intramembranous formation, the bone forming cells create bone directly without the cartilaginous template.

Bone cells responsible for producing the bone matrix of collagen and ground substance are called osteoblasts. Several signaling factors including growth factors and hormones

influence pre-osteoblastic cells to differentiate into mature osteoblasts and subsequently synthesize and mineralize the extracellular matrix to form mature bone. It is during the process of bone mineralization that the Pb ion (Pb^{2+}) can become incorporated by substituting for the calcium ion (Ca^{2+}). The bone cells responsible for bone resorption are the osteoclasts. Osteoclasts, which are large and multicellular (4 to 20 cells), dissolve bone matrix and hydroxyapatite by synthesizing and releasing lysosomal enzymes and acidifying the extracellular surroundings. It is during the process of dissolving bone, or demineralization, that Pb stored in bone can be released locally and into the general system.

Bone cell function may be compromised both directly and indirectly by exposure to Pb. Regulation of bone cells occurs by numerous local and systemic factors, including growth hormone (GH), epidermal growth factor (EGF), transforming growth factor-beta 1(TGF-β1), and parathyroid hormone-related protein (PTHrP). As discussed further below in this section, the presence of lead can potentially interfere with each of these factors. The bones of the skeleton serve as the primary reservoir for calcium and phosphate in the body and help to maintain homeostasis of these ions in the serum through bone turnover or remodeling. Vitamin D [1,25-$(OH_2)D_3$] maintains the normal range of calcium in the serum by increasing the efficiency of calcium absorption in the intestines and facilitating differentiation of stem cells into osteoclasts, which break down bone and mobilize calcium (and lead) stores. Parathyroid hormone (PTH), in turn, regulates the production of vitamin D in the kidney. Lead has been shown to interfere with the action of both of these hormones. Other substances influenced by lead and discussed in this section are alkaline phosphatase, an enzyme necessary for mineralization of bones and teeth, and osteocalcin, a noncollagenous protein whose spatial and temporal pattern of expression suggests a role in bone mineralization. Both substances are also markers for osteoblast activity and, by default, bone formation. Alkaline phosphatase is a potential carrier of ionic calcium and is capable of hydrolyzing inhibitors of mineral deposition such as pyrophosphates.

5.8.2 Summary of Information Presented in the 1986 Lead AQCD

Lead has been shown to become localized and accumulate in bones and teeth, with accumulation beginning as early as fetal development. Lead administered to rats as a single dose results in blood lead concentrations that are initially elevated, but rapidly fall as Pb is transferred

to bone or excreted. The dose of Pb administered does not apparently affect distribution to the various body compartments; however, the rate-limiting step in the clearance of Pb from rats and mice involves absorption into/clearance from the skeletal system. The loss of Pb from various organs and tissues follows first-order kinetics, except from bone. More absorbed Pb is retained by young animals compared with adult animals, leading to higher tissue levels. Moreover, once Pb is incorporated into the young animal's body, the long-term rate of retention is greater than that of adults. In Pb-exposed animals, Pb is distributed subcellularly, preferentially to the nucleus and mitochondrial fractions.

During lactation in mice, a redistribution of tissue Pb occurs (mobilization), resulting in the transfer of Pb and calcium from mother to pups via the milk, and subsequent overall loss of Pb in the mothers. Lead transfer to suckling rats via mother's milk has been reported to be approximately 3% of the maternal body burden or more, if Pb exposure continues during lactation. Eight days after a single injection of Pb, the content of Pb in rabbit's milk was 8-fold higher than the maternal blood level, suggesting Pb transfer can occur against a concentration gradient. Transplacental transfer of Pb from mother to fetus also occurs in various animals.

In rats, a significant reduction of calcium in the diet leads to enhanced uptake of lead into the bones and other tissues. In general, an enhanced uptake of Pb into tissues is also seen in rats fed diets deficient in iron, zinc, copper, or phosphorus, and in the presence of low or excess vitamin D.

5.8.3 Bone Growth in Lead-Exposed Animals

Lead is readily taken up and stored in the bone of experimental animals, where it can potentially manifest toxic effects that result in stunted skeletal growth. In experiments reported since the 1986 Pb AQCD, Hac and Krechniak (1996) determined uptake and retention of Pb in bone from rats exposed to plain water or water containing Pb-acetate (41.7 to 166.6 mg/L) for 12 to 16 weeks. After 4 weeks, the skeletal Pb in animals receiving the lowest dose was almost 5 times higher than control animals (5.9 versus 1.2 µg Pb/g bone, respectively). Lead levels in bones from animals receiving 83.3 mg/L and 166.6 mg/L were dose-dependently higher at 11.7 and 17.0 µg Pb/g bone, respectively, after 4 weeks of exposure. All bone Pb levels were maintained essentially in a steady state until the completion of exposure, when all animals were placed on control water. Approximately 64% of Pb remained in the bones of rats in the

83.3 mg/L exposed group at 64 days postexposure. Similarly, airborne Pb can be inhaled and subsequently incorporated into bone. Grobler and co-workers (1991) exposed 6-week-old rats to either "clean air" (0.05 μg Pb/m^3) or air containing 77 μg Pb/m^3 and found significant differences in the amount of Pb incorporated into the alveolar bones of the animals. After 70 days, a mean of only 0.2 μg Pb/g of bone dry mass was found in bone from control animals, while 16.9 μg Pb/g was present in bone from the 77 μg Pb/m^3 exposure group. Exposure to air containing 249 μg Pb/m^3 for 28 days or 1,546 μg Pb/m^3 for 50 days, resulted in mean values of 15.9 and 158 μg Pb/g dry weight of Pb incorporation into the bone, respectively, highlighting the fact that dose and length of exposure are determinates of amount of Pb contained in the bones of these animals. The uptake of Pb by bone has the potential for immediate toxic effects on the cellular processes occurring during bone growth, development, and maintenance, with the additional potential for delayed toxicity from release of stored Pb during periods of normal or accelerated bone remodeling.

Numerous studies have examined growth suppression associated with developmental Pb exposure. Hamilton and O'Flaherty (1994) examined the effects of Pb on growth in female rats, and subsequently, on growth and skeletal development in their offspring. Administration of drinking water containing either 250 or 1,000 ppm lead to weaning female rats for 49 days produced no alteration in growth rate in these future dams. The rats were then bred, with Pb exposure continuing through parturition and lactation. Lead did not affect gestation time nor Day 1 suckling body weight, however, pup body weight and tail length were subsequently decreased in both exposure groups. A 10% increase in tibial growth plate width and disruption of chondrocyte organization were observed in offspring from the high exposure group.

In male rats exposed to 100 ppm Pb in drinking water and a low calcium diet for up to one year, bone density was significantly decreased after 12 months, while rats exposed to 5,000 ppm Pb had significantly decreased bone density after 3 months (Gruber et al., 1997). Pb content of femurs was significantly elevated over the content of control rats at all time points (1, 3, 6, 9, 12 months). Trabecular bone from the low dose animals was significantly decreased from 3 months forward. Young female rats exposed to 17 mg of Pb-acetate per kg of feed for 50 days showed no differences in the length of the femurs, but the mean length of the 5th lumbar vertebra was significantly decreased (Gonzalez-Riola et al., 1997; Escribano et al., 1997). The mean length of the femur growth plate cartilage was also significantly decreased in Pb-exposed animals.

In a dose-response study, Ronis et al. (1998a, 1998b) exposed pregnant rats to Pb-acetate in drinking water (0.05% up to 0.45% w/v) beginning at gestation Day 5 and continuing through weaning of offspring at Day 21. Early bone growth was significantly depressed in a dose-dependent fashion in pups of all Pb-exposed groups, with growth suppression in male offspring considerably greater than in females. Significant decreases in plasma insulin-like growth factor and plasma sex steroids and increased pituitary growth hormone were also observed. This is somewhat in contrast to the findings of Camoratto and coworkers (1993), who reported low exposure to 0.2% Pb nitrate (125 ppm Pb) did not significantly affect growth, though males weighed significantly less than females. Between age 57 and 85 days Ronis et al. (1998b) noted that growth rates were similar in control and Pb-exposed pups, suggesting exposure at critical growth periods such as puberty and gender may account for differences in growth reported by various investigators. In a series of follow-up experiments (Ronis et al., 2001) reported a dose-dependent decrease in load to failure in tibia from Pb-exposed (0.15% and 0.45% Pb-acetate in drinking water) male pups only. Hormone treatments (estradiol in females or L-dopa, testosterone or dihydrotestosterone in males) failed to attenuate Pb deficits during the pubertal period. Distraction osteogenesis experiments performed after stabilization of endocrine parameters (at 100 days of age) found decreased new endosteal bone formation and gap x-ray density in the distraction gaps of Pb-exposed animals (Ronis et al., 2001).

Hamilton and O'Flaherty (1995) found Pb disrupted mineralization during growth when they implanted demineralized bone matrix subcutaneously into male rats. In the matrix that contained 200 μg Pb/g of plaque tissue, alkaline phosphatase activity and cartilage mineralization were absent, though calcium deposition was enhanced. Separate experiments found enhanced calcification and decreased alkaline phosphatase activity in rats implanted with a control (no Pb) matrix and given 1,000 ppm Pb in drinking water for 26 days.

In summary, results from animal studies suggest Pb exposure is capable of adversely affecting bone growth and density, potentially manifesting its action through interference with growth and hormonal factors as well as toxic effects directly on bone.

5.8.4 Regulation of Bone Cell Function in Animals – Systemic Effects of Lead

Lead may exhibit multiple complex systemic effects that ultimately could influence bone cell function. As discussed in the animal studies below, Pb can modulate alterations in calcium binding proteins and in calcium and phosphorus concentration in the blood stream, in addition to potentially altering bone cell differentiation and function by altering plasma levels of growth hormone and calciotropic hormones such as vitamin D_3 [1,25-$(OH_2)D_3$] and parathyroid hormone.

5.8.4.1 Hypercalcemia/Hyperphosphatemia

Intravenous injection of Pb has been shown to produce both an acute hypercalcemia and hyperphosphatemia in rats (Kato et al., 1977). Injection of a relatively high dose of 30 mg/kg Pb resulted in maximum values of calcium (17 mg%) after one hour and maximum values of phosphorus (13.5 mg%) after 30 minutes. After 12 hours the levels of both calcium and phosphorus had returned to baseline levels. Histochemical examination demonstrated deposition of Pb into bone and dentin in the rats, suggesting a direct action of Pb on bone and/or teeth, ultimately displacing calcium and phosphorus and thereby producing hypercalcemia and hyperphosphatemia.

5.8.4.2 Vitamin D [1,25-(OH2)D3]

As discussed above, vitamin D [1,25-$(OH_2)D_3$] modulates the normal range of calcium in serum. In rats fed a low calcium or low phosphorus diet, ingestion of 0.82% Pb in the diet reduced plasma levels of 1,25-$(OH_2)D_3$; however, this effect is lost when a high calcium or normal phosphorus diet is given (Smith et al., 1981), suggesting a high calcium/phosphorus diet reduces the susceptibility of vitamin D system to the effect of Pb. No mobilization of calcium from bone or elevation of inorganic phosphorus was seen. Ronis et al. (2001) also reported no effects of Pb on plasma concentrations of vitamin D metabolites, 25-OH D_3 or 1,25-$(OH_2)D_3$, in pubertal male rats exposed to either 0.15% or 0.45% Pb acetate in drinking water and maintained on an adequate diet. Fullmer (1995) found vitamin D function was severely compromised in young growing chicks given a diet low in calcium (0.1% calcium) for two weeks and then exposed to 0.2% or 0.8% Pb in their diet for an additional one or two weeks. In chicks

maintained on an adequate diet (1.2% calcium), exposure to 0.2% or 0.8% Pb in the diet resulted in increased plasma levels of 1,25-$(OH_2)D_3$ as well as significantly increased intestinal Calbindin-D protein [a calcium binding protein induced by 1,25-$(OH_2)D_3$] and its associated mRNA, when compared with unexposed control chicks. Levels of intestinal Calbindin-D mRNA and protein and plasma levels of 1,25-$(OH_2)D_3$ were elevated during the first week of Pb exposure to chicks fed a diet deficient in calcium, but were significantly decreased by the second week of Pb exposure. The study suggested Pb was mediating its effect through 1,25-$(OH_2)D_3$, rather than via a direct action on the Calbindin-D protein. Follow up studies by Fullmer et al. (1996) confirmed dose dependent increases in serum 1,25-$(OH_2)D_3$ levels (and Calbindin-D protein and mRNA) with increasing dietary Pb exposure (0.1% to 0.8%) in similar experiments performed on Leghorn cockerel chicks fed an adequate calcium diet.

5.8.4.3 Parathyroid Hormone

At least one animal study has associated experimental Pb exposure with secondary hyperparathyroidism. Szabo et al. (1991) exposed Wistar Kyoto rats to either 1% Pb acetate in water for a short term (10 weeks) or varying concentrations (0.001 to 1% Pb acetate) for a longer term (24 weeks) to assess the influence of Pb on the interaction of the parathyroids with 1,25-$(OH_2)D_3$. Short term administration of 1% Pb resulted in significant increases in bone Pb; however, total serum calcium and ionized serum calcium were significantly decreased, as compared to controls. Circulating levels of 1,25-$(OH_2)D_3$ were also decreased, though the rats were maintained on a normal calcium diet (0.95%). Parathyroid glands from rats exposed short term to Pb were significantly increased in size over those in control animals (178 μg per gland versus 96 μg per gland) and specific binding of 1,25-$(OH_2)D_3$ to parathyroid and intestinal tissue was increased. Likewise, long term administration of 1% Pb resulted in significant increases in bone Pb and normalized parathyroid gland weights, and a significant decrease in the level of 1,25-$(OH_2)D_3$. In the long term study, a dose-dependent increase in parathyroid weight occurred with increasing exposure to Pb in drinking water. The authors concluded the secondary hyperparathyroidism was associated with, and/or a result of, the hypocalcemia and decreased 1,25-$(OH_2)D_3$ levels secondary to Pb exposure.

5.8.4.4 Growth Hormone

As discussed in Section 5.8.3, exposure to Pb has been associated with altered bone metabolism and decreased growth and skeletal development (Hamilton and O'Flaherty, 1994, 1995; Gruber et al., 1997; Gonzalez-Riola et al., 1997; Escribano et al., 1997; Ronis et al., 1998a,b, 2001; Camoratto et al., 1993), suggesting perturbation of one or more endocrine factors such as growth hormone. To examine the effect of exposure to low-level Pb on pituitary growth hormone release, Camoratto et al. (1993) exposed pregnant female rats to 0.02% Pb nitrate (125 ppm Pb) beginning on gestational day 5 and continuing in pups through postnatal day 48. Basal release of growth hormone from control and Pb-exposed pups at age 49 days was not significantly different. Growth hormone releasing factor-stimulated release of growth hormone from pituitaries of Pb-exposed pups was smaller than the stimulated release of growth hormone from pituitaries of control animals (75% increase over baseline vs. 171% increase, respectively), but the difference did not achieve significance ($p = 0.08$). Growth hormone content of the pituitary glands was also not influenced by Pb exposure. Ronis et al. (1998b) reported similar findings in rat pups exposed to 0.05%, 0.15%, or 0.45% Pb acetate in drinking water from gestation day 5 through postnatal day 85, with the exception being significantly elevated pituitary growth hormone levels at postnatal day 55. Taken together, these rat studies suggest that differences in growth seen with Pb exposure may not necessarily be the result of alterations in secretion of growth hormone.

5.8.5 Bone Cell Cultures Utilized to Test the Effects of Lead

5.8.5.1 Bone Organ Culture

In an early bone organ culture study utilizing incorporated radioactive Pb into fetal radii and ulnae, Rosen and Wexler (1977) reported release of Pb as the concentration of calcium in the media was reduced or with addition of parathyroid hormone, but that calcitonin inhibited the release of Pb as expected, verifying the capacity of this model system. The bone organ system was subsequently used to evaluate the efficacy of Pb chelating agents, such as D-Penicillamine and $CaNa_2EDTA$ (Rosen and Markokwitz, 1980; Rosen et al., 1982).

5.8.5.2 Primary Cultures of Osteoclasts and Osteoblasts

The ability to isolate primary cultures of osteoclasts and osteoblasts from mouse calvaria provided an additional experimental model system to study the effects of Pb on specific bone cells. Using isolated osteoclasts and osteoblasts, Rosen (1983) reported that uptake of radioactive Pb by osteoclasts was rapid, almost linear, while osteoblasts showed very little increase in uptake of Pb at increasing media concentrations. Physiological concentrations of parathyroid hormone markedly increased uptake of Pb and calcium by osteoclast cells and, once loaded with Pb, osteoclasts were capable of releasing Pb slowly into the media. Further kinetic analysis of cultured osteoclastic bone cells indicated that cellular Pb is primarily associated with the mitochondrial fraction (~78%) and that this Pb is readily exchangeable with the outside media (Pounds and Rosen, 1986; Rosen and Pounds, 1988). Experiments conducted to characterize the steady-state kinetic distribution and metabolism of calcium and Pb supported the concept that the two elements are metabolized similarly in the osteoclasts cells (Rosen and Pounds, 1989).

5.8.5.3 Rat Osteosarcoma Cell Line (ROS 17/2.8)

In recent years, the rat osteosarcoma cell line ROS 17/2.8 has been used extensively to investigate the influence of Pb on various cellular processes and kinetics within these osteoblast-like cells. The ROS 17/2.8 cell model is useful in that the cells are capable of producing osteocalcin (a bone protein important for proper bone mineralization), have high alkaline phosphatase activity (an enzyme normally associated with mineralization of cartilage), possess vitamin D receptors, and respond to parathyroid hormone. In comparisons of cellular lead toxicity and metabolism between primary cell culture from mouse calvaria and the rat osteosarcoma cell line, Long and coworkers (1990a) reported remarkable similarities in the profile of radiolabeled Pb kinetics and intracellular Pb distribution. Using this cell line, Schanne and coworkers (1989) simultaneously measured intracellular Pb and calcium concentrations and found 5 and 25 micromolar Pb produced sustained 50% and 120% (respectively) increases in intracellular calcium over a 5 hour period, and that measurable entry of Pb into the cells could be demonstrated at the higher concentration. These findings advanced the hypothesis that perturbation of intracellular calcium concentration may be the mechanism of Pb bone toxicity. Schirrmacher and coworkers (1998) reported that calcium homeostasis is upset within

20 minutes of its addition to calvarial bone cell culture. Their results suggested that the calcium-ATPases of intracellular stores were potentially poisoned by Pb entering the cells. Wiemann et al. (1999) demonstrated that Pb was also capable of interfering with the calcium release activated calcium influx (CRAC) in calvarial bone cell cultures. Pb was found to partially inhibit the influx of calcium into the bone cells, plus influx of Pb into the cells was greatly enhanced (2.7 fold) after CRAC had been induced. These effects of Pb were found to be independent of any inhibitory effect on calcium-ATPase.

Miyahara et al. (1995) performed a series of experiments in ^{45}Ca-labeled bone organ culture to determine whether the Pb-induced hypercalcemia was the result of the active process of biological bone resorption or simply physiochemical mineral dissolution. Lead introduced into the culture at concentrations of 50 μM and above stimulated the release of calcium and hydroxyproline into the medium, however no release was elicited from bones inactivated by freezing and thawing. Pb-stimulated ^{45}Ca release was inhibited by eel calcitonin, bafilomycin A_1, and scopadulcic acid B, suggesting the release was secondary to osteoclastic bone resorption. Further evidence to support this conclusion came from experiments examining the influence of two inhibitors of cyclooxygenase on Pb-induced bone resorption. Lead was found to stimulate prostaglandin E_2 release and in cultures, there was a high correlation between prostaglandin E_2 released into the media and ^{45}Ca release. In the presence of cyclooxygenase inhibitors (blocking prostaglandin synthesis), Pb-stimulated ^{45}Ca release was inhibited suggesting the mechanism of bone resorption in this instance was via a prostaglandin E_2-mediated mechanism.

Lead has been demonstrated to directly impair production of osteocalcin by ROS 17/2.8 cells by 70% after 24 hours of exposure to 25 micromolar Pb (Long et al., 1990a). The resulting decrease in cell proliferation is in agreement with similar studies by Sauk et al., 1992). Interestingly, exposure of dental pulp cells, which also produce osteocalcin, to a similar concentration of Pb reduced osteocalcin production by 55% after 12 hours of exposure (Thaweboon et al., 2002). Vitamin D has been shown to increase osteocalcin production in ROS 17/2.8 cells; however, Pb inhibited the vitamin D-stimulated osteocalcin production in a dose-dependent manner from 0 up to 25 micromolar concentrations, plus was shown to be capable of attenuating basal (non-vitamin D-stimulated) osteocalcin production (Long et al., 1990a). Lead (5 to 20 micromolar) inhibition of vitamin D stimulation of osteocalcin in ROS cells was also reported by Guity and coworkers (2002). Later studies suggested that Pb acts by inhibiting

vitamin D activation of calcium channels and interferes with regulation of calcium metabolism (Schanne et al., 1992), though apparently this effect is not mediated via PKC (Guity et al., 2002). Angle and coworkers (1990) reported that 24 hours of incubation with vitamin D (10 nM) was capable of evoking a 4 to 5 fold increase in osteocalcin production and a 100% increase in cellular alkaline phosphatase activity in ROS cells. Osteocalcin production and cellular DNA contents were increased 100% and 20% respectively by addition of insulin-like growth factor (92.5 ng/mL). Consistent with a toxic effect of Pb on osteoblast function, the addition of 1 to 10 μM Pb to the system inhibited both basal and stimulated osteocalcin secretion, alkaline phosphatase activity and DNA contents (Angle et al., 1990). Dose- and time-dependent reduction in alkaline phosphatase activity with Pb exposure (2 to 200 micromolar) has also been reported in osteosarcoma cells, along with parallel reductions in steady state levels of alkaline phosphatase mRNA levels (Klein and Wiren, 1993). No effect on cell number or DNA and protein synthesis was seen at these levels of Pb exposure.

Though the exact mechanism of Pb toxicity on osteocalcin was unclear, Pb was known to inhibit some of the functional properties of osteocalcin including inhibition of osteocalcin adsorption to hydroxyapatite. An investigation by Dowd and coworkers (1994) utilized the ability of osteocalcin added to a solution of $^{43}CaCl_2$ to broaden ^{43}Ca resonance, as a method to examine binding of calcium to osteocalcin and the influence of Pb on calcium binding. It was determined that the dissociation constant of calcium for osteocalcin was 7 micromolar, while the dissociation constant for Pb was determined by competitive displacement to be 2 nM, indicating more than three orders of magnitude tighter binding of Pb than calcium to osteocalcin and the likelihood that even submicromolar levels of free Pb would significantly inactivate osteocalcin. Circular dichroism indicated that upon binding, Pb induces a similar structural change in osteocalcin to that found with calcium binding, but the binding with Pb occurs at 2 orders of magnitude lower than with calcium (Dowd et al., 2001). Similarly, hydroxyapatite binding assays indicated Pb causes an increased absorption to hydroxyapatite that is similar to calcium, but again at 2 to 3 orders of magnitude lower concentration, potentially leading to low bone formation rates and/or density (Dowd et al., 2001).

Besides perturbation of calcium metabolism, Pb has been shown to reduce intracellular free magnesium concentrations by 21% in osteosarcoma cells incubated in 10 micromolar Pb for 2 hours (Dowd et al., 1990). Under these same conditions, the unidirectional rate of ATP

synthesis (i.e. P_i to ATP) was reduced by a factor greater than 6 over control cultures. Impairment of both of these processes by Pb could ultimately influence bone growth and development.

Lead has also been show to perturb Epidermal Growth Factor's (EGF) control of intracellular calcium metabolism and collagen production in ROS cells (Long and Rosen, 1992). EGF is known to activate protein kinase C (PKC), resulting in increased calcium influx and through this mechanism, decreased collagen synthesis. Incubation of ROS cells with 5 micromolar Pb and 50 ng/mL EGF for 20 hours resulted in a 50% increase in total cell calcium versus the calcium increase seen in cells treated with EGF alone, suggesting more than one site of action is involved in calcium messenger perturbation. A similar finding was reported by Long and coworkers (1992) who found that treatment of Pb (25 micromolar) intoxicated osteosarcoma cells with parathyroid hormone (PTH, 400 mg/mL) resulted in a greater increase in cell calcium than with either treatment alone. Supplementary inhibition of collagen synthesis has also been reported with the addition of 25 micromolar Pb plus 50 ng/mL EGF, suggesting more than one site of action for the effect of Pb on collagen synthesis (Long and Rosen, 1992). Additional study has since suggested that Pb activates PKC in ROS cells and that PKC mediates the rise in intracellular calcium (Schanne et al., 1997). The observation that calphostin C, an inhibitor of PKC, prevented the Pb-induced elevation of intracellular calcium supported this hypothesis, as did the fact that free Pb at concentrations of 10^{-11} to 10^{-7} M directly activated PKC in the absence of activating concentrations of calcium. This would suggest Pb is capable of activating PKC at concentrations approximately 3,000 times lower than calcium.

Finally, Pb has been shown to be capable of inhibiting secretion of osteonectin, a bone related protein found in areas of active morphogenesis (Sauk et al., 1992). Treatment of ROS 17/2.8 cells with lead (4.5×10^{-6} M to $4.5\ 10^{-7}$ M) demonstrated that intracellular osteonectin levels were actually enhanced; however, the secretion of osteonectin into the media was delayed or inhibited. Protein production of collagen and the endoplasmic reticulum protein, Asp47, were relatively unaffected by Pb at these concentrations. The intracellular retention of osteonectin coincided with a decrease in levels of osteonectin mRNA, suggesting the processes associated with translation and secretion of osteonectin are sensitive to Pb.

5.8.5.4 Human Osteosarcoma Cells (HOS TE 85)

Evidence exists that Pb is directly osteotoxic to bone cells in culture. Studies examining the sensitivity of human osteosarcoma cells (HOS TE 85) to Pb found proliferation of the cells was inhibited at Pb concentrations of 4 μmol/l, while cytotoxicity occurred at the 20 μmol/l Pb concentration (Angle et al., 1993). In parallel experiments, rat osteosarcoma cells (ROS 17/2.8) were found to be somewhat less sensitive to the effects of Pb with inhibition of proliferation occurring at 6 μmol/l Pb concentration and cytotoxicity at Pb concentrations over 20 μmol/l.

5.8.5.5 Chick Chondrocytes

The effects of Pb on cartilage biology have been examined in isolated avian chondrocytes obtained from 3 to 5 week old chicks (Hicks et al., 1996). Exposure to media containing 0.1 to 200 μM Pb acetate or chloride were found to decrease thymidine incorporation, suppress alkaline phosphatase, and suppress both type II and type X collagen expression at the mRNA and protein levels. Cytotoxicity of the cultures from Pb exposure was dismissed as proteoglycan synthesis was found to be augmented, suggested Pb selectively inhibits specific aspects of the chondrocyte growth plate. Using the avian chondrocyte model, Zuscik et al. (2002) similarly reported Pb exposure (1 to 30 μM) causing a dose-dependent inhibition of thymidine incorporation into the growth plate, with a 60% reduction in proliferation at the highest concentration. Addition of TGF-β1 and PTHrP, regulators of growth plate, both separately stimulated thymidine incorporation, an effect that was dose-dependently blunted in the presence of Pb. At the highest Pb concentration (30 μM), inhibition was significantly less in the chondrocytes treated with Pb + TGF-β1 (24%) and Pb + PTHrP (19%) than for Pb alone (60%), suggesting the interaction of Pb with these growth factors may be independent of its primary action on the chondrocyte cells. Support for a direct action of Pb on these growth regulators is supported by the finding that normal TGF-β1 and PTHrP suppression of type X collagen expression is significantly reversed in a dose-dependent fashion in the presence of Pb. This effect evidently was not mediated by BMP-6 (Bone Morphogenic Protein), an inducer of terminal differentiation known to partially reverse the inhibitory effect of PTHrP, because in the presence of Pb, PTHrP significantly suppressed BMP expression, while combined exposure to Pb and TGF-β1 increased BMP expression approximately 3-fold. Further experiments performed on chick sternal chondrocyte cultures, utilized PTHrP responsive (AP-1) and non-responsive (NF-κB) reporter constructs to

examine potential effects of Pb on signaling. While having no effect on the basal activity of the AP-1 reporter, Pb dose-dependently enhanced PTHrP induction of the responsive AP-1 reporter. Lead dose-dependently inhibited the basal activity of the non-PTHrP responsive, NF-κB reporter. Taken together, these studies demonstrate that Pb has an inhibitory effect on the process of endochondral bone formation and that the effects of Pb are likely from its modulation of growth factors and second messengers involved in cell signaling responses.

5.8.6 Bone Lead as a Potential Source of Toxicity in Altered Metabolic Conditions

Lead is avidly taken up by bone and incorporated into bone matrix, where a substantial amount can remain over the lifetime of an organism. The uptake and incorporation of Pb into bone during acute exogenous exposures may be of short term benefit by limiting the exposure of other, more sensitive tissues; however, this does not eliminate Pb from the system. Subsequent release of Pb from this endogenous storage can produce a lifetime of steady, low level Pb exposure during periods of normal bone remodeling, while elevated Pb release during times of increased bone metabolism and turnover (i.e., pregnancy, lactation, menopause, and osteoporosis) can elevate blood levels of Pb significantly, potentially to toxic concentrations. This is especially relevant when there is concurrent exogenous exposure to Pb, as current blood Pb levels are a composite of current and past Pb exposure. Of greater concern is the mobilization of Pb during pregnancy and subsequent transfer to the developing brain of the fetus across the poorly developed blood:brain barrier. Maternal Pb also appears in breast milk, providing further exposure of the infant to Pb during lactation. Currently, the majority of animal studies examining mobilization of Pb from bone stores have focused principally on elevation of Pb levels or transfer of Pb, rather than reporting toxic effects associated with these exposures. Note that in most instances the mobilization and elimination of Pb is much faster in laboratory animals than in humans. For example, as discussed in Section 5.8.3, Hac and Kruchniak (1996) reported approximately 64% of Pb given over a 12 week period remained in the bones of rats 64 days post exposure. Therefore, the caveats of experiments performed in small animals, especially when examining mobilization of Pb stores, must be taken into consideration.

5.8.6.1 Pregnancy and Lactation

Pregnancy, and to a much greater extent, lactation, place significant calcium demands on the mother as she provides all the necessary calcium requirements of the developing fetus/infant. During these times of metabolic stress, increased demineralization of maternal bone occurs to supplement demand, unfortunately accompanied by the concurrent mobilization and release of Pb stored in the maternal skeleton from past exposure. Studies in several animal models have shown that maternal bone Pb can be mobilized during pregnancy and lactation, ultimately being transferred to the fetus during gestation and breast feeding. Keller and Doherty (1980) administered radiolabeled Pb drinking water (200μg/mL) to female mice for 105 days prior to mating or 105 days prior to mating and during periods of gestation and lactation (total 160 days of exposure). The results suggested very little Pb was transferred from mother to fetus during gestation, however, Pb transferred in milk and retained by the pups accounted for 3% of the maternal body burden of those mice exposed to Pb prior to mating only. The amount of Pb retained in these pups exceeded that retained in the mothers, suggesting lactation effectively transfers Pb burden from mother to suckling offspring. Transfer of Pb from mothers was significantly higher when Pb was supplied continuously in drinking water, rather than terminated prior to mating. Considerably higher lactational transfer of Pb from rat dams compared to placental transfer has also been reported (Palminger Hallén et al., 1996). Continuous exposure of rat dams to Pb until day 15 of lactation resulted in milk Pb levels 2.5 times higher than in whole blood, while termination of maternal Pb exposure at parturition yielded equivalent blood and milk levels of Pb, principally from Pb mobilized from maternal bone.

Using rats chronically exposed to Pb in drinking water, Maldonado-Vega et al. (1996) studied intestinal absorption of Pb, its mobilization, and redistribution during lactation. In rats exposed to Pb 144 days prior to lactation, the process of lactation itself elevated blood Pb and decreased bone Pb, indicating mobilization of Pb from bone as there was no external source of Pb during the lactation process. Rats exposed to Pb for 158 days (144 days prior to lactation and 14 days during lactation) also experienced elevated BLLs and loss of Pb from bone. Lead exposure only during the 14 days of lactation was found to significantly increase intestinal absorption and deposition (17 fold increase) of Pb into bone compared to non-pregnant rats, suggesting enhanced absorption of Pb takes place during lactation. As in other previous studies, the highest concentration of Pb in bone was found in non-pregnant non-lactating control animals,

with significantly decreased bone Pb in lactating rats secondary to bone mobilization and transfer via milk to suckling offspring. Follow-up studies examining the influence of dietary calcium found when calcium was altered from the normal 1% to 0.05%, bone calcium concentration decreased by 15% and bone Pb concentration decreased by 30% during the first 14 days of lactation (Maldonado-Vega et al., 2002). In non-lactating rats on the 0.05% calcium diet, there were also decreases in bone calcium, but neither incremental bone resorption nor Pb efflux from bone, suggesting the efflux from bone during lactation was related to bone resorption. Of interest, enhancement of calcium (2.5%) in the diet of lactating rats increased calcium concentration in bone by 21%, but did not decrease bone resorption, resulting in a 28% decrease in bone Pb concentration and concomitant rise in systemic toxicity. In both studies, the authors concluded that Pb stored in bone should be considered a major source of self-intoxication and of exposure to suckling offspring.

In one of few studies showing a toxic effect, Han et al. (2000) demonstrated adverse effects in rat offspring born to females whose exposure to Pb ended well before pregnancy. Five week-old-female rats had been given Pb-acetate in drinking water (250 mg/mL) for five weeks, followed by a one month period without Pb exposure before mating. To test the influence of dietary calcium on Pb absorption and accumulation, some pregnant rats were fed diets deficient in calcium (0.1%) while others were maintained on a normal calcium (0.5%) diet. As expected, all Pb-exposed dams and pups had elevated blood Pb levels; however, pups born to dams fed the diet deficient in calcium during pregnancy had higher blood and organ Pb concentrations compared to pups from dams fed the normal diet. Significantly, pups born to Pb-exposed dams had lower mean birth weights and birth lengths than pups born to non-Pb-exposed control dams ($p < 0.0001$), even after confounders such as litter size, pup sex, and dam weight gain were taken into account. The authors concluded that while increases in dietary calcium during pregnancy are capable of reducing Pb accumulation in the fetus, they cannot prevent the decreases in birth weight and length associated with pre-maternal Pb exposure and subsequent mobilization. This has relevance in human pregnancy, as many women experience exposure to Pb during their lifetimes (especially during childhood) and mobilization of the Pb from bone stores during pregnancy could present toxic complications.

Within the last decade, an invaluable method to explore the kinetics of Pb transfer from bone to blood has been developed and evaluated (Inskip et al., 1996; O'Flaherty et al., 1998).

The method utilizes recent administration of sequential doses of Pb mixes enriched in stable isotopes (^{204}Pb, ^{206}Pb, and ^{207}Pb) to female cynomolgus monkeys (*Macaca fascicularis*) that have been chronically (1,300 to 1,500 µg Pb/kg body weight per day for ten years or greater) administered a common Pb isotope mix. The stable isotope mixes serve as a marker of recent, exogenous Pb exposure, while the chronically administered common Pb serves as a marker of endogenous (principally bone) Pb. From thermal ionization mass spectrometry analysis of the Pb isotopic ratios of blood and bone biopsies collected at each isotope change, and using end-member unmixing equations, it was determined that administration of the first isotope label allows measurement of the contribution of historic bone stores to blood Pb. Exposure to subsequent isotopic labels allowed measurements of the contribution from historic bone Pb stores and the recently administered enriched isotopes that incorporated into bone (Inskip et al., 1996). In general the contribution from the historic bone Pb (common Pb) to blood lead level was constant (~20%), accentuated with spikes in total blood Pb due to the current administration of the stable isotopes. After cessation of each sequential administration, the concentration of the signature dose rapidly decreased. Initial attempts to apply a single-bone physiologically based model of Pb kinetics were unsuccessful until adequate explanation of these rapid drops in stable isotopes in the blood were incorporated (O'Flaherty et al., 1998). Once revisions were added to account for rapid turnover of the trabecular bone compartment and slower turnover rates of cortical bone compartment, an acceptable model evolved. From this model it was reported that historic bone Pb from 11 years of continuous exposure contributes approximately 17% of the blood Pb concentration at Pb concentration over 50 µg/dL, reinforcing the concept that the length of Pb exposure and the rates of past and current Pb exposures help determine the fractional contribution of bone Pb to total blood Pb levels (O'Flaherty et al., 1998). The turnover rate for cortical (~88% of total bone by volume) bone in the adult cynomolgus monkey was estimated by the model to be ~4.5% per year, while the turnover rate for trabecular bone was estimated to be 33% per year.

Using the method of sequential stable isotope administration, Franklin et al. (1997) examined flux of Pb from maternal bone during pregnancy of 5 female cynomolgus monkeys who had been previously exposed to common Pb (approximately 1,100 to1,300 µg Pb/kg body weight) for about 14 years. In general, lead levels in maternal blood attributable to Pb from mobilized bone were reported to drop 29 to 56% below prepregnancy baseline levels during the

first trimester of pregnancy. This was ascribed to the known increase in maternal fluid volume, specific organ enlargement (e.g., mammary glands, uterus, placenta), and increased metabolic activity that occurs during pregnancy. During the second and third trimesters, when there is a rapid growth in the fetal skeleton and compensatory demand for calcium from the maternal blood, the Pb levels increased up to 44% over pre-pregnancy levels. With the exception of one monkey, blood Pb concentrations in the fetus corresponded to those found in the mothers, both in total Pb concentration and proportion of Pb attributable to each isotopic signature dose (common = 22.1% vs. 23.7%, ^{204}Pb = 6.9% vs. 7.4%, and ^{206}Pb = 71.0% vs. 68.9%, respectively). From 7 to 25% of the Pb found in fetal bone originated from maternal bone, with the balance derived from oral dosing of the mothers with isotope during pregnancy. Of interest, in offspring from a low Pb exposure control monkey (blood Pb <5 μg/100 g) ~39% of Pb found in fetal bone was of maternal origin, suggesting enhanced transfer and retention of Pb under low Pb conditions.

Clearly, the results of these studies show that Pb stored in bone is mobilized during pregnancy and lactation, exposing both mother and fetus/nursing infant to blood/milk Pb levels of potential toxicity. Of equal concern, a significant proportion of Pb transferred from the mother is incorporated into the developing skeletal system of the offspring, where it can serve as a continuing source of toxic exposure. The above study by Franklin et al. (1997) illustrates the utility of sequentially administered stable isotopes in pregnancy; however, its use may also be applicable in studies of lactation, menopause, osteoporosis, and other disease states where mobilization of bone and release of Pb stores occurs. Furthermore, given that isotopic ratios of common Pbs vary by location and source of exposure, when humans migrate from one area and source of exposure to another, it is possible to document changes in mobilized Pb, especially during times of metabolic stress.

5.8.6.2 Age/Osteoporosis

The age of an animal at the time of exposure to Pb has been shown to influence the uptake and retention of Pb by bone. In experiments to determine the influence of age on this process, Han et al. (1997) exposed rats for five weeks to 250 mg/L Pb-acetate in drinking water beginning at 5 weeks of age (young child), 10 weeks of age (mid-adolescence), or 15 weeks of age (young adult), followed by a 4 week period of without Pb exposure. An additional group of rats were exposed to Pb beginning at 5 weeks, but examined following an 8 or 20 week period after

cessation of Pb. Significantly lower blood and bone Pb concentrations were associated with greater age at the start of Pb exposure and increased interval since the end of exposure. However, young rats beginning exposure to Pb at 5 weeks and examined 20 weeks after cessation of exposure, still had bone Pb concentrations higher than those found in older rats only 4 weeks after cessation of exposure. This demonstrated that exposure to Pb at a young age leads to significant skeletal Pb accumulation and retention, despite the high rate of bone remodeling that occurs during growth and development at that time.

At the opposite end of the spectrum, Cory-Slechta et al. (1989) studied differences in tissue distribution of Pb in adult and old rats. Adult (8 months old) and old (16 months old) rats were exposed to 50 ppm Pb-acetate in drinking water for 11 months, at which time the experiment was completed. Bone (femur) Pb levels in older rats were found to be less than those in younger rats; however, blood lead levels were higher in the older rats. Of interest, brain Pb concentrations in the older rats exposed to Pb were significantly higher, and brain weights were significantly less than the brain Pb concentration and weights of unexposed older control rats or adult rats exposed to Pb, suggesting a potential detrimental effect. The authors suggested that a possibility for the observed differences in tissue concentrations of Pb was due to changes in the capacity of bone to store Pb with advanced age. In a subsequent study, Cory-Slechta (1990b) examined kinetic and biochemical responses of young (21 day old), adult (8 months old), and old (16 months old) rats exposed to Pb at 0, 2, or 10 mg Pb acetate/kg/day over a 9.5 month experimental period. Results suggested that older rats may have increased vulnerability to Pb due to increased exposure of tissues to Pb and greater sensitivity of the tissues to the effects of Pb. As in the previous study (Cory-Slechta et al., 1989), lower bone levels of Pb were present in older rats with concomitant elevated levels of Pb in brain and other tissues, supporting the hypothesis that exposure to Pb over a lifetime may contribute to deterioration of health in old age, potentially during times of heightened bone remodeling such as occurs during osteoporosis. In studies of bone Pb metabolism in a geriatric, female nonhuman primates exposed to Pb approximately 10 years previously, McNeill et al. (1997) reported no significant changes in bone Pb level over a 10 month observation period as measured by ^{109}Cd K X-ray fluorescence. The mean half-life of Pb in bone of these animals was found to be 3.0 ± 1.0 years, consistent with data found in humans, while the endogenous exposure level due to mobilized Pb was 0.09 ± 0.02 μg/dL blood. Results examining Pb accumulation in the bones of aging male mice suggest

low levels of bone Pb contributing to the osteopenia observed normally in C57BL/6J mice (Massie and Aiello, 1992). The mice were maintained on regular diet (0.258 ppm Pb) and water (5.45 ppb Pb) from 76 to 958 days of age. While the Pb content of femurs increased by 83%, no significant relationship was found between Pb and bone density, bone collagen, or loss of calcium from bone.

5.8.6.3 Weight Loss

The relationship between body mass and bone mass is highly correlated and during times of loss of body weight, such as dietary restriction, a concomitant loss of bone mass also occurs. It is therefore possible that Pb stored in bone from prior exposures could be released into the system as skeletal bone is mobilized and result in Pb toxicity. To examine the influence of weight loss on release of stored Pb, Han et al. (1996) first exposed rats to Pb in drinking water (250 mg/l of Pb as acetate) for 5 weeks, followed by a 4 week washout period without Pb to allow primarily accumulation in the skeleton. Rats were then randomly assigned to a weight maintenance group, a moderate weight loss group (70% of maintenance diet), or a substantial weight loss group (40% of maintenance diet) for a four week period. At the end of this experimental period the blood and bone levels of Pb did not differ between groups, however, the amount and concentration of Pb in the liver increased significantly. A follow up study in rats previous exposed to Pb for two weeks was undertaken to determine the effect of weight loss and exercise on the distribution of Pb (Han et al., 1999). They found weight loss secondary to dietary restriction to be the critical factor elevating organ Pb levels and, contrary to their first study, elevated blood levels of Pb. No significant difference in organ or blood Pb concentrations were reported between the exercise vs. no exercise groups. These studies suggest Pb toxicity could occur in those previously exposed to Pb during times of dietary restriction.

5.8.7 Bone and Lead Summary

Lead substitutes for calcium and is readily taken up and stored in the bone of experimental animals, potentially allowing bone cell function to be compromised both directly and indirectly by exposure. In general, relatively short term exposure of mature animals to Pb does not result in significant growth suppression, however, chronic Pb exposure during times of inadequate nutrition have been shown to adversely influence bone growth, including decreased bone density,

decreased trabecular bone, and growth plates. Exposure of developing animals to Pb during gestation and the immediate postnatal period has clearly been shown to significantly depress early bone growth in a dose-dependent fashion, though this effect is not manifest below a certain threshold. Numerous mechanisms for the toxic effect of Pb on bone have been explored using various animal models. Systemically, Pb has been shown to disrupt mineralization of bone during growth, to alter calcium binding proteins, and to increase calcium and phosphorus concentration in the blood stream, in addition to potentially altering bone cell differentiation and function by altering plasma levels of growth hormone and calciotropic hormones such as vitamin D_3 [1,25-$(OH_2)D_3$].

Bone cell cultures of both animal and human derivation have substantially contributed to the general understanding of the adverse effects of Pb on bone cell metabolism directly and its indirect effect on bone and bone cells by perturbation of numerous local and systemic factors. These in vitro studies have indicated that Pb is primarily taken up by osteoclasts and likely perturbs intracellular calcium homeostasis secondary to osteoclastic bone resorption. Bone cell proliferation is also inhibited. Exposure of bone cell cultures to Pb has been shown to impair vitamin D-stimulated production of osteocalcin, inhibit secretion of bone-related proteins such as osteonectin and collagen, and suppress bone cell proliferation, potentially by interference with such factors as GH, EGF, TGF-β1, and PTHrP.

Finally, several animal studies have suggested Pb stored in bone can serve as a continuing, endogenous source of exposure for an individual or can be transferred from mother to offspring during pregnancy and/or lactation, with potentially toxic consequences. Periods of extensive bone remodeling, (i.e., during weight loss, advanced age, altered metabolic state, and pregnancy and lactation) are all associated with mobilization of Pb stores from bone of animals. During pregnancy, transfer of Pb from mother to offspring has been documented, however, available evidence suggests a more significant transfer from mother to offspring occurs during lactation when the concentration of Pb in mother's milk can be several times higher than corresponding blood levels. Despite the extensive remodeling of bone that occurs during growth and development of young animals, a significant amount of Pb can be accumulated and retained during times of exposure.

5.8.8 Teeth – Introduction

There was little information in the prior 1986 AQCD relating lead exposure to adverse outcomes in the teeth of animals. At that time, the incorporation of Pb into teeth was recognized as was the fact that tooth Pb increased with age, proportional to the rate of exposure and roughly proportional to the blood Pb concentration.

Teeth consist of a hard outer layer of enamel, supported by an underlying layer of dentin, which itself is supported by a connective tissue known as the dental pulp. Enamel is the hardest substance in the body and the most highly mineralized, consisting of ~96% mineral (calcium hydroxyapatite substituted with carbonate ions) and 4% other organic materials, while dentin is only ~70% mineral. The formation of enamel (amelogenesis) occurs as a two stage process of organic matrix production with ~30% mineralization, followed by removal of water and proteins from the matrix with concurrent further mineralization. As in bone, Pb ions are apparently capable of substituting for calcium ions in the mineralizing tooth, becoming essentially trapped. However, unlike bone, the tooth, with subtle exceptions, does not undergo a remodeling process. Dentin formation (dentinogenesis) can be likened to endochondral bone formation, in that an unmineralized matrix (predentin, rather than cartilage) is laid down first, followed by mineralization to mature dentin. The cells responsible for amelogenesis and dentinogenesis, called ameloblasts and odontoblasts respectively, are similar to osteoblasts in that they respond to various signaling factors, secrete matrix proteins, and create an environment favorable to deposition of minerals. After enamel formation on a specific tooth is completed, ameloblasts are lost and no additional enamel is laid down with the exception of certain teeth in rodents. These teeth, typically incisors on rats, mice, and most other rodents, continuously erupt to offset the attrition that occurs with daily use. Therefore, the process of amelogenesis is ongoing, albeit confined to a localized area, throughout the life of the animals. For this reason rodents have been utilized extensively to examine the processes of amelogenesis and the influence of various toxic agents, such as Pb, on tooth development. Ameloblasts are especially sensitive to toxins and altered metabolic conditions and respond to such insults with disruption of enamel formation. When disruption occurs, defects in the enamel can occur, typically as a band of malformed or altered enamel. As described below, exposure of animals to various concentrations of Pb during tooth development is not only capable of creating distinctive marking of enamel ("Pb lines"), but may influence the resistance of the enamel to dental decay.

Within the dental pulp, a layer of odontoblasts continue to reside against the inner layer of the primary dentin for the life of the tooth. During this time the odontoblasts are systematically slowly putting down thin layers of secondary dentin, slowly decreasing the size of the pulp chamber with age. Lead present during this process has been shown to be readily taken up by this dentin layer, providing a potential marker of historic Pb exposure. Though the enamel is a non-living substance, it is not entirely inert. The external surface of enamel is more or less in a continuous state of flux or turnover as it chemically demineralizes from acids consumed or produced in the mouth by bacteria, followed by remineralization of demineralized enamel when contact with saliva supersaturated with calcium and phosphate ions occurs. Lead present during this process can easily be released from enamel and/or incorporated initially or back into it depending on the circumstances.

In summary, Pb has the potential to disrupt the various processes associated with formation of teeth, plus incorporate itself into all mineralized tooth tissues during formation. Posteruptively, Pb can become incorporated into the secondary dentin, and can be taken up or released from the outer surface layer of enamel during times of remineralization/ demineralization. As described below, exposure of animals to Pb has been associated with adverse dental outcomes.

5.8.9 Uptake of Lead by Teeth

As seen with bone, uptake of Pb into the teeth of animals has been demonstrated in a number of studies and by multiple routes of administration. Twenty four hours after a single intraperitoneal injection of radioactive Pb-203 (^{203}Pb, 1 μg/kg) to young (15 day suckling rats) and old (120 day) female rats, 0.7% of the injected dose was present in the four incisor teeth of the younger animals and 0.6% was present in the same teeth of the older animals (Momcilovic and Kostial, 1974). These percentages jumped to 1.43% and 0.88%, respectively, 192 hours after the injection, suggesting incorporation and retention of Pb by teeth is greater in younger animals than in adults, as found in bone. Lead has also been shown to be incorporated into incisors of rats exposed to airborne Pb. Grobler and coworkers (1991) exposed 6 week old rats to either "Clean Air" (0.05 μg Pb/m^3) or air containing 77 μg Pb/m^3 and found significant differences in the amount of Pb incorporated into the incisors of the animals. After 70 days, a mean of only 0.8 μg Pb/g of incisor dry mass was found in incisors from control animals, while

11.0 µg Pb/g was present in incisors from the 77 µg Pb/m^3 group. Exposure to air containing 249 µg Pb/m^3 for 28 days or to 1,546 µg Pb/m^3 for 50 days resulted in mean values of 13.8 and 153 µg Pb/g incisor dry weight of Pb incorporation, respectively, highlighting the fact that dose and length of exposure are determinates of amount of Pb contained in the teeth of these animals. Lead has also been shown to be taken up into the teeth of weanling rats whose mothers were exposed to Pb in drinking water. The offspring of pregnant rats exposed during gestation and lactation until 21 days post partum to water containing 0, 3, or 10 ppm Pb showed dose-dependent, significant increases in the Pb content of incisors, first molars, and second molars (Grobler et al., 1985). Taken together, these studies confirm the uptake of Pb into teeth as delivered by various means and suggest that maternal exposure can result in uptake in offspring, during gestation and/or lactation.

5.8.10 Effects of Lead on Enamel and Dentine Formation

Early microscopic studies by Eisenmann and Yaeger (1969) confirmed alterations in rat incisor enamel formation 7 days after a single SC dose of Pb (0.15 or 1.5 mM/100g animal weight); however, no effect was seen at the 0.075 mM/100g dose. Lead was found to have inhibited mineralization of both enamel and dentin, but only to a "mild to moderate" extent with the mineralization of dentin more affected. It was speculated at the time that Pb could affect the production of normal, mineralizable organic matrix; affect enzymes specific to enamel or dentin formation; affect crystal structure and/or growth; or affect a combination of these factors. In studies of dentinogenesis, incubation of fixed rat molar germs with Pb-pyrophosphate has shown localization of Pb to the mineralization front of dentin (i.e., the area of recently formed dentin), to the stratum intermedium, and to subodontoblastic cells, suggesting Pb may react with mineral components located in the mineralization zone or have a high affinity for these incompletely mineralized areas (Larsson and Helander, 1974). Localization of Pb was also seen at the area of the dentino-enamel junction. Similar examination of first molar germs from 3-day-old rats showed that Pb also localized to the periphery of dentinal globules (Larsson, 1974). A single injection of Pb-acetate (30 mg/kg body weight) produces an immediate (within 6 h) response in the growing dentin of the rat incisor, leading to the formation of a so-called "Pb line" (Appleton, 1991). A transient rise in serum calcium and phosphorus accompanied the injection, leading to speculation that lead may have been replacing these minerals in the apatite structure. However,

backscattered electron imaging of the Pb line showed it to be composed of continuous hypomineralized interglobular dentin with some incomplete fusion of calcospherites resulting in uneven mineralization, but no localized concentration of Pb was detectable. This is consistent with Featherstone and co-workers (1981) who reported that Pb incorporation during apatite synthesis was widely dispersed, rather than concentrated in areas of calcium deficiency. Once synthesis is complete, however, Pb is capable of entering calcium deficient areas in enamel, substituting for calcium (Featherstone et al., 1979). This is essentially the process that occurs during demineralization/remineralization of enamel. Appleton (1991, 1992) suggested that Pb has a direct effect on odontoblasts, creating a local disturbance of calcium metabolism, a process similar to that described in bone (Pounds et al., 1991). Interestingly, no ultrastructural changes in ameloblasts from rat pups whose mothers had been drinking water containing Pb was observed.

During the normal process of amelogenesis, water and proteins contained within the organic matrix are lost, leaving densely mineralized enamel. The removal of enamel proteins during this phase is facilitated by enamel proteinases, which are believed to degrade the proteins into smaller units capable of diffusing from the matrix. Using crude extracts from scrapings of rat incisor teeth, Gerlach and co-workers (2000a) demonstrated that Pb inhibited these proteinases in vitro at micromolar concentrations. In rats given drinking water containing Pb at either 0, 34, or 170 mg/L as Pb-acetate for 70 days, increased amounts of proteins were found in enamel matrix from animals exposed to Pb (Gerlach et al., 2002). Moreover, enamel microhardness analysis of upper incisors revealed a significant decrease in microhardness in regions of enamel maturation, but not in areas of fully mature enamel, suggesting Pb exposure mediates a delay in enamel mineralization. In adult rats with incisors trimmed to remove occlusal (biting) contact, a single IP dose of Pb-acetate (40 mg/kg) significantly delayed the continuous eruption of the incisor at all time points between 8 and 28 days after dosing, compared with controls (Gerlach et al., 2000b). It is of interest that delayed eruption of teeth in children living in areas of heavy metal contamination (Pb and zinc) has been reported previously (Curzon and Bibby, 1970).

5.8.11 Effects of Lead on Dental Pulp Cells

Hampered by a general lack of cell cultures specifically for teeth, there remains a paucity of information regarding both the cultures themselves and the effect of Pb upon such cultures. In a single in vitro study using a human dental pulp cell culture obtained from teeth extracted for orthodontic purposes, Thaweboon and co-workers (2002) examined the effects of three concentrations (4.5×10^{-5} M, 4.5×10^{-6} M, 4.5×10^{-7} M) of Pb-glutamate on cell proliferation, protein production, and osteocalcin secretion. Under serum free conditions (DMEM only) all concentrations of Pb significantly increased cell proliferation on day 1, day 3 and day 5 of exposure, as measured indirectly by mitochondrial dehydrogenase enzyme assay. In the presence of 2% fetal bovine serum only, the higher concentration of Pb significantly increased protein production, suggesting an influence of serum constituents on cell growth or binding of free Pb in the medium. Similar results were reported when rat osteosarcoma cells (ROS 17/2.8) were exposed to identical concentrations of Pb over 2-, 4-, and 6-day time points (Sauk et al., 1992). Concentrations of Pb less than 4.5×10^{-5} M concentration did not affect osteosarcoma cell proliferation in the presence of serum, but in the absence of serum 4.5×10^{-7} M Pb increased cell proliferation at day 4, while at day 6, 4.5×10^{-6} M Pb inhibited proliferation. Further testing of human dental pulp cells in serum-free conditions showed that Pb exposure caused dose-dependent decreases in intracellular protein and procollagen type I production over the 5-day period experimental period (Thaweboon et al., 2002). Short-term exposure of the cells to Pb significantly decreased osteocalcin production in a dose-dependent manner at 8- and 12-h exposure time points. These results suggest that Pb is capable of exerting multiple toxic effects on cells derived from human dental pulp.

5.8.12 Adverse Effects of Lead on Teeth—Dental Caries

In a recent review, Bowen (2001) highlighted 12 epidemiological studies that examined the association between Pb exposure and dental caries (decay), reporting that 8 studies supported the concept that Pb is a caries-promoting element. Unfortunately, the source and actual exposure to Pb and measurement of prevalence of caries varied greatly, providing less than completely satisfactory evidence in the opinion of the author. There is also a paucity of well-controlled animal studies examining this issue.

In an early study examining the effect of drinking solutions containing various metallic ions on dental caries in hamsters, Wisotzky and Hein (1958) reported post-eruptive ingestion of drinking water containing 0.5 mEq of Pb significantly increased caries scores in molar teeth of males after 84 days, but, perplexingly, not in females after 98 days of exposure. It should be noted that in animal studies such as these it is routine to maintain the animals on cariogenic or caries-promoting diets high in fermentable sugars. Clear evidence supporting Pb's role in enhancing susceptibility to dental caries was reported by Watson and co-workers in 1997. In their study, female rats were exposed to Pb in drinking water (34 ppm as Pb-acetate) as young adults, during pregnancy, and during lactation. Lead exposure of the subsequent offspring from the dams was, therefore, from transfer of endogenous Pb from dam to pup during gestation and lactation, with no further exposure after weaning. This pre- and perinatal exposure to Pb resulted in a significant, almost 40%, increase in the prevalence of dental caries over control animals. The study was significant for other reasons, as it mimicked the conditions found in many inner cities where young females are exposed to Pb in their environment and later transfer this Pb to their own fetuses during the extensive bone remodeling that occurs during pregnancy and lactation. The mean blood Pb level in the dams upon weaning was 48 μg/dL, which is not unlike upper levels reported in humans.

The mechanisms by which Pb enhances susceptibility to caries remain uncertain, though clearly altered mineralization and/or incorporation of Pb into enamel as described above could enhance its solubility in acid. Lead also appears in the saliva of rats at about 5% of the whole blood level and at about 61% of the plasma filtrate Pb level (Mobarak and P'an, 1984), providing an avenue for post-eruptive interaction with the exposed enamel in the oral cavity. Notably, decreased salivary flow has been reported in rats exposed to Pb, and decreased salivary function is known to increase caries risk. Stimulated parotid function was decreased by nearly 30% in the Pb-exposed offspring in the study by Watson and co-workers (1997), an effect that could have been mediated by the salivary gland requirement of intact parasympathetic and sympathetic nervous systems for normal development (Schneyer and Hall, 1970) and Pb's known adverse effect on neurotransmitters (Bressler and Goldstein, 1991). Acute infusion of 4 μg of Pb per min has been reported to significantly reduce pilocarpine-stimulated salivary secretion in rats over a 50-min period (Craan et al., 1984), while 24-day administration of 0.05% Pb-acetate significantly reduced the concentration of protein and calcium in pilocarpine-stimulated rat

submandibular saliva (Abdollahi et al., 1997). Of potential interest, postnatal exposure of rats to Pb (10 or 25 ppm in drinking water) and a caries-enhancing diet containing fluoride (sucrose containing 15 ppm fluoride) was not associated with an increased risk of dental caries, suggesting that Pb does not interfere with the protective effect of fluoride (Tabchoury et al., 1999). Clearly though, the effect of Pb exposure on salivary gland function and the mechanism by which Pb exposure enhances caries risk needs to be further explored.

5.8.13 Lead from Teeth as a Potential Source of Toxicity

Although no studies currently document the contribution of Pb incorporated into teeth as a source of endogenous Pb exposure, the potential exists during the process of exfoliation of the primary dentition. As described above (Section 5.8.9) Pb is avidly incorporated into the developing dentin and enamel components of teeth. Like bone, the uptake and incorporation of Pb into teeth during acute exogenous exposures may be of short-term benefit by limiting the exposure of other, more sensitive tissues, but, unlike bone, teeth do not undergo a gross remodeling process (the continuous, superficial demineralization/remineralization of the exposed tooth surfaces, principally enamel, are assumed here to be insignificant). However, during the exfoliative process, the erupting secondary tooth erodes away the root (composed of cementum and dentin) of the overlying primary tooth along with some surrounding alveolar bone. Any Pb incorporated into these portions of bone and primary tooth would be released by the erosive process, with the potential to produce highly elevated local concentrations of Pb in the proximity of remodeling alveolar bone and developing secondary teeth. A more modest contribution to circulating blood Pb would be predicted. Animal research in this area has been hampered, as most common rodents (i.e., rats, mice) are monophyodonts (have only one set of teeth). Although monkeys are an acceptable model, it is problematic how release of Pb stored in teeth could be differentiated from that of remodeling skeletal bones formed at a similar time point, plus the disproportionate size of the skeletal mass compared to the dentition may mask any contribution of Pb mobilized by exfoliation.

5.8.14 Teeth and Lead Summary

As found with bone, Pb substitutes for calcium and is readily taken up and incorporated into the developing teeth of experimental animals. Unlike bone, teeth do not undergo

remodeling per se and, with few exceptions, most Pb incorporated into tooth structure remains essentially in a state of permanent storage. Administration of high doses of Pb to animals has demonstrated the formation of a Pb line, visible in both the enamel and dentin and localized to areas of recently formed tooth structure. Within this Pb line, areas of inhibition of mineralization are evident in enamel and dentin. Lead has been shown to decrease cell proliferation and production of intracellular protein, procollagen type I, and osteocalcin in human dental pulp cells in culture. Studies of Pb exposure in adult rats have reported inhibition of post-eruptive enamel proteinases, delayed teeth eruption times, and decreased microhardness of surface enamel. During the process of enamel formation, Pb is apparently widely dispersed when first incorporated into the developing apatite crystal; however, post-formation, Pb is capable of entering and concentrating in calcium-deficient areas within the enamel. Whether Pb incorporation into the enamel surface compromises the integrity and resistance of the surface to dissolution, and ultimately increases risk of dental decay, is unclear. Numerous epidemiologic studies suggest Pb is a caries-promoting element. Animal studies (both post-eruptive Pb exposure and pre- and perinatal Pb exposure studies) support this concept, although the exact mechanism of action remains elusive. No animal studies have examined the role exfoliation of the primary dentition in release of Pb previously stored in tooth structure, though it is likely this process could serve as an additional source of Pb exposure in childhood.

5.9 EFFECTS OF LEAD ON THE IMMUNE SYSTEM

The immune system, along with the neurological system, has emerged as one of the more sensitive targets of Pb-induced toxicity. However, because Pb exposure at low to moderate levels does not produce overt cytotoxicity of immune cells, immune-associated health effects result from misregulation and shifts in functional capacity rather than profound lymphoid deficiencies. As a result, the most sensitive biomarkers of Pb-induced immunotoxicity are those associated with specific functional capacities as opposed to measures of cell enumeration and/or lymphoid organ pathology. This distinguishes Pb from some other types of immunotoxicants. The following sections provide a survey of the reported immune effects resulting from exposure to Pb in humans and animal models. In general, the focus is on those studies that have been reported since the 1986 AQCD (U.S. Environmental Protection Agency, 1986) was prepared and

have altered our understanding of lead-induced immunotoxicity and the associated immune-related health risks.

5.9.1 Introduction

The comparative development of the immune system in humans and animal models used for immunotoxicology was reviewed in recent years by Payne and Crooks (2002) and Holsapple et al. (2003). Pluripotent hematopoietic stem cells arise from uncommitted mesenchymal stem cells located in the spanochnopleure area near the heart and appear in the yolk sac (Holsapple et al., 2003). During human gestation, these stem cells first migrate at approximately 5 weeks and produce lymphoid and myeloid stem cells. Lymphoid stem cells can be found in the liver at approximately 7–8 weeks of gestation. In the mouse, the hematopoietic stem cells migrate to the liver on gestational day (GD) 10.

Migration of stem cells to the thymus occurs in humans about the 9th week of gestation and in mice on GD 11. The equivalent migration probably happens in the rat at GD 13 or later. Bone marrow lymphopoieis begins in humans about week 12 of gestation and in mice about GD 18. Immune development continues postnatally in humans as well as rodents. During embryonic development, immune maintenance of the pregnancy is important, and Th2 development is favored over Th1. Among other things, the capacity of dendritic cells to promote Th1 activity is dramatically suppressed in the newborn (Langrish et al., 2002). However, Th1 cytokines can be stimulated shortly after birth in humans (Malamitsi-Pichner et al., 2005). However, it is clear that, at birth, rodents lag behind in immune development compared with humans (Dietert et al., 2000; Holsapple et al., 2003).

Immune maturation continues in the thymus and bone marrow to give rise to the broad spectrum of myeloid and lymphoid cells that contribute to host defense and tissue homeostasis. The thymus-derived (T) lymphocytes provide regulatory cells facilitating a wide range of acquired immune responses and also produce cytotoxic T lymphocytes capable of attacking tumor and virally infected cells. Among regulatory T lymphocytes are at least two types of helper populations termed T helper 1 (Th1) and T helper 2 (Th2). The former regulatory cells promote immune responses helpful against intracellular pathogens, while the latter are important in defense against extracellular pathogens. However, skewing of the Th1/Th2 balance too far in

either direction is problematic in terms of health risk. Such skewing is a large factor in the consideration of lead-induced immunotoxicity (see Sections 5.9.2, 5.9.4, and 5.9.8).

B lymphocytes are named for the Bursa of Fabricius, an organ important in their development in avian species. They constitute the other major lymphoid cell type important in acquired immunity. B lymphocytes produce first membrane-bound and then secreted immunoglobulins (antibodies) that are a significant part of humoral immunity. Different classes of immunoglobulins produced during class switching, and promoted by different T lymphocyte cytokines, are tailored to be effective against different types of pathogens (e.g., viruses vs. extra-cellular parasites). The potential of Pb on B lymphocytes is discussed along with humoral immunity in Section 5.9.3.1.

Another lymphoid cell type is the natural killer (NK) cell. These cells function during innate immunity as a front line defense against tumor cells and virally infected cells. NK cells have the capacity to recognize a limited number of receptors on target cell surfaces, including the loss of Class I (major histocompatibility complex) proteins. Such self-protein identity loss is usually associated with viral infection of host cells. NK cells also produce cytokines capable of regulating macrophage and T cell activity and, in turn, NK cells can be activated by lymphoid-produced cytokines. Consideration of the effect of Pb on NK cells is presented in Section 5.9.8.

Myelomonocytic cells such as macrophages and polymorphonuclear leukocytes (neutrophils) are also important in innate immunity. Neutrophils are usually short-lived cells that are capable of leaving the circulation and migrating into tissues. From there they can phagocytize pathogenic targets, utilize phagolysosomes to destroy bacteria, and secrete significant quantities of reactive oxygen intermediates (ROIs) into the local environment. They are also capable of producing nitric oxide (NO) in most species. The impact of Pb on neutrophils is presented in Section 5.9.7.

Macrophages are much longer-lived and can perform many of the same functions as neutrophils. Unlike neutrophils, macrophages can inactivate much of the ROIs they produce internally. However, they can produce vast quantities of NO and have major functional roles in tissue homeostasis, lymphoid regulation, and antigen presentation. In fact, macrophages reside in virtually every tissue, although their morphology can vary widely and their function spectrum can be quite distinct among different specialized organs. Kupffer cells in the liver and alveolar

macrophages in the lungs are two examples of highly specialized forms of macrophages. Misregulated or misdirected macrophage activity is a major cause of immune-inflicted tissue damage. When the cells are activated within tissues and chronically overproduce proinflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) in addition to NO and ROIs, the result is usually tissue damage and loss of function, if not ultimately cancer. A classic example of the potentially destructive role of misregulated macrophages is found in the case of asbestos-induced pathology of the lung (Holian et al., 1997; Driscoll, 2000). Misregulation of macrophages is a major consideration in the case of Pb (discussed in Section 5.9.6).

Dendritic and Langerhans cells are related in lineage to macrophages. These cells are vitally important in antigen trafficking and presentation, particularly in lymph nodes and skin. However, far too little is known about their potential sensitivity to lead, largely because their isolation, complete phenotypic and functional characterizations, and inclusion in assessment methodologies are relatively recent developments within immunology.

The other major cell types important in a consideration of lead-induced immunotoxicity are basophils, eosinophils, and mast cells. Basophils are involved in various inflammatory reactions, but little is known about the direct effect of Pb on this cell population. Mast cells are fixed tissue cells surrounding the vasculature in many organs. These cells can secrete preformed highly vasoactive products with inflammatory potential (e.g., kinins and histamine) in response to cell-surface-initiated signals. Mast cells can be triggered by numerous signals including both substance P and immunoglobulin E (IgE). Because mast cell-induced inflammation is associated with IgE-mediated allergic reactions, these cells are important in the clinical ramification of lead-induced immunotoxicity. Eosinophils are a granulocytic cell type associated with Th2-driven inflammatory reactions. They frequently appear in association with allergic reactions and are regulated by numerous lymphoid cells as well as by mast cells. Remarkably little is known about the direct effects of Pb on eosinophil function despite the probable role of these cells in certain allergic manifestations following exposure to lead.

Life-stage related differences in immunotoxicological risk have been reviewed by several authors (Barnett 1996; Holladay and Smialowitz, 2000; Dietert et al., 2002; Holladay, 2005), and it seems clear that the vulnerability of the developing immune system to immunotoxic insult is significantly greater than that of the fully-matured and dispersed immune system for the vast

majority of immunotoxicants (Luebke et al., 2005). Dietert et al. (2000) and Holsapple et al. (2003) have considered the likely existence of critical windows during immune development when the immune system as a target may have increased sensitivity or increased resistance to xenobiotic-induced immunotoxic alteration. These windows correspond to different dynamic stages of functional development within the embryonic, fetal, and early neonatal immune system. One issue of immune development particularly pertinent to Pb is the fact that Th1 and Th2 functional capacities do not develop at the same time in either humans or rodents. The need to protect against maternal-fetal allogeneic reactions results in Th1 function being acquired largely after birth. Therefore, any environmental exposure that interferes with the rapid development of Th1 function might leave the individual with a Th2-biased immune system. The heavy metal Pb apparently represents one of the xenobiotics that are capable of suppressing Th1 capacity, resulting in dysregulated immune balance. This is discussed further in Sections 5.9.4, 5.9.8, and 5.9.10.

5.9.2 Host Resistance

Host resistance to disease has been used as an effective measure of the impact of environmental toxicants on immune function. Because different diseases require different combinations of immune effector functions for host protection, analysis of environmental modulation of host resistance across a spectrum of diseases can help identify clinically relevant immunotoxicity.

The 1986 AQCD presented a range of studies in which exposure to Pb inhibited host resistance to disease. Since the time of that report, few new infectious diseases have been added to the list of those that Pb is known to influence. Instead, a much broader understanding of the likely basis for the increased disease susceptibility to these pathogens has become evident. Additionally, recognition of an increased risk for some atopic and autoimmune diseases arising from lead-induced immunotoxicity has occurred in recent years. This is discussed under Section 5.9.8. Lead-induced alterations of host resistance against infectious and neoplastic diseases are considered in the following sections.

To date, there has been either no effect or an increased susceptibility to disease resulting from exposure to lead for virtually every infectious agent examined. Given the capacity of Pb to shift immune responses toward Th2, one might expect that enhanced resistance might occur for

diseases where robust Th2 responses were required. For example, an increased resistance against helminth parasitic disease might be hypothesized. However, this possible association has not been widely examined to date.

5.9.2.1 Viral Diseases

In general, exposure to Pb increases the susceptibility to viral infections. Studies include host resistance directed against the encephalomyocarditis virus (Gainer, 1977; Exon et al, 1979), Langat virus (Thind and Khan, 1978), and Semliki Forrest virus (Gupta et al., 2002). In the last example, oral dosing of Swiss mice with Pb-acetate (250 mg/kg for 28 days) significantly increased mortality to sublethal doses of the virus. Ewers et al. (1982) reported that occupational exposure to Pb resulted in an increased incidence of influenza cases among workers. In chickens administered Pb-acetate orally (20 and 40 mg/100g body weight) for 56 days, antibody production against Newcastle virus vaccine was reduced, while mortality against viral challenge was increased (Youssef et al., 1996). It seems likely that the reduced Th1 capacity (including effective CTL generation) combined with increased TNF-α, ROI, and prostaglandin E_2 (PGE_2) production by responding macrophages would contribute to increased tissue pathology but reduce viral clearance for many infections.

5.9.2.2 Bacterial Diseases

Most of the lead-associated host resistance research has been conducted on bacterial diseases. Hemphill et al. (1971) first described the increased susceptibility of mice exposed to Pb (250 μg given i.p. for 30 days) to *Samonella typhimurium*, while Selye et al. (1966) reported increased susceptibility of rats to bacteria endotoxins. Cook et al. (1975) found increased susceptibility of lead-exposed rats (2 mg/100g body weight given i.v. once) to both *Eschrichia coli* and *Staphylococcus epidermidis.*

The vast majority of studies have been conducted using the intracellular bacterium, *Listeria monocytogenes,* in mice. *Listeria* infection and host resistance to the disease have been well characterized. Essentially, this infection requires an effective antigen presentation (probably involving toll-like receptor 2 involvement), a robust response by activated macrophages leading to interlukin-12 (IL-12) and interferon-γ (IFN-γ) production and robust Th1 driven host protection (Torres et al., 2004; Lara-Tejero and Pamer, 2004). Ideally, activated

macrophages would produce NO in an effective response against *Listeria* (Ito et al., 2005). In the case of lead-induced immunotoxicity, everything works against this type of response. First, macrophages have severely suppressed NO production. Yet, overproduction of TNF-α, ROIs and PGE_2 leads to tissue inflammation and damage. The skewing of the response toward Th2 means that both IL-12 and IFN-γ are lacking. Excessive production of IL-6 and other pro-inflammatory cytokines results in what has been termed "sickness behavior" which involves both the immune and central nervous systems (Dantzer et al., 1998; Dyatlov et al., 1998a,b; Lawrence and Kim, 2000; Dyatlov and Lawrence, 2002). Lead-induced impairment in host resistance to *listeria* was reported by Lawrence (1981). CBA/J mice exposed orally to 80 ppm or greater of Pb-acetate for 4 weeks had 100% mortality (after 10 days) compared with no mortality for mice exposed to 0 or 16 ppm lead.

In an important study concerning individual variation to lead-induced immunotoxicity and host resistance, Kim and Lawrence (2000) demonstrated that neurological circuitry as it pertains to brain lateralized behavior could impact the effect of Pb on immune responses and host resistance to *Listeria*. Not surprisingly, this suggests that host genotype and epigenetic factors can be influenced by Pb exposure to the individual. Using female BALB/c mice, Kishikawa and Lawrence (1997) demonstrated that exogenously administered recombinant IL-12 (1 μg each for three days i.p.) could enhance production of IFN-γ as well as host resistance to *Listeria* in lead-exposed (2 mM in water for 3 weeks) mice. However, lead-exposed mice continued to have excess IL-6 production (part of the sickness behavior phenotype). The result with IL-12 validates the importance of the Th skewing and macrophage impairment induced by Pb on host resistance to certain diseases.

Additional bacterial infections in which Pb exposure has been reported to reduce host resistance include *Serratia marcesens* (Schlipkopter and Frieler, 1979) and *Pasteurella multocida* (Bouley et al., 1977).

5.9.2.3 Parasitic Diseases

Few studies have been conducted to date regarding the effects of Pb on host resistance to parasitic diseases. This is unfortunate as some parasitic disease challenges require effective Th2 responses for optimal resistance. Hence, it is not clear that Pb exposure would depress host resistance in every case (e.g., for helminth parasites). Since the AQCD in 1986, one study was

conducted examining the effect of Pb on the killing ability of *Leishmania enriettii* parasites in vitro by mouse macrophages (Mauel et al., 1989). The authors found that 30–100 mM Pb-acetate interfered with the killing ability of macrophages without producing macrophage cytotoxicity.

5.9.2.4 Tumors

The primary study concerning tumor immunity/tumor growth and Pb was already known at the time of the 1986 AQCD. In this study, male C57Bl/6 mice were exposed to Pb-acetate in the drinking water at concentrations of 0, 13, 130, or 1300 ppm. Moloney sarcoma virus (MSV)-induced tumor formation and growth were compared following the exposure of mice to Pb for 10-12 weeks. MSV-induced transplantable tumors were also used in this study. Primary tumor growth was enhanced in animals that received 130 and 1300 ppm of Pb vs. the control. However, all tumors regressed eventually. Most other studies involving Pb exposure and tumors describe the fact that Pb can exacerbate the ability of other toxins to promote tumor formation (Kobayashi and Okamoto, 1974; Hinton et al., 1979). Much of the tumor-promoting activity of Pb would seem to involve depressed Th1 and macrophage function as well as the promotion of excessive ROI release into tissues.

5.9.3 Humoral Immunity

The irony of Pb as an immunotoxicant is that the overall effects on humoral immunity are reasonably modest compared to those reported for macrophages and T lymphocytes (McCabe 1994). McCabe et al. (1991) discussed the fact that Pb is not profoundly cytotoxic for most immune cells yet can cause major functional shifts within the immune system as well as decreased host resistance to disease. In many cases, antibody production can remain robust in lead-exposed animals and humans. However, the nature and spectrum of the antibodies produced is the more significant cause for concern. Lead appears to alter the course of T lymphocyte-driven B cell maturation such that class switching may be skewed in lead-exposed animals and humans. If Pb dosage and duration of exposure is sufficient, antibody production may be depressed overall. However, with low-level Pb exposure, skewed isotype production is the greater health risk.

5.9.3.1 General Effects on B lymphocytes and Immunoglobulins

Despite the fact that T lymphocytes and macrophages appear to be the more sensitive targets of lead, the metal can alter B lymphocyte maturation and shift immunoglobulin production. The 1986 AQCD describes the fact that some early studies reported no effect of Pb on antibody production (Reigart and Graber, 1976; Ewers et al., 1982), while others reported a significant decrease in the humoral immune response (Koller, 1973; Koller and Kovaic, 1974; Blakley et al., 1980). In retrospect, this apparent discrepancy may have been caused by the various concentrations of Pb administered as well as variations in the duration of exposure. Additionally, as mentioned in the 1986 AQCD, the temporal relationship of Pb exposure to antigen challenge may be important.

In studies measuring generation of plaque forming cells (PFCs) against sheep red blood cells (SRBCs), Pb incubation with lymphocytes in vitro caused an increased response (Lawrence, 1981). In a comprehensive study using several strains of mice, Mudzinski et al. (1986) reported that Pb-acetate administered in the drinking water (10 mM for 8 weeks) elevated the response in the one strain (BALB/c mice) but failed to alter the humoral response to SRBCs (either PFCs or antibody titers) in all other strains. McCabe et al. (1990) reported that Pb caused an elevation in B cell expression of Class II molecules, thereby influencing B cell differentiation. Lead seemed to impact Class II molecule density at the cell surface via the levels of mRNA translational and/or the posttranslational stages of cell surface protein synthesis (McCabe et al., 1991).

Some human epidemiological and occupational studies have reported lead-associated differences in levels of circulating immunoglobulins. However, Tryphonas (2001) discussed the pitfalls of relying on total serum immunoglobulin in assessing immunotoxic effects in humans. Sun et al. (2003) reported that immunoglobulin M (IgM) and immunoglobulin G (IgG) were lower but that IgE was higher among females within their high-Pb group. Basaran and Undeger (2000) found that IgM, IgG, and some complement proteins were reduced among battery workers with high Pb exposure. Results of Undeger et al. (1996) were similar as well. In contrast, Sarasua et al. (2000) reported an elevation in immunoglobulin A (IgA), IgG, and IgM associated with environmental Pb exposure. Pinkerton et al. (1998) found no major effects but reported a significant lead-associated decline in serum IgG and an elevation in B cell percentage. In a human in vitro study, Borella and Giardino (1991) showed that Pb exposure caused an increased IgG production following stimulation of cells with pokeweed mitogen.

In more recent animal studies, Miller et al. (1998) and Chen et al. (1999) reported no effect on antigen-specific IgG titers against keyhole limpet hemocyanin (KLH) protein in F344 strain rats that had been exposed in utero to Pb (0–500 ppm Pb-acetate in drinking water).

It seems likely that Pb exposure may be capable of reducing serum immunoglobulin levels given sufficient dose and duration of exposure. However, the more critical issue pertains to the distribution of class and subclass of immunoglobulins produced after exposure to lead. Because Pb can alter the development of T cells involved in specific antigen responses, this can impact the spectrum of immunoglobulins produced in response to T-dependent antigens. As discussed in the following section, production of IgE (a class of immunoglobulin that is poorly represented in serum but of great clinical significance) is a central issue for lead-induced immunotoxicity. One additional health concern is the potential for Pb to enhance the likelihood of autoantibody production (Lawrence and McCabe, 2002; Hudson et al., 2003). This latter concern is discussed under Section 5.9.8.

5.9.3.2 IgE Alterations

One of the three predominant hallmarks of lead-induced immunotoxicity is an increase in IgE production. This can occur in the context of antigen-specific responses or as measured by total serum IgE. For this endpoint, the human and animal findings are very similar. Virtually all of the information concerning the capacity of Pb to elevate IgE production in humans and animals has been obtained since the 1986 AQCD. As a result, this represents a relatively new biomarker for lead-induced immunomodulation, and one not included in most animal or human studies conducted prior to 1990 (e.g., Wagerova et al., 1986).

Table 5-9.1 lists the studies reporting lead-induced elevation of IgE. The disease implications of lead-induced increases in IgE production are potentially significant and may help to address, in part, the allergy epidemic that has occurred in the last several decades (Isolauri et al., 2004). A relationship has been established between relative Th2 cytokine levels, serum IgE levels, and the risk of allergic airway inflammation (Maezawa et al., 2004; Cardinale et al., 2005). In fact, attempts to manage allergic inflammation use IgE as one of the major targets (Stokes and Casale, 2005). IgE levels are directly related to the production of Th2 cytokines such as interlukin-4 (IL-4), among others (Tepper et al., 1990; Burstein et al., 1991; Carballido et al., 1995; Takeno et al., 2004; Wood et al., 2004). The relationship between Th2 cytokines

Table 5-9.1. Recent Studies Reporting Lead-Induced Increase in IgE

Species	Strain/Gender	Age	In vivo Ex vivo	Lowest Effective Dose	Exposure Duration	Reference
Human	Both genders	Children	Yes	Not available	Not Available	Karmous et al. (2005)
Human	Both genders, 91% males	Adult	Yes	Not Available	Not Available	Heo et al. (2004)
Human	Females	Children	Yes	Not Available	Not Available	Sun et al. (2003)
Mouse	Balb/c males and females	Fetal	Yes	0.1 mM	3 days	Snyder et al. (2000)
Human	Both genders, 56% male	Juvenile	Yes	Not Available	Not Available	Lutz et al. (1999)
Rat	F344 females	Embryo – fetal	Yes	100 ppm	5 weeks to dam (2 and 3 gestational)	Miller et al. (1998)
Mouse	Balb/c females	Adult	Yes	50 µg 3x per week s.c.	3 weeks	Heo et al. (1996)
Human	Males	Adult	Yes	Not Available	Not Available	Horiguchi et al. (1992)

(e.g., IL-4), IgE levels, and allergic airway disease is supported through various pharmacological interventions in both animals and humans that either induce Th2 cytokine and promote allergic airway disease (Wu et al., 2004) or interfere with Th2 cytokine-driven IgE production and inhibit allergic inflammation (Holgate et al., 2005; Ban and Hettich, 2005). The production of IgE is of importance in terms of potential inflammation. Not only is the level of IgE a consideration, but also the expression of the Fc receptor for the epsilon (ε) chain of IgE on mast cells and basophils.

In humans, Karmaus et al. (2005) reported a positive association of blood Pb levels with serum IgE concentration among second grade children living near a waste incinerator or other lead-emitting industries. Sun et al. (2003) also found a positive association of blood lead and serum IgE levels among children in Taiwan. Lutz et al. (1999) reported a correlation of blood lead levels and serum IgE levels in children in Missouri from 9 months–6 years of age. This association appears to hold not only for children but also for adults. Heo et al. (2004) recently showed that battery workers with blood leads > 30 µg/dL differed significantly in serum IgE levels from those with blood leads < 30 µg/dL. Additionally, serum IgE concentration correlated with blood lead among the populations examined (r = 0.0872).

Animal data support this relationship between blood lead concentration and IgE level and further suggest that even very low-level Pb exposure early in development may produce elevated IgE production in the juvenile offspring. Miller et al. (1998) found that gestational exposure of rats to 100 ppm Pb-acetate in the drinking water could produce elevated IgE in the adult offspring. Snyder et al. (2000) showed that gestational and/or neonatal exposure of mice to Pb-acetate produced neonatal blood lead levels not above background (5.0 μg/dL), but nevertheless, could result in elevated IgE production in the juvenile mouse. In most cases, Pb exposures associated with elevated IgE were also associated with increases in IL-4 production by T cells (Chen et al., 1999; Snyder et al., 2000). This is consistent with the fact that high IL-4 production can predispose B lymphocytes to undergo a specific class switch for the production of IgE.

One importance of these findings is that, in each case, the elevation in IgE persisted long after blood Pb levels had returned to normal. This means that Pb exposure could occur early in life and produce an increased risk of later-life allergic disease with no residual evidence that the individual had ever been exposed to lead. This should provide a cautionary note for future human studies examining Pb body burden and immune function.

5.9.4 Cell-Mediated Immunity

Cell-mediated immunity (CMI) essentially involves all host resistance beyond the soluble components of defense, i.e., antibody and complement. CMI includes any action of the immune system that is a direct effect of leukocytes on neoplastic or virally-infected cells or against extracellular targets such as bacteria. Even macrophage functional processes involving antibodies, such as antibody-dependent cellular cytotoxicity (ADCC), are considered to be CMI. One of the hallmarks of CMI is that cellular activation is usually required for the effector cells to attack the target. In the case of macrophages, this is usually activation with the Th1-associated cytokine, IFN-γ.

For NK cells, activation can occur through various pathogenic components such as double stranded RNA. However, recently Borg et al. (2004) showed that mature dendritic cells produced a Th1-promoting cytokine, IL-12, and this in turn activates NK cells to produce the further Th1-promoting cytokine, IFN-γ. Interleukin-18 (IL-18) produced by macrophages is also an activator of NK cells, facilitating Th1-promoting cytokine release while interleukins-2 and -15 (IL-2, IL-15) are growth factors for NK cells. NK cells would appear to be relatively

resistant to the effects of Pb compared to some T lymphocytes and macrophages. For a detailed consideration of the effects of Pb on NK cells, see Section 5.9.7.

Cytotoxic T lymphocytes are generated in response to antigen presentation delivered with Th1 cytokines. These cells are capable of mediating antigen specific destruction of neoplastic and virally-infected cells via binding and release of cytolytic proteins into the intracellular space. Frequently, the most effective antigen targets of CTLs are the early viral proteins produced in the first phase of host cell infection by viruses. IL-12, produced largely by dendritic cells, appears to be important in the generation of antigen CTL cells and IFN-γ produced by Th1 lymphocytes. NK cells are a potent regulator of CTL activity. Cell signaling via certain toll-like receptors on antigen presenting cells seems to have a role in determining the nature of the Th activation (Th1 vs. Th2) and can, therefore, influence the extent of CTL production.

Because T lymphocytes and their regulator and effector functions are so critical in CMI, the maturation of thymocytes within the thymus microenvironment and the selection of repertoire among the maturing T lymphocytes are crucial issues for potential developmental immunotoxicants. In fact, lead seems to be capable of disrupting several aspects of T cell maturation, activation, and repertoire usage (McCabe and Lawrence, 1991; Heo et al., 1998; Miller et al., 1998; McCabe et al., 2001, Lee and Dietert, 2003).

5.9.4.1 General Effects on Thymocytes and T lymphocytes

In general, cells of the T cell lineage appear to be relatively sensitive to the toxic effects of Pb compared to other lymphoid populations. At the time of the 1986 AQCD, there was some understanding of this sensitivity. However, there appear to be considerable differences in sensitivity across various T cell subpopulations (McCabe and Lawrence, 1991; Heo et al., 1996; 1997; 1998). This was largely unknown when the prior AQCD was prepared as the partitioning of T helper cells into functionally distinct subpopulations (e.g., Th0, Th1, and Th2) was not known until the latter part of the 1980s. The differential impact of Pb on T helper cell populations and on immune balance was established during the 1990s. This has become one of the four hallmarks of lead-induced immunotoxicity.

Original observations of both in vivo and in vitro T-dependent immune responses in the presence of Pb suggest that T helper function, as well as the spectrum of cytokines produced, are skewed toward the Th2. The cytokine skewing is discussed as well in Section 5.9.5.3. Smith

and Lawrence (1988) have shown that Pb can inhibit antigen presentation and stimulation of a T cell clone of the Th1 phenotype. McCabe and Lawrence (1991) were the first to show that this was caused by the novel capacity of Pb to inhibit Th1 stimulation while promoting presentation to Th2 clones. Heo et al. (1996) provided both in vitro and in vivo results supporting this immunomodulation of lead. Cytokine skewing accompanied the differential stimulation of Th cells.

Using naïve splenic CD4+ T cells derived from D11.10 ovalbumin-transgenic mice, Heo et al. (1998) developed T cell clones in vitro in the presence of lead. The authors found the T cells that developed from the naïve precursors were significantly skewed toward the Th2 helper phenotype and away from the Th1 phenotype. If IL-4 was inhibited with the addition of anti-IL-4 to the cultures or if the Th1- promoting cytokine IL-12 was added exogenously to the culture, the effects of Pb could be largely overcome. This study provided firm evidence that Pb can directly promote Th2 development among precursor Th(0) cells and impair development of Th1 cells. Among its effects, Pb enhanced adenyl cyclase activity and increased the levels of cAMP. The authors suggested that Pb may influence cell signaling in such as manner as to promote the Th2 pathway.

Beyond the biasing of immune responses at the level of the T lymphocyte based on Th1/Th2 balance, Pb has the capacity to bias usage of certain Vβ genes (Vβ 5, Vβ 7, and Vβ 13) among T lymphocyte clones in mice (Heo et al., 1997). This is of concern, as it suggests that exposure to Pb may alter the T cell repertoire and skew its representation. Heo et al. (1997) discussed the fact that many autoimmune diseases are characterized by a disproportionate usage of certain Vβ genes. Different autoimmune conditions are associated with the differential overabundant usage of a specific Vβ gene. They suggest that this feature of lead-induced T lymphocyte immunotoxicity may contribute to and enhance the risk of autoimmunity.

Lee and Dietert (2003) exposed the developing thymus of embryonic day 12 (E12) chickens to Pb-acetate (single injection of 400 μg) and evaluated the capacity of thymocytes (ex vivo) from juvenile chickens to produce IFN-γ. They found that embryonic exposure at doses that impair juvenile delayed type hypersensitivity (DTH) also inhibit IFN-γ production. Similarly, IFN-γ production was decreased when thymocytes from juvenile chickens were exposed to Pb in vitro (0.45 μM). However, in vitro exposure of thymic stroma to Pb did not result in suppression of control thymocyte IFN-γ production in co-cultures. There is a suggestion

that the balance of reproductive hormones in early life may influence the impact of Pb on developing thymocytes (Hussain et al., 2005).

5.9.4.2 Delayed Type Hypersensitivity

The DTH assay is an in vivo assay requiring antigen-specific T lymphocytes to be primed, expanded, and then recruited to a local site of antigen deposition. The most common application of the DTH is the tuberculin assay for TB in humans. The assay has a long history of application in immunotoxicology, and its utility within the national toxicology program assessment in the mouse has been previously reported (Luster et al., 1992). The assay is known to depend largely on Th1 participation and is, therefore, an effective measure of Th1-dependent function. However, there are at least two different portions of the response that are under somewhat separate control. Priming and expansion of the antigen-specific T lymphocytes is largely Th1 dependent. However, recruitment of T lymphocytes to the periphery involves a variety of locally-produced chemotactic signals that may not be under the same regulation. In fact, Chen et al. (1999) showed that a commonly used chelator for Pb poisoning (succimer, meso-2,3-dimercaptosuccinic acid [DMSA]) fails to restore lead-induced suppression of DTH in rats, because the chelator itself somehow interferes with the production of chemotactic factors necessary for T lymphocyte recruitment. The DTH assay is also generally useful in questions of possible developmental immunotoxicity, because of the natural skewing toward Th2 that occurs during gestation through birth and the issue of effective Th1 functional acquisition in the newborn.

Lead-induced suppression of the DTH response is one of the four hallmarks of lead-induced immunotoxicity. At the time of the 1986 AQCD, the capacity of Pb to suppress DTH function was already known from two studies conducted during the late 1970s. However, the association of the function with Th1 help had not been established. Muller et al. (1977) were among the first to demonstrate lead-induced suppression of DTH. Using mice, these investigators administered Pb-acetate i.p. for 30 days prior to assessment of primary and secondary DTH responses against SRBCs. Both primary and secondary responses were severely depressed following exposure to Pb, even at the lowest dose tested (0.025 mg). Faith et al. (1979) exposed developing Sprague-Dawley rats to Pb-acetate in the drinking water (lowest dose at 25 ppm) first via the dams during gestation and through weaning and then with direct exposure

of the offspring until 6 weeks of age. In this case, the purified protein derivative (PPD) of tuberculin was used as the antigen compared against the saline injection control. Rats administered the lowest dose of Pb evaluated (producing a BLL of 29.3 µg/dL) had a significantly reduced DTH response. Laschi-Loquerie et al. (1984) measured the contact hypersensitivity reaction against picryl chloride in mice that had received 0.5 mg/Kg Pb via s.c. administration. Lead administration was given from 3-6 days in duration at varying times relative to the sensitization period. These investigators reported that Pb suppressed the DTH type of response regardless of the window (before or during sensitization) in which it had been administered.

More recently, Miller et al. (1998) found that female F344 rats gestationally exposed to 250 ppm of Pb-acetate in drinking water had a persistently reduced DTH reaction against KLH protein. Chen et al. (1999), Bunn et al. (2001a,b,c) and Chen et al. (2004) had similar findings in studies that included both the F344 and CD strains of rats. In the last study conducted in F344 rats, a BLL of 6.75 µg/dL at 4 weeks of age, postgestational exposure to Pb-acetate (250 ppm in drinking water) was associated with depressed DTH against KLH in the 13-week-old adult female offspring (Chen et al., 2004). McCabe et al. (1999) were among the first to draw attention to the relationship between lead-induced suppression of DTH and the prior observations of lead-induced Th skewing. These authors gave varying doses of Pb-acetate in drinking water (32,128, 512, 2048 ppm) to female BALB/c mice for 3 weeks prior to measuring the DTH against SRBCs. They found that the 512 ppm dose producing a BLL of 87 µg/dL significantly impaired the DTH response. Antigen routes proved to be important as Pb depressed DTH when an i.v. primed with SRBCs was used, but not when SRBCs were administered i.p. Timing of Pb administration was found to be important relative to the capacity to depress the DTH response. Lee et al. (2001) showed that Pb-acetate (200 µg) administered in ovo to chicken embryos at 9 days of incubation failed to depress juvenile DTH against bovine serum albumin (BSA), but when the same dose of Pb was administered 3 days later producing the same BLL, juvenile DTH was severely reduced. Using the latter model, embryonic administration of exogenous thymulin was found to partially restore juvenile DTH function following embryonic exposure to Pb (Lee and Dietert, 2003).

Regarding developmental sensitivity of the DTH response to lead-induced immunosuppression, parallel findings were obtained in the developing rat (CD strain females)

(Bunn et al., 2001c) in agreement with those found in the chicken. Administration of 500 ppm Pb-acetate during gestational days 3 to 9 or 15 to 21 produced no DTH effect compared with DTH suppression in the corresponding adult offspring. As shown in Figure 5-9.1, the sensitivity of the DTH response to Pb appears to develop sometime between days 9 and 15 of rat embryonic development. Apparently, the status of the developing thymus may be a consideration in the capacity of Pb to impact the subsequent DTH response. This is discussed further in Section 5.9.10.

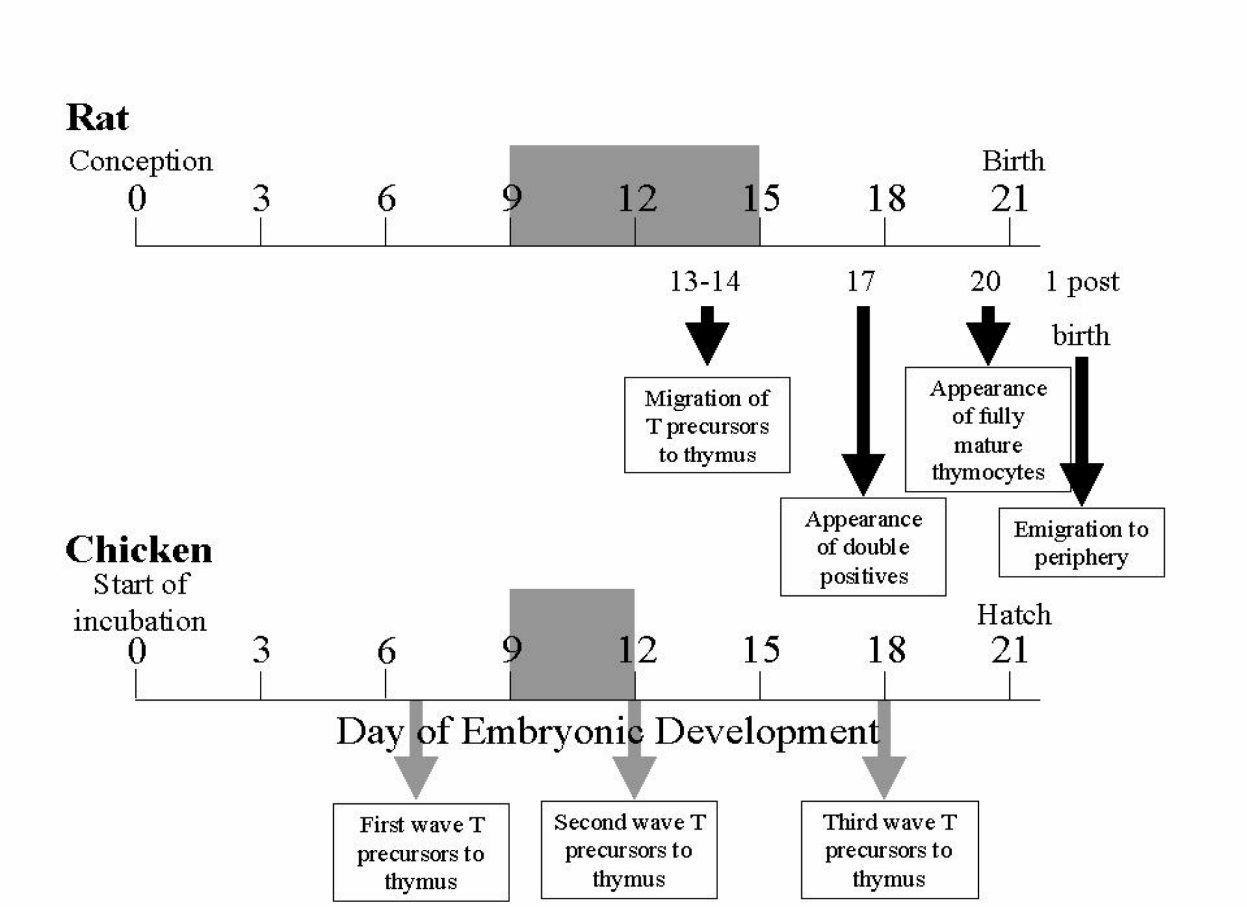


Figure 5-9.1. Windows during prenatal development (days postconception for rat) or embryonic development (days postincubation initiation for chicken) during which sensitivity of DTH to lead emerges.

It should be noted that in several studies, lead-induced suppression of the DTH response was associated with reduced capacity to produce the Th1 cytokine, IFN-γ (Chen et al., 1999; Lee et al., 2001).

5.9.4.3 Other T-Dependent Cell-Mediated Immune Changes

The in vitro response of T lymphocyte populations to various mitogens (e.g., Concavavalin A [ConA], Phytohemagglutinin A [PHA]) has been used as a surrogate measure of antigen-driven T lymphocyte stimulation. The impact of Pb on these parameters is presented in Section 5.9.5. Another T cell response altered by exposure to Pb is the mixed lymphocyte response (MLR). This in vitro assay is a measure for the responsiveness of T cells to the presentation of allogeneic major histocompatibility complex (MHC) molecules by antigen presenting cells. The in vivo correlate of the MLR is usually considered to be the graft vs. host (GvH) reaction. Several investigators have reported Pb alteration of the MLR as summarized in Table AX5-9.4.

McCabe et al. (2001) demonstrated that Pb at very low physiological concentrations (0.1 μM or approximately the equivalent of 10 μg/dL) in vitro significantly enhanced the proliferation and expansion of murine alloreactive CD4+ T lymphocytes in the MLR reaction. In fact, the resulting population was found to have a high density of CD4 molecules on the cell surface-making them phenotypically similar to memory T lymphocytes. The authors hypothesized that lead-induced creation of an exaggerated pool of memory-type T lymphocytes (possessing a lower threshold required for subsequent activation) would be problematic for the host. In a study using Lewis strain rats, Razani-Boroujerdi et al. (1999) also found evidence for lead-induced stimulation of the in vitro MLR response. In this case, both the alloreactive mixtures of cells as well as syngeneic mixtures were elevated in proliferation when cultured in the presence of Pb-acetate (e.g., 50 ppm or approximately 131 μM). When concentrations of Pb were significantly higher (200 ppm or greater), proliferation was inhibited in these cultures.

Figure 5-9.1 illustrates the developmental appearance of initial sensitivity for Pb-induced suppression of the DTH function. The mid-embryonic developmental window is the time during which the capacity of Pb to impair later-life DTH responses first emerges. Earlier pulsed exposure to Pb fails to impair juvenile and/or adult DTH despite the continuing of presence of Pb in the embryo. However, during the second half of embryonic development the embryo becomes remarkably sensitive to lead-induced suppression of DTH. Both the rat and chicken are similar in this window of emerging Th1-dependent functional sensitivity. Thymus-related developmental events are indicated along with the emergence of DTH functional sensitivity to

lead. Information was derived from Gobel (1996), Vicente et al. (1998), Dunon et al. (1999), Dietert et al., (2000), Bunn et al. (2001c), Lee et al. (2001) and Holsapple et al. (2003).

5.9.5 Lymphocyte Activation and Responses

Many of the broader functional ramifications of Pb exposure on lymphocytes are discussed under Sections 5-9.3 and 5-9.4. However, the capacity of Pb to directly alter lymphoid responses is a significant component of lead-induced immunotoxicity and is summarized within the present section. Lymphoid responses are usually assessed in terms of proliferation and activation (functional changes). One of the recent endpoints reflecting functional status is the production of cytokines. These both autoregulate the producing cells and significantly impact the activity of other immune and nonimmune cells carrying the appropriate receptors. The spectrum and levels of cytokines produced by a population of immune cells tends to reflect their capacity to regulate the host immune response.

5.9.5.1 Activation by Mitogens

The capacity of certain plant- and bacterially derived products to stimulate lymphoid populations to enter the cell cycle and undergo mitogenesis has been used for decades to assess the potential capacity of lymphocytes to receive proliferation signals and expand their population. Among the mitogens employed within the Pb exposure studies are the T lymphocyte subpopulation mitogens, PHA and Con A; the dual T and B cell mitogen, pokeweed mitogen (PWM; the B lymphocyte mitogen derived from gram-negative bacteria, lipopolysaccharide (LPS), and the B cell mitogen, *Staphylococcus aureus* enterotoxin (SE). It should be noted that these mitogens do not necessarily stimulate all T lymphocytes or all lymphocytes but, instead, stimulate selected populations of the cells. The mitogens react with a large array of cell surface molecules producing cross-linking and appropriate signal transduction to initiate mitogenesis. In the case of the plant-derived mitogens, lectins, numerous glycoproteins and glycolipids carrying the correct carbohydrate residues serve as the cell surface binding sites for cross-linking. Mitogen stimulation in vitro has been used as a surrogate for antigen-driven stimulation and proliferation of antigen-specific T and B cell clones. However, it should be noted that while the assays have been used for decades, there are now more specific assays utilizing more functionally relevant cell surface receptors to assess lymphoid activation potential.

The 1986 AQCD has an extensive review of mitogenic responses of lymphocytes following both in vivo and in vitro treatment by lead. The results at that time showed no clear pattern. At low to moderate levels, Pb was potentially co-mitogenic for some cells and at very high concentrations could suppress proliferation. Little has changed in conclusions for this assessment measure since the 1986 report. The most significant findings from the mitogenic studies are that at doses encountered physiologically Pb is not a potent cytotoxic agent for most immune cells. At low concentrations, it can marginally stimulate lymphoid mitogenesis. However, as one examines more refined subpopulations of lymphocytes than what were able to be identified prior to 1986 (e.g., Th1 vs. Th2 clone of T lymphocytes), it becomes clear that Pb can promote expansion of some lymphoid populations while suppressing others.

Annex Table AX5-9.5 for this section summarizes results of Pb effects on mitogen-stimulated proliferation of lymphoid populations.

5.9.5.2 Activation via Other Receptors

In recent years, lymphoid activation and population expansion has been measured using the triggering of specific T and B cell surface receptors (e.g., CD3 on T cells) as well as antigen-driven proliferation of T cell clones known to be specific for the antigen in question. The latter has provided the opportunity to simulate in vivo lymphoid activation and antigen-driven proliferation by using receptors in vitro, which are more physiologically relevant than those activated by plant lectins. Because Pb does not cause profound population loss across the entire population of T or B lymphocytes, these more refined and functionally-relevant assay systems have enabled a much clearer picture to emerge concerning lead-induced changes in lymphoid population than was available for the 1986 AQCD report.

Smith and Lawrence (1988) and McCabe and Lawrence (1991) utilized antigen-specific mouse T clones. They found that Pb directly promoted antigen presentation and stimulation of the T cell clones when these clones were Th2 cells. However, when the Th1 clones were used, Pb suppressed the antigen-specific presentation signal. In the McCabe and Lawrence study, direct comparisons were made between Th1 and Th2 clones specific for mouse allogeneic MHC molecules. These studies provided the first clear picture of the differential effects of Pb on Th1 vs. Th2 cells. Several studies since these have verified this major effect of Pb (Heo et al., 1996; 1997, 1998). Many of these later studies utilized the transgenic mouse strain (DO11.10 OVA-tg)

that carries T cells specific for a peptide fragment of ovalbumin. These enabled the same comparisons to be made with the presentation of a soluble protein antigen as the stimulating signal. Heo et al. (1998) showed that Pb not only selectively stimulates Th2 cells and suppresses Th1 cells but that it preferentially causes precursor Th0 cells to mature into Th2, rather Th1 cells, as well. Additionally, the T cell clones in the presence of Pb are skewed in terms of their usage of Vβ genes (as reflected in their cell surface receptors) (Heo et al., 1997). This is of particular concern relative to the risk of autoimmunity. More recently, McCabe et al. (2001) examined Pb exposure in the context of the allogeneic MLR against allogeneic MHC molecules. In vitro exposure to Pb (as low as 1.0 μM) enhanced the primary MLR response, but not the secondary MLR response and not the mitogenic response using PHA. Significantly, the T cell clones that emerged from the primary MLR were in greater proportion than normal and were of the specialized phenotype CD4-plus high density ($CD4+^{high}$). Because these fit the phenotype of memory cells, it is likely that an overabundance of memory cells was produced during the primary response, where the antigen may be of lesser biological significance than in a secondary response. The authors discussed the fact that Pb may cause T cells to respond under conditions of low antigen concentration, which could waste valuable and limited resources by generating T memory cell clones when they are not needed (against unimportant antigens) or even increase the risk of autoimmune responses by altering the threshold requirements for stimulation. The putative mechanisms suggested for the differential effects of Pb on Th cells are presented in Section 5.9.9.

5.9.5.3 Cytokine Production

At the time of the 1986 AQCD, immune cytokines were essentially absent from the information available for consideration. Only the antiviral interferons (α,β) had been examined among studies available for that report. Therefore, one of the most important effects of Pb on the immune system, i.e., Pb-induced cytokine production was not known at that time.

Most studies since 1986 have shown that Pb exposure at low to moderate levels causes a significant shift in the production of Th1 vs. Th2 cytokines with the bias toward the latter. Hence, production of IFN is decreased and IL-12 is inadequate for effective host resistance. In contrast, production of IL-4, IL-6, and, frequently, interlukin-10 (IL-10) is elevated. Table 5-9.2 illustrates the studies reporting shifts in cytokine production induced by lead.

Table 5-9.2. Studies Reporting Lead-Induced Shifts in Th1 vs. Th2 Cytokines

Species	Strain/ Gender	Age	Cytokine Alterations	In vivo/ Ex vivo	Lead Dose/ Concentration	Duration of Exposure	References
Rat	F344 Females	Embryo-fetal	↑IL-4 ↓IFN-γ splenic lymphocytes	Yes	250 ppm in water to dams	2 weeks prior and 3rd week of gestation for dam	Chen et al. (2004)
Human	Males	Adults	↑ IFN-γ PHA stimulated peripheral blood lymphocytes	Yes	Not available	Not available	Mishra et al. (2003)
Chicken	Cornell K females	Embryonic	↓IFN-γ stimulated thymocytes	Yes	400 μg	Single injection E12	Lee and Dietert (2003)
Mouse	Balb/c	Neonatal/ Juvenile	↑IL-6 serum during infection	Yes	0.5 mM in water to dams and their pups	4 weeks (3 via dams)	Dyatlov and Lawrence (2002)
Rat	CD females	Fetal	↑IL-10	Yes	550ppm in water to dams	6 days via gestation of dam	Bunn et al. (2001c)
Chicken	Cornell K females	Embryonic	↓IFN-γ	Yes	50 μg	Single injection	Lee et al. (2001)
Mouse	Balb/c male	Adults	↑IL-6 serum during infection in certain groups	Yes	2 mM	8 weeks	Kim and Lawrence (2000)
Mouse	NOD Autoimmune strain adult	Adult	↓IFN-γ, no change long term ↓TGF-β intestinal levels	Yes	Oral 10 mM and ovalbumin antigen	10 days	Goebel et al. (2000)
Mouse	C57 Bl/6 females NOD autoimmune strain females	Adult	No effect on gut balance in normal mice ↓TGF-β in autoimmune mice	Yes	0.5 mg/kg injection and oral ovalbumin	6 injections over 2 weeks	Goebel et al. (1999)
Rat	F344 females	Embryo-fetal	↓IFN-γ ↑IL-10	Yes	250 ppm to dams	2 weeks before and 3rd week of gestation	Chen et al. (1999)

Table 5-9.2 (cont'd). Studies Reporting Lead-Induced Shifts in Th1 vs. Th2 Cytokines

Species	Strain/ Gender	Age	Cytokine Alterations	In vivo/ Ex vivo	Lead Dose/ Concentration	Duration of Exposure	References
Mouse	DO11.10 ova-tg, ova mice and RAG knockouts	Adult	↓IFN-γ	No	25 μM	3 days	Heo et al. (1998)
Rat	F344 females	Embryo-fetal	↓IFN-γ	Yes	500 ppm to dams	2 weeks before and 3rd week of gestation	Miller et al. (1998)
Mouse	Balb/c ByJ females	Adult	↓IFN-γ ↑IL-6	Yes	2 mM	3 weeks	Kishikawa et al. (1997)
Mouse	Balb/c and DO11.10 ova-tg mice	Adult	↓IFN-γ ↓IFN-γ/IL-4 ratio	Yes	50 μg each injection (s.c.) 3 per week	2 weeks	Heo et al. (1997)
Mouse	Balb/c ByJ female or male	Adult	↓IFN-γ ↑IL-4	Yes	50 μg each injection (s.c.) 3 per week	2 weeks	Heo et al. (1996)
Mouse	Balb/c ByJ female or male	Adult	↓IFN-γ ↑IL-4	No	10 μM – 50 μM	2 days	Heo et al. (1996)

(Please note that TNF-α production is considered in the macrophage section, Section 5.9.6). These shifts in cytokine production are remarkably consistent, occur even at low levels of exposure, and are reported following both in vivo and in vitro exposure to lead. Furthermore, the effects are persistent even when exposure to Pb was restricted to early development and cytokine assessment was performed in the subsequent juvenile or adult (Miller et al., 1998; Bunn et al., 2001c; Lee et al., 2001; Chen et al., 2004).

The only exceptions to lead-induced biasing in favor of Th2 occur in the reports by Goebel et al. (2000) and Mishra et al. (2003). In the latter case, the authors attributed this difference (in humans) to the very high Pb levels considered in the study. In the prior case, Goebel et al. (2000) saw a local bias to Th1 in the intestinal tract of a specialized autoimmune diabetes-prone strain of mice (NOD) but not in normal mice. Initially, the Pb-induced cytokine skewing favored Th2 (after 1 day), but this shifted to Th1 with more prolonged Pb exposure (after 10 days). Loss of oral tolerance accompanied this long-term shift. These results suggest that in most cases, lead-induced skewing would favor Th2. But with some genotypes or additional disease conditions, an imbalance may occur in the direction of a gut-associated Th1 environment, increasing risk for loss of oral tolerance and the potential for increased food allergies.

One ramification for the capacity of Pb to promote Th2 cells is the impact of elevated IL-4 on IgE. It seems clear that lead-induced overproduction of IgE (seen in virtually all animal models examined as well as humans) is directly linked with the overproduction of IL-4. Excessive IL-4 and the resulting IgE production increases the risk for IgE-mediated atopy and asthma.

Additionally, Kishikawa et al (1997) demonstrated that administration of the potent Th1-promoting cytokine, IL-12, to lead-exposed mice can restore the balance of Th1 (IFN-γ) vs. Th2 cytokines (e.g., IL-6), reduce corticosterone levels, and enhance host resistance in *Listeria*-infected mice. This observation supports the critical role of Th1/Th2 balance in overall risk to host resistance against disease presented by Pb disruption of that balance.

5.9.6 Macrophage Function

Macrophages represent a diverse population of cells that play critical roles in both host defense and tissue homeostasis. Macrophage subpopulations provide a front line of defense

against bacteria, parasites, viruses, and tumors via the innate immune response. Additionally, they are important in tissue repair and remodeling as well as in the removal of senescent cells. Some forms of macrophages are efficient in the processing of antigens and the presentation of antigen fragments to T lymphocytes. Additionally, macrophages can regulate lymphoid activity through the secretion of a variety of cytokines and through the production of various immunomodulatory metabolites (e.g., NO, ROIs) and the products of the cyclooxygenase and lipoxygenase pathways.

Because macrophages can be found residing in most tissues, lead-induced modulation of macrophage functional capacity has the potential to alter overall organ function. Macrophages originate in the bone marrow from pluripotent stem cells that give rise to both the monocyte-macrophage lineage as well as polymorphonuclear leukocyte populations. Bone marrow-derived macrophages mature under the influence of various cytokine growth factors to become the full array of mature cell subpopulations. Various investigators have examined the effects of lead on the maturation of macrophages in vitro as well as on the functional capacity on fully mature cells both in vitro and in vivo. Blood monocytes represent a functional, yet not fully specialized, form of macrophage. As a result the influence of environmental toxicants on monocytes may not be fully predictive of the effects of the same toxicants on splenic or alveolar macrophages, glial cells, or Kupffer cells.

Because macrophages give rise to several specialized populations, e.g. Kupffer cells in the liver, glial cells in the brain, and various skin macrophage populations, it is important to realize that different specialized macrophage populations are likely to have somewhat different sensitivities to lead, as well as potentially different responses following exposure. Not surprisingly, blood monocytes may not always be an appropriate model to accurately predict the outcome of lead-induced immunotoxicity for alveolar macrophages following an inhalation exposure.

The 1986 AQCD identified macrophages as a significant target for lead-induced immunotoxicity. Research since the mid-1980s has served to underscore this point. The understanding of lead-induced alterations in macrophage function has increased significantly since the prior AQCD report. The following sections describe the reported immunotoxic effects of lead on macrophages. It should be noted that for a number of endpoints, such as lead-induced alterations in the production of NO, ROIs and TNF-α, there is a general consensus among a

majority of immunotoxicology studies and agreement with the effects described for the cardiovascular system (see Chapter 5.5).

5.9.6.1 Nitric Oxide (NO) Production

Nitric oxide is a short-lived metabolite produced in large quantities by macrophages during cellular activation. The enzyme responsible is an inducible form of nitric oxide synthase (iNOS), which, utilizing a bioptrin cofactor, converts the amino acid arginine into NO and citrulline. A competing alternative pathway utilizing arginine leads to the production of polyamines, which themselves are immunomodulatory for lymphocytes. Nitric oxide is critical in the defense against certain infectious agents, including various bacteria.

Among the most sensitive immunomodulatory effects of Pb exposure is the capacity to impair NO production by macrophages (Table AX5-9.6). Several research groups have shown that in vitro as well as in vivo exposure to Pb results in significantly reduced production of NO (Tian and Lawrence, 1995, 1996; Chen et al., 1997; Lee et al., 2001; Pineda-Zavaleta et al., 2004 [also reviewed in Singh et al., 2003]). Similar results were obtained in human, mouse, rat and chicken. Depression of NO production capacity usually occurs shortly after exposure to lead. However, the long-term effects of Pb on NO production following very early life exposure are less clear (Miller et al., 1998; Chen et al., 1999; Bunn et al., 2001a).

Tian and Lawrence (1996) have hypothesized that because very low Pb concentrations (in vitro equivalents to 10 μg/dL) can impair NO production, impaired NO production may be responsible for reduced host resistance to *Listeria* seen among lead-exposed rodents as well as for lead-induced hypertension among humans (Pirkle et al., 1985). Indeed, impaired NO production by macrophages seems to be one of the more sensitive endpoints for immediate lead-induced immunotoxicity.

5.9.6.2 Other Functional Alterations

TNF-α Production

Early studies identified the fact that Pb exposure could predispose animals for a dramatically increased sensitivity to bacterially-derived endotoxin (Trejo et al., 1972; Filkins and Buchanan, 1973; Schlick and Friedberg, 1981).

It is now known that the increased sensitivity to endotoxin is linked to the capacity of Pb to increase production of TNF-α among macrophages (Dentener et al., 1989; Zelikoff et al., 1993; Guo et al., 1996; Miller et al., 1998; Chen et al., 1999; Krocova et al., 2000; Flohe et al., 2002). Studies in mouse, rat, rabbit, and human provide a clear indication that one effect of Pb on macrophages is to boost production of the proinflammatory cytokine TNF-α. While most studies examined the immediate effects of Pb exposure on TNF-α production, studies by Miller et al. (1998) and Chen et al. (1999, (2004) showed that the effects of early gestational exposure to Pb on macrophages could persist well into later life, including adulthood. Additionally, Chen et al. (1999) showed that chelation of Pb with succimer in developing female rats in utero could eliminate the persistent effect of elevated TNF-α production in the adult offspring. Flohe et al. (2002) found evidence that lead-induced elevation in TNF-α production is sensitive to both PKC signaling as well as to protein production. While the production of TNF-α can be elevated following exposure to lead, the expression of the receptor for TNF-α (TNF-R) was also increased during the in vitro exposure of human blood monocytes to Pb-chloride (Guo et al., 1996). Therefore, the combined effect of elevated cytokine production by macrophages as well as increased receptor expression would be expected to contribute to problematic inflammatory responses.

Production of Other Proinflammatory Cytokines

Several studies have indicated that macrophage production of cytokines (or that levels of cytokines known to be produced primarily by macrophage populations) is altered after exposure to lead. These vary somewhat, depending upon the exposure protocol and the source of macrophages examined. In addition to the previously discussed elevation of TNF-α by lead, the most significant and consistent lead-induced effects seem to involve elevated production of the other major proinflammatory cytokines, interleukin-1β (IL-1β) and IL-6. Increased production of IL-6 following exposure to Pb has been reported by Dyatlov and Lawrence (2002), Flohe et al. (2002), Kim and Lawrence (2000), Krocova et al. (2000), Kishikawa and Lawrence (1998) and Kishikawa et al. (1997). Because IL-6 is a proinflammatory cytokine, its increased production following Pb exposure has the potential to influence many different tissues. Dyatlov et al. (1998a,b) provided evidence that lead, IL-6 and LPS can combine to exert a significant impact on the permeability of the blood brain barrier as well as the properties of brain neurons and

endothelial cells. Lead-induced elevation of IL-1β production has been reported by Dyatlov and Lawrence (2002). It is probable that enhanced co-production of IL-1β and IL-6 would increase the likelihood of local tissue inflammation.

Production of Reactive Oxygen Intermediates (ROIs)

Reactive oxygen intermediates (ROIs) are important metabolites in the capacity of macrophages and other inflammatory cells to kill invading bacteria and to attack cancer cells. However, increased overall production or inappropriate triggering of ROI release by macrophages can be a major contributor to tissue damage and the oxidation of cell surface lipids as well as DNA. The latter is one mechanism through which improperly regulated macrophages can actually increase the incidence of cancer. Results from many studies suggest that lead-exposure of macrophages can increase the release of superoxide anion and/or hydrogen peroxide at least shortly after exposure. Key studies are summarized in Table AX5-9.6.

In a recent study on environmentally exposed children in Mexico, Pineada-Zavaleta et al. (2004) reported that production of superoxide anion by directly activated (interferon-gamma + LPS) monocytes was directly correlated with blood Pb level. This was in contrast with the effect of arsenic, which had a negative association. In other studies involving low levels of exposures, Zelikoff et al. (1993) demonstrated that rabbits exposed to Pb via inhalation had pulmonary macrophages that produced elevated levels of both H_2O_2 and superoxide anion upon stimulation in vitro. In an in vitro study, Shabani and Rabani (2000) reported that Pb nitrate exposure produced a dose dependent increase in superoxide anion by rat alveolar macrophages. Baykov et al. (1996) fed BALB/c mice dietary Pb and found that peritoneal macrophages had an increased spontaneous release of H_2O_2.

Other studies have reported no effects of Pb on superoxide anion production when a long recovery period was included following in vivo exposure (Miller et al., 1998) as well as negative effects of Pb on oxidative metabolism by certain macrophages or macrophage cell lines (Castranova et al., 1980; Hilbertz et al., 1986; Chen et al., 1997). These somewhat different results suggest that the subpopulations of macrophages examined (e.g., alveolar vs. splenic vs. peritoneal) and the timeframe of assessment relative to exposure may be important factors in the effect of Pb on ROI production.

The biological importance of increased ROI production by lead-exposed macrophages should not be underestimated. Fernadez-Cabezudo et al. (2003) demonstrated that the potent antioxidant, vitamin E could protect TO strain mice against some lead-induced immunosuppressive alterations. Hence, macrophage-associated oxidative damage following exposure to Pb may be a mitigating factor in nonlymphoid organ lead-induced pathologies.

Arachidonic Acid Content and Prostaglandin Production

Archidonic acid (AA) is a major surface component of many cells, including macrophages, and is the precursor of cyclooxygenase and lipoxygenase metabolites. As a result, the specific AA content of membranes and the capacity of macrophages to produce immunomodulatory metabolites from AA are important to overall health of the individual. One of the findings since 1986 concerning lead-induced modulation of macrophage function is the impact of Pb on PGE_2 production. One study (Knowles and Donaldson, 1990) reported that diets supplemented with Pb at 500 ppm and fed to chicks produced an increase in the percentage of AA included in cell membranes. Such an increase would be expected to raise the risk of overall inflammation.

Several groups have reported that Pb exposure increases macrophage production of the immunosuppressive metabolite PGE_2. Lee and Battles (1994) reported that mouse macrophages exposed to Pb (10 μM) in vitro had elevated basal PGE_2 production, but under some stimulatory conditions, had decreased production of PGE_2. When Knowles and Donaldson (1997) fed Pb to turkey poults in the diet at a level of 100 ppm, macrophage production of prostaglandin F2 (PGF_2), PGE_2 and thromboxane production were all significantly elevated vs. the control. Flohe et al. (2002) showed that exposure of mouse bone marrow-derived macrophages to Pb-chloride resulted in increased production of PGE_2 that correlated with increased mRNA production for the necessary enzyme, prostaglandin H synthase type-2.

Tissue Homeostasis

In an important observation reflecting the impact of lead-induced immunotoxicity on nonlymphoid tissues, Pace et al. (2005) showed that neonatal exposure of mice to Pb-acetate via drinking water (0.1 ppm for 6 weeks, both through maternal nursing and direct) produced a significant reduction in the testicular macrophage population. This correlated with increased

estradiol levels in the testis and reduced male reproductive performance. The authors hypothesized that lead-induced alteration among testicular macrophages is linked to an impaired tissue environment that likely includes increased oxidative stress, apoptotic somatic cells, and reduced fertility of males.

Colony Formation and Population Distribution

The ability of bone marrow-derived macrophages (BMDM) to form colonies in response to certain growth factors (e.g., colony stimulating factor-1 [CSF-1]) is a property related to the growth and differentiation of subsequent macrophage populations. Kowelenko et al. (1991) found that exposure to CBA/J female mice to Pb-acetate (0.4 mM in drinking water for 2 weeks) reduced colony formation of macrophages in response to CSF-1. Infection of the mice with *Listeria* only exacerbated this effect of lead. The same authors (Kowelenko et al., 1989) had previously demonstrated that when BMDM were cultured in vitro with Pb-chloride (0.1 μM), colony formation was significantly impaired. These combined results suggest that exposure to Pb can impair the generation of macrophage populations as well as modulate the functional spectrum of fully matured macrophages. Bunn et al. (2001a) reported that gestational exposure of CD rats to 50 ppm Pb-acetate via the drinking water of the dams resulted in female adult offspring with a significantly decreased percentage (58% reduced) of circulating monocytes. A 100 ppm dose of Pb-acetate produced a significant reduction (74% reduced) in the absolute numbers of monocytes as well. The blood lead level at birth associated with the decreased percentage of macrophages in the adult offspring was 8.2 μg/dL. In general agreement, Lee et al. (2002) reported a significant decrease in the absolute numbers of circulating monocytes and polymorphonuclear leukocytes (PMNs) in juvenile female chickens exposed in ovo on embryonic day (E) 12 to 200 μg Pb-acetate. The corresponding blood lead level at hatching was 11.0 μg/dL. However, in this case, the lead-induced reduction in monocytes and PMNs was only seen in concert with an airway viral infection (viral stressor) and not in the resting uninfected animal.

Antigen Presentation and Lymphoid Stimulation

Exposure to Pb influences the interaction between macrophages and T lymphocytes, and as a result, the capacity of macrophages to support T lymphocyte proliferation and activation can

be altered as well. Kowelenko et al. (1988) found that mouse macrophages exposed to Pb (both in vivo and in vitro) can induce an increased proliferative response of T lymphocytes in co-culture but that antigen-specific stimulation of primed T cells is significantly reduced. Lead-suppressed antigen presentation capabilities of mouse macrophages were also reported by both Smith and Lawrence (1988) and Blakley and Archer (1981).

Chemotaxis

Chemotactic activity of macrophages is an important function required for the directed migration of macrophages to sites of infection and tumor growth. However, it is a functional capacity that has not been systematically examined within the lead-immune literature. Using female Moen-Chase guinea pigs, Kiremidjian-Schumacher et al. (1981) showed that Pb chloride exposure of peritoneal macrophages in vitro (10-6 μM) inhibited the electrophoretic mobility of the cells.

Phagocytosis and Clearance of Particles

Phagocytosis of targets and removal/clearance of dead cells and particles are major functions of macrophages. However, phagocytosis can involve a variety of different cell surface receptors on macrophages, depending upon both the nature of the target encountered and the subpopulation of macrophages examined. In general, phagocytic capacity of macrophages seems to be relatively insensitive to lead-induced immunomodulation compared with the effects on NO and TNF-α production.

However, differences in outcome in phagocytosis evaluations are likely to be based on the differences in the source of macrophages used and their relative activation state at the time of assessment. A few studies have described significant effects on phagocytosis, but these have usually relied upon phagocytosis mediated through the Fc receptor on macrophages. Because cell adherence to surfaces may be influenced negatively by Pb (Sengupta and Bishali, 2002), impairment of phagocytosis may also involve some lack in efficiency with macrophage anchoring to substrates. De Guise et al. (2000) reported no effect on bovine macrophage phagocytosis of latex beads by Pb at in vitro treatment concentration of 104 M. This was in contrast with suppressive effects of both cadmium and mercury. Using Sephadex-elicited peritoneal macrophages derived from young turkeys fed 100 ppm Pb in the diet, Knowles and

Donaldson (1997) found a 50% reduction in the percentage of phagocytic macrophages using SRBC targets. The activity per phagocytic macrophage was also reduced.

Kowolenko et al. (1988) studied the effect of Pb-acetate at 10 mM in the drinking water of CBA/J mice. They reported no effect on phagocytosis of *Listeria monocytogenes* targets, yet they found an overall decreased resistance to *Listeria.* When the same investigators exposed peritoneal and splenic macrophages to Pb in vitro (100 μM), they also found no significant effect of Pb on phagocytic activity. Jian et al. (1985) reported that New Zealand white rabbit-derived alveolar macrophages exposed to Pb in vitro at 10^{-5} M concentration were significantly impaired in the phagocytosis of opsonized chicken erythrocytes (Fc receptor-mediated phagocytosis). Trejo et al. (1972) reported that a single i.v. injection of Pb (5 mg/rat) into male Sprague Dawley (SD) strain rats produced an inhibition in the phagocytic capacity of Kupffer cells.

Several studies have reported a decreased clearance capacity of the reticuloendothelial system following in vivo exposure to lead. Filkins and Buchanan (1973) found that injection of 5 mg of Pb-acetate i.v. into male Holtzman strain rats produced reduced carbon clearance. Similarly, Trejo et al. (1972) reported that a single i.v. injection of Pb (2.5 mg) into male SD strain rats significantly reduced clearance of colloidal carbon.

In contrast, Schlick and Friedberg (1981) found that 20 μg/kg Pb-acetate in a single i.p. injection of NMRI strain mice significantly increased the clearance of India ink. Ironically, oral administration of Pb for 10, but not 30, days of 10 μg/kg resulted in an increase in clearance activity. Difference in route of Pb administration may be a factor in the different results obtained.

Induction of Heat Shock Proteins

One study (Miller and Qureshi, 1992), using a macrophage cell line, reported that exposure of macrophages (MQ-NCSU) in culture to Pb-acetate (1000 μM) induced the same set of four heat shock proteins as when the macrophages were subjected to thermal stress. This result fits the hypothesis that Pb produces a profound immunomodulatory effect in macrophages that has similarities with the exposure of macrophages to certain pathogens.

Apoptosis

Significant differences exist in the literature concerning the potential role of Pb in the apoptosis of macrophages. The difference may be based on the exposure methodologies (in vivo vs. in vitro) as well as the source of macrophages utilized. De la Fuente et al. (2002) found that human monocytes exposed to Pb in vitro at high concentrations did not undergo apoptosis. This was in direct contrast with the apoptosis-promoting effects of cadmium in the same assessment protocol. In contrast, Shabani and Rabibani (2000) exposed rat alveolar macrophage to Pb nitrate in vitro and found that 60 μM concentration produced a significant increase (2x) in DNA fragmentation after 3 to 24 h in culture.

5.9.7 Granulocytes and Natural Killer (NK) Cells

Other cell types important in innate immunity, as well as in immunoregulation, are the lymphoid population of natural killer cells and granulocytes, including PMNs (i.e., neutrophils). Neither population appears to be a major target for lead-induced immunotoxicity, although both may be influenced indirectly via immune cell-cell interactions as well as by changes in cytokine production. Among the two, neutrophils may be the more sensitive cell type based on assays conducted to date. For neutrophils, several groups have reported alteration in chemotactic activity following exposure to lead. Queiroz et al. (1993) found impaired migration ability of neutrophils from battery workers occupationally exposed to lead. Likewise, Valentino et al. (1991) had a similar observation among male occupationally exposed workers. Lead exposure of young SD strain rats can increase the population of neutrophils (Villagra et al., 1997), although, as the authors indicated, this does not necessarily afford enhanced host protection against disease. Baginski and Grube (1991) reported that human neutrophils exposed to Pb had increased killing capacity, probably via increased release of ROIs despite having reduced phagocytic capacity. This would fit the same general profile as the effects of Pb on macrophages. Therefore, neutrophils may contribute to lead-induced tissue inflammation and damage via increased ROI release. Yet, their effectiveness in protection against disease challenge may be no greater following exposure to Pb, because some impairment in chemotaxis and phagocytosis has been reported as well.

Yucesoy et al. (1997) reported that either Pb exposure or simultaneous exposure to Pb and cadmium in human workers did not impair NK cytotoxicity activity. This finding was supported

by studies using in vivo exposure to Pb in rats (Kimber et al., 1986) and mice (Neilan et al., 1983). Therefore, it would appear that NK cells are not a prime target associated with lead-induced immunotoxicity, although more subtle effects may certainly exist within the cell type.

Eosinophils represent an important granulocytic cell type in type 2 associated inflammatory and allergic reactions. However, few studies have examined Pb exposure and eosinophil activity. Villagra et al. (1997) reported that exposure of female juvenile SD rats to Pb [four alternate-day s.c. injections of 172 mg/g body wt Pb-acetate] increased the degranulation of eosinophils (in animals given estrogen 1 day later). Such a response would be expected to contribute to increased inflammation.

5.9.8 Hypersensitivity and Autoimmunity

At the time of preparation of the 1986 AQCD, little was known about the potential for Pb to influence the risk of allergic and autoimmune diseases. However, since the early 1990s, a significant number of studies have all pointed toward the fact that Pb causes a profound dysregulation of the immune system. It skews the balance of responses in directions that reduce certain host defenses against infectious diseases while enhancing the risk of allergic and autoimmune disease. Lead exposure at low to moderate levels appears to alter T lymphocyte responses in such a way as to increase the risk of atopy, asthma, and some forms of autoimmunity. Increased IgE production following exposure to Pb is among the most frequently reported immune alterations. Elevated IgE levels would be an associated risk factor for atopy and allergic disease. Several investigators have discussed the fact that Pb is a likely risk factor associated with the increased incidence of childhood allergic asthma (Miller et al., 1998; Heo et al., 1998; Snyder et al., 2000; McCabe et al., 2001; Dietert et al., 2004; Transande and Thurston, 2005) as well as later life allergic disease (Heo et al., 2004). Joseph et al. (2005) observed no association for childhood BLL and risk of asthma among an African-American population. However, results on other populations from this study, including those involving Caucasian children with BLLs above 5 µg/dL, led the authors to call for further studies into the possible linkage of early life lead exposure and risk of asthma (Joseph et al., 2005).

As described by McCabe et al. (1991) and discussed by Dietert et al. (2004), lead-induced immunotoxicity is novel in that profound cellular toxicity is not evident following exposure at low to moderate exposure concentrations. In fact, antibody responses overall are usually

unaffected or may be increased depending upon the class/isotype measured. However, the functional responses mounted following Pb exposure do not reflect the normal immune balance that would otherwise occur. This dysregulation can alter the risk of certain autoimmune diseases based on several observations. Holladay (1999) has considered the importance of the timing of exposure and the fact that early life exposure may establish the immune profile that then contributes to later disease including autoimmunity.

Hudson et al. (2003) reported that exposure to Pb can exacerbate systemic lupus erythmatosus (SLE) in lupus-prone strains of mice. In contrast with the effect of mercury, these authors found that for lupus, Pb exposure would not induce this autoimmune condition in genetically resistant mice but would increase severity of the disease in genetically prone animals. The authors noted some gender effects within certain strains (e.g., NZM88). Using early in ovo exposure to Pb (10 μg/egg), Bunn et al. (2000) found that Pb-acetate-exposed male chicks could be induced to produce autoantibodies against thyroglobulin, which were not present in acetate-exposed controls. No lead-induced alteration was observed in females that were predisposed to mount anti-thyroglobulin responses. The gender effect is intriguing in that autoimmune thyroiditis in genetically predisposed strains is always more severe in females than in males.

Two lines of evidence suggest that the capacity of Pb to influence the risk of autoimmunity is not always associated with simply a strict shift from Th1 to Th2 responses. Hudson et al. (2003) discussed the fact that lupus is not purely a Th2-mediated disease, but rather seems to occur under conditions associated with skewing in either direction. McCabe et al. (2001) found that Pb can increase the stimulation of alloantigen reactive T cells (where macrophage processing of antigen is required) but not enhancement of T cell clonotypic responses against either mitogens or superantigens (where processing is not required). This suggests that the role of Pb in influencing risk of autoimmune disease goes beyond a simple consideration of Th1/Th2 balance. In fact, Goebel et al. (2000), studying mucosal immunity, reported that administration of Pb-chloride to NOD strain mice produced a gut cytokine microenvironment that was skewed toward Th2 over the short run, but later was shifted toward Th1 with increased production of IFN-γ. This shift to Th1 was accompanied by a loss of tolerance and capacity to mount an immune response against a diet-associated protein (chicken ovalbumin). The authors proposed that reduction of the capacity for oral tolerance would predispose an individual toward autoimmune disease.

Finally, Waterman et al. (1994) and El-Fawal et al. (1999) have described the production of autoantibodies against neural proteins in both battery workers and rats exposed to low levels of Pb via drinking water. These authors have suggested that exposure to Pb may precipitate the autoimmunity by altering antigen immunogenicity and/or the capacity of the immune system to respond to certain antigens. This, in turn, may contribute to the eventual lead-associated neurological disease.

5.9.9 Mechanism of Lead-Based Immunomodulation

In the 1986 AQCD, there was little direct information available about the immune system regarding the molecular mechanism(s) of lead-induced immunotoxicity. Binding to thiol groups and altering cell surface receptors were indicated as possible factors in altered immune function. Since that time, some additional information has been generated through a variety of studies on human and animal immune cells. However, a clear or simple explanation remains to be determined. Table 5-9.3 lists studies on the immune system that have contributed to a better understanding of potential mechanisms or have forwarded potential hypotheses with some supporting data.

At the level of cell-cell interactions, it seems clear that Pb alters metabolism and cytokine production by macrophages and antigen presenting cells. It also reduces their capacity to respond to growth factors such as CSF-1 (Kowelenko et al., 1989). Pace et al. (2005) discussed the hypothesis that reduced populations of functionally altered macrophages (because of lead-induced unresponsiveness to CSF-1and over production of ROIs) in tissues can produce nonimmune problems. The model they used is the homeostatic presence of testicular macrophages and the likelihood that lead-induced macrophage immunotoxicity contributes directly to lead-associated reduction in male fertility.

Additionally, Pb is known to selectively alter cell signaling to CD4+ T cell subpopulations, promoting proliferation in some but not others. The outcome is enhanced tissue inflammation, reduced CMI, and increased production of atopy-inducing antibodies. Risk of autoimmune reactions is increased in some models of lead-induced immunotoxicity. For example, Heo et al. (1997) reported that lead-exposed murine T lymphocytes are biased in expression of Vβ genes. This is potentially problematic as this phenotype is common among a

Table 5-9.3. Suggested Mechanisms of Lead-Induced Immunotoxicity

Species	Strain/Gender	Suggested Endpoints	Associated Functional Alteration	Lowest Effective Dose	Duration	References
Mouse	Balb/c	CSF-1 Responsiveness of Macrophages	↓Testicular macrophages ↓Fertility	0.1 ppm	6 weeks	Pace et al. (2005)
Mouse	TO strain males	Vitamin E protection against lead-induced splenomegaly	↑Putative ROI associated splenomegaly	1 mg/kg	2 weeks	Fernandez-Cabezudo et al. (2003)
Chicken	Cornell K Strain	Thymulin partial reversal of Th skewing	↓Lead-induced DTH suppression	400 μg	Single in ovo injection	Lee and Dietert, (2003)
Mouse	Balb/c females C57 Bl/6 females	Lead disruption of antigen processing and presentation signals	↑Alloreactive $CD4+^{high}$ cells ↑Risk of autoimmunity	0.5 μM in vitro	4 days	McCabe et al. (2001)
Mouse	C 57Bl/6	PKC activation	↑TNF-α, ↑IL-6 ↑PGE_2	20μM in vitro	4.5 hrs	Flohe et al. (2002)
Rat	PC-12 cells	NF-κB activation AP-1 induction C-Jun kinase induction	↑ROI	1 μM in vitro	5-120 min	Ramesh et al. (1999)
Mouse	DO11.10 ova-mice	Adenylcyclase activation with elevated cAMP levels	↑Th skewing	2.5 μM in vitro	15 mins-6 hrs	Heo et al. (1998)
Mouse	DO11.10 ova-tg mice	Vβ gene usage	↑Risk of autoimmunity	50 μg 2x/week s.c.	8 weeks	Heo et al. (1997)
Human	-	NF-κB activation in CD4+ cells	↑Risk of autoimmunity and hypersensitivity	1 μM	30 min	Pyatt et al. (1996)
Mouse	CBA/J females	↑Immunogenicity of neural proteins	↑Autoimmune mediated neurological damage	Lead-altered proteins used as antigens	3 injections of lead-modified neural proteins	Waterman, et al. (1994)
Mouse	Swiss Females	↑TNF-α production	↑Sensitivity to endotoxin	5 mg	Single i.p. injection	Dentener et al. (1989)

variety of human and animal model autoimmune conditions. A variety of exogenous factors have been reported to partially ameliorate the immunotoxic effects of lead. Chelation of Pb in lead-exposed dams corrected some lead-induced immunotoxic problems in the rat female offspring, but it left the animals with some DMSA-induced immune alterations (Chen et al., 1999). Other exogenously administered factors that have been reported to partially restore lead-suppressed immune function are vitamin E (Fernandez-Carbezudo et al., 2003) and thymulin (Lee and Dietert, 2003).

At the subcellular level, the bases for immunotoxic changes remain speculative. McCabe et al. (2001) suggested that altered antigen processing and subsequent cell signaling to T cells may be an explanation for the capacity of Pb to selectively increase CD4+ (high density) cells. Certainly Pb appears to alter signal transduction. It appears to elevate expression of the nuclear transcription factor NF-κB (Pyatt et al., 1996; Ramesh et al., 1999) as well as increase expression of AP-1 and cJun (Ramesh et al., 1999). Flohe et al. (2002) found evidence that Pb can elevate the activation of PKC. The authors speculated that this might be involved in lead-induced increases in TNF-α production. Additionally, Heo et al. (1998) reported that Pb increases adenyl cyclase activity among T lymphocytes, generating elevated cAMP levels. The authors hypothesized that this effect, in conjunction with differences in cell signaling pathways for promoting Th1 vs. Th2 cells, may be involved in the capacity of Pb to skew Th0 helper cells toward Th2.

5.9.10 Age-Based Differences in Sensitivity

With the literature available at the time of the 1986 AQCD, it was virtually impossible to evaluate age-based differences in susceptibility to lead-induced immunotoxicity. However, in recent years, this has become a major topic of study for many toxicants including lead. Several studies have added to the available data assessing the developmental immunotoxicity of Pb (reviewed in Barnett [1996], Dietert et al. [2000, 2004], Lee and Dietert [2005]). Several patterns have emerged from exposure data using animals of different ages.

First, it seems clear that blood Pb levels at or near birth of below 10 µg/dL can be associated with juvenile and/or adult immunotoxicity. Several studies reported effects in the range of 5-8 µg/dL. These low levels would seem to place the immune system on par with the

neurological system in terms of potential sensitivity to lead. Table 5-9.4 shows examples of studies in which low blood lead levels were linked with immunotoxicity.

Table 5-9.4. Immunomodulation Associated with Low Blood Lead Levels in Animals

Species	Blood lead (µg/dL)	Age at Measurement	Immune Parameter(s)	Age at Assessment	Reference
Mouse	~5.0	1 week	↑IgE, ↓ Splenic T Cell Populations	2 weeks	Snyder et al. (2000)
Rat	8.2	1 day	↓monocytes	13 weeks	Bunn et al. (2001a)
Rat	6.75	4 weeks	↓DTH, ↓IFN-γ, ↑IL-4	13 weeks	Chen et al. (2004)
Rat	8.0	4 weeks	↑TNF-α ↑Rel. Spleen weight	13 weeks	Lee et al. (2002)
Chicken	8.2	1 day	↓circulating lymphocytes post infection	5 weeks	Lee et al. (2002)
Chicken	11.0	1 day	↓DTH and ↓TLC, monocytes, PMNs post infection	5 weeks	Lee et al. (2001)
Chicken	7.0	1 day	↑autoantibody production	10 weeks	Bunn et al. (2000)

A second finding is that the immunotoxic effects induced by Pb are persistent long after blood levels and potential body burdens of Pb are significantly reduced. Miller et al. (1998), Chen et al. (1999), Snyder et al. (2000), and Lee et al. (2001) all emphasize this latter point. In fact, in most of these studies immunotoxic alterations were present when Pb levels in exposed animals were not distinguishable from control levels. This should provide a cautionary note regarding studies in humans. Data from adult exposures provides little insight into the potential persistence following adult exposure to lead. However, rather than the developing immune system being more regenerative postexposure and able to withstand immunotoxic insult, it appears that the non-dispersed developing immune system is a particularly susceptible target to many immunotoxicants (Dietert et al., 2002).

A third, and somewhat surprising, finding concerning early exposure to Pb is that qualitative differences in the spectrum of immune alterations can exist, depending upon the

developmental window of exposure. Figure 5-9.1 illustrates this point. Early embryonic exposure of rats and chickens to Pb failed to alter juvenile DTH responses, despite significant effects on macrophage function. However, exposure to Pb after the mid-embryonic point of embryonic development readily suppressed subsequent DTH. As shown in Figure 5-9.1, the development window in which sensitivity to DTH suppression emerges is quite similar in the two species. This observation suggests that both quantitative (LOAELs) and qualitative (range of immune alterations) differences in sensitivity to Pb can exist across different age groups.

Additionally, some studies in animals have noted gender differences in the effects of Pb following exposure (Bunn et al., 2000, 2001a,b, c; Hudson et al., 2003). Gender differences have also extended to results in humans as per lead-induced immune and inflammatory alterations (Karmaus et al., 2005; Fortoul et al., 2005). It seems feasible that, even in the embryo, hormonal differences among females and males may impact some outcomes of low-level Pb exposure.

Table 5-9.5 shows comparisons of the lowest reported blood Pb levels at different ages associated with the same immunotoxic endpoint. From these limited comparisons, it would appear that different ages of rodents (e.g., embryonic vs. adult) differ in dose sensitivity for lead-induced immunotoxicity somewhere in the range of 3 to 12-fold. Clearly, additional direct comparisons would help to refine this estimate.

A fourth observation from the early exposure studies is that exposure to even very low levels of Pb can predispose the immune system for unanticipated postnatal responses when the system is stressed. This general phenomenon is called latency. Lee et al. (2002) provided an example of this following the single in ovo exposure of embryonic day 5 chick embryos to low levels of Pb (10 μg; blood lead level 1 day post hatch of 8.2 μg/dL). The leukocyte profiles of the animals appeared to be completely normal. However, when these animals were exposed to a respiratory virus, their pattern of leukocyte mobilization was completely aberrant from controls. Therefore, some immunotoxic alterations following early exposure to low levels of Pb may only be evident during periods of postnatal stress.

Several studies have reported the positive association of blood Pb levels in children with elevated serum IgE (Karmaus et al., 2005; Sun et al., 2003; Lutz et al., 1999). These observations are supported by the animal data in rats and mice (Miller et al., 1998; Snyder et al., 2000) and suggest that lead-induced risk of atopy and asthma may be a particular health issue.

Table 5-9.5. Comparisons of Age-Based Sensitivity to Lead-Induced Immunotoxicity

Species	Altered Endpoint	Embryo – fetal*	Neonatal*	Adult*	References
Mouse	↑IgE	~5µg/dL	12 µg/dL	38 µg/dL	Snyder et al. (2000) Heo et al. (1996)
Rat	↓DTH (persistent effect assessed 13 weeks post-exposure)	34 µg/dL	-	>112 µg/dL (measured at birth for persistent effect)	Miller et al. (1998) Bunn et al. (2001b)
Mouse	↓DTH	-	29 µg/dL	87 µg/dL	Faith et al. (1979) McCabe et al. (1999)
Rat	↑TNF - α (persistent effect assessed 13 weeks post-exposure)	8 µg/dL	–	>112 µg/dL (measured at birth for persistent effect)	Miller et al. (1998) Chen et al. (2004)

* Lowest blood lead concentration reported with effect

Trasande et al. (2005) recently discussed the fact that, despite progress in reducing the deposition of Pb in the environment, Pb continues to be a concern relative to asthma and children's health.

5.9.11 Summary and Conclusions

The immune system appears to be one of the more sensitive systems to the toxic effects of lead. The 1986 AQCD provided an excellent summary of the studies that had been conducted prior to that date. But knowledge of fundamental immunology has progressed greatly during the past 20 years. Not surprisingly, the large number of studies conducted since the mid-1980s provided a much clearer understanding of the immune-associated problems that can arise from problematic exposure to lead. Studies across humans and a variety of animal models are in general agreement concerning both the nature of the immunotoxicity induced by Pb as well as the exposure conditions that are required to produce immunomodulation. Figure 5-9.2 summarizes the basic immunotoxic changes induced by Pb that result in Th skewing, impaired macrophage function, and increased risk of inflammation-associated tissue damage.

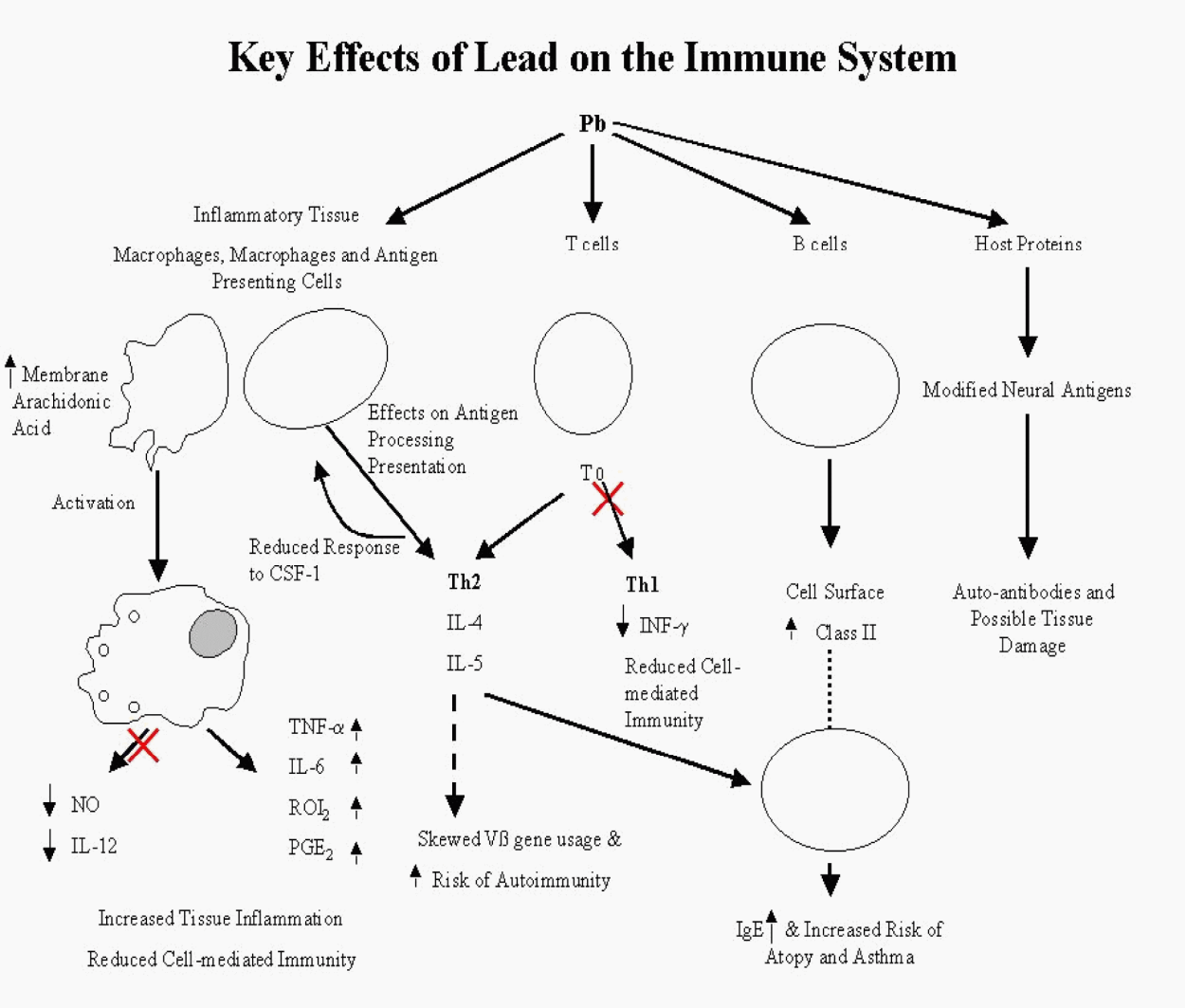


Figure 5-9.2. This figure shows the fundamental alterations to the immune system and to immunological response and recognition induced by exposure to lead. The functional shifts are disproportionate compared to the relatively modest changes among leukocytes with low to moderate exposure to lead.

Lead is unlike many immunotoxicants in that, at low to moderate levels of exposure, it does not produce overt cellular cytotoxicity or lymphoid organ pathology. However, it can induce profound functional alterations that influence risk of disease. Lead preferentially targets macrophages and T lymphocytes, although effects have been reported in B cells and neutrophils as well. There are three major hallmarks of lead-induced immunotoxicity. First, Pb can dramatically suppress the Th1-dependent DTH response, as well as production of associated Th1

cytokines. Second, Pb can dramatically elevate production of IgE while increasing production of Th2 cytokines, such as IL-4. Third, and perhaps most sensitive, is the modulation of macrophages by Pb into a hyperinflammatory phenotype. After exposure to lead, macrophages significantly increase production of the proinflammatory cytokines TNF-α and IL-6 (and in some studies IL-1). Many studies also reported elevated release of ROIs and prostaglandins. Ironically, production of one of the most important host defense factors, NO, is consistently and severely suppressed by exposure to lead. This package of lead-induced changes among macrophages makes them more prone to promote tissue destruction but actually less capable of killing bacteria or possibly presenting antigens to T lymphocytes. The Pb-induced shift in phenotype explains the capacity of inhaled Pb to promote bronchial inflammation while bacterial resistance is severely depressed.

Lead-induced skewing of Th activity (biasing responses toward Th2) across a population would lead to the expectation of a greater risk of atopy, asthma, and some forms of autoimmunity. Concomitantly, resistance to some infectious diseases could be reduced. This predicted change of risk might help explain some recent trends in the incidence of diseases, such as the epidemic rise in allergy and some forms of asthma in the United States.

Sensitivity of the immune system to Pb appears to differ across life stages. Studies in rats and mice suggest that the gestation period is the most sensitive life stage followed by the early neonatal stage. But even during embryonic, fetal, and early neonatal development, critical windows of vulnerability are likely to exist. Compared to adults, the increased dose sensitivity of the embryo-fetus would appear to fall in the range of 3-10x depending upon the immune endpoint considered. Some studies have found evidence for gender differences in the impact of Pb on the immune system particularly with early life exposures. Potential gender differences in immunotoxic outcome may be important in the evaluation of those populations at greatest risk.

Recent studies have suggested that exposure of embryos to Pb producing neonatal blood lead concentrations below 10 μg/dL can also produce later-life immunotoxicity (see Table 5-9.4). Furthermore, immunotoxicity persists long after any evidence of prior embryonic Pb exposure. This latter observation from several laboratories may have implications for the design of human epidemiological studies.

5.10 EFFECTS OF LEAD ON OTHER ORGAN SYSTEMS

In the 1986 Pb AQCD, the discussion of other organ systems included cardiovascular, hepatic, gastrointestinal (GI), and endocrine systems. Due to our increased understanding on the effects of Pb on cardiovascular and renal systems and their contribution to potential health effects of Pb, separate sections (5.5, 5.7) were dedicated earlier in this chapter to detailed discussions on these aspects. Similarly, with our increased understanding on the effects of Pb on endocrine functions and its inherent role with respect to neurotoxicological, reproductive, and developmental effects, literature reviewed for Pb effects on the endocrine system is discussed in the respective sections. This section focuses on the discussion of Pb effects on the hepatic and GI systems.

5.10.1 Effects of Lead on the Hepatic System

The liver is a highly active metabolic tissue. Apart from its roles in fatty acid metabolism and limited heme synthesis function, the liver also has a major role in guarding other systems from the toxic effects of xenobiotic compounds using a huge complement of detoxification machinery referred to as phase I and phase II enzyme systems. Limited studies on experimental animals reported in the 1986 Pb AQCD indicated that Pb induced effects in the hepatic system. Laboratory animals, especially rats, exposed to Pb-nitrate have exhibited increased liver cell proliferation, DNA synthesis, cholesterol synthesis, and glucose -6-phosphate dehydrogenase (G6PD) activity indicative of Pb-induced hyperplasia. Further, the literature reviewed in the 1986 Pb AQCD reported alterations in the levels of drug metabolizing enzymes in experimental animals given large doses of Pb. The evidence for such effects in humans was less consistent. The 1986 document also concluded that the effects on the liver occurred only at high exposure levels. The majority of studies on the effects of Pb on the hepatic system in experimental animals that are reviewed in this document report functional and biochemical changes in the liver, clearly pointing to metabolic perturbations in liver. For ease in understanding and integration of these functional changes, the discussion is divided into the following four subsections: hepatic drug metabolism, lipid and glycogen metabolism and lipid peroxidation, heme synthesis, and toxicity mitigation by chelation and other interventions.

5.10.1.1 Hepatic Drug Metabolism

Approximately 75% of the hepatic blood comes directly from the gastrointestinal viscera, with the majority of drugs or xenobiotics absorbed coming directly to the liver in concentrated form. The liver is equipped with a huge complement of drug metabolizing enzymes that detoxify many of the xenobiotics but also activate the toxicity of others. Oxidation and conjugation of xenobiotics have historically been referred to as phase I and phase II reactions. The phase I enzymes include cytochrome P450 (CYP450) heme-containing monoxygenases, flavin-containing monoxygenases, and epoxide hydrolases. The phase II enzymes include glutathione (GSH) S-transferases (GST), UDP-glucuronyl transferases (UGT), N-acetyltransferases (NAT), and sulfotransferases (SULT). Xenobiotic metabolism by these two complements of enzyme systems are essential for catabolizing and eliminating of drugs; however, this process can also produce activated toxicants and carcinogens. A limited number of these CYP450s are involved in the biosynthetic pathways of steroid and bile acid production. It has been increasingly recognized that, under certain circumstances, CYP P450s can produce ROS that result in oxidative stress and cell death.

Liver is an active tissue. In addition to xenobiotic metabolism, it also participates in gluconeogenesis, fatty acid metabolism, and cholesterol biosynthesis. Research concerning the effects of Pb on the hepatic system in the past 15 years has provided some preliminary indications of Pb-induced alterations in many of the hepatic functions described above. The following discussion presents, as much as possible, the effects of Pb on individual enzymes, but due to the multifarious interactions of many of these metabolic enzymes, there may be places such separation was not possible.

Phase I Enzyme

Earlier studies on the toxic effects of Pb on hepatic drug metabolizing enzymes demonstrated that acute exposure to Pb-acetate decreased rat hepatic CYP450s with increased levels of urinary δ-aminolevulinic acid (ALA). Co-treatment with phenobarbitol, a CYP450 inducer, was shown to reverse the decrease CYP450 levels, suggesting a Pb-acetate-mediated inhibition of heme synthetic enzymes. Decreased activities of estradiol-17 beta enzyme observed in rat liver treated with triethyl Pb-chloride (Odenbro and Arhenius, 1984) suggest that both Pb and organo-Pb compounds are capable of inhibiting CYP450 activities. Roomi et al.

(1986) also observed decreased levels of hepatic microsomal CYP450s and decreased aminopyrene-N-demethylase activity on exposure to a single dose of Pb-nitrate (5-10 mmol/kg body wt). This decrease in phase I enzymes was followed by increased levels of phase II components such as GSH, GST, and DT diaphorase, suggesting that Pb-nitrate and Pb compounds can induce biochemical properties characteristic of hepatocyte nodules. Subchronic (2-3 months) exposure to Pb-acetate (5-50 mg/kg body wt) had been found to induce CYP450s and cytochrome b5 in rat liver and kidney (Nehru and Kaushal, 1992). As described earlier, multiple isoforms of CYP450s exist in the liver.

To identify the inhibitory effect of acute Pb exposure on specific isoform(s), Degawa et al. (1994) exposed male F344 rats to Pb nitrate (20,100 μmol/kg body wt) and evaluated liver CYP450s 24 h postexposure. Lead-nitrate exposure preferentially inhibited cytochrome P4501A2 enzyme activity in liver microsomal preparations as assayed for mutagenic conversion of substrates 2-amino-6-methyl-dipyridol [1,2-a; 3',2-d] imidazole and 3-amino-1-methyl-5H-pyridol[4,3,-b]indole. Lead-nitrate exposure also inhibited the induction of cytochrome P4501A2 by the inducers 3-methylcholanthrene and 2-methoxy-4-aminoazobenzene at both the protein and mRNA levels. The authors further concluded that the specific inhibition of P4501A2 by Pb-nitrate observed may have been due to inhibition of heme synthesis, as Pb-nitrate was not found to inhibit P4501A2 activity in vitro. Additional studies carried out by the same group using various metal ions (e.g., Pb, Ni, Co, and Cd) found that the specific inhibition of P4501A2 was unique to Pb-nitrate (Degawa et al., 1994, 1995). Degawa et al. (1996) also investigated the effect of Pb-nitrate-mediated inhibition of CYP1A gene activity in rat liver by specific inducers and reported that Pb-nitrate inhibited the induction of CYP1A mRNA by aromatic amines, but not by aryl hydrocarbons, suggesting the role of other cellular factors in the transcriptional activation of CYP1A genes. Lead-nitrate has been reported to induce the production of TNF-α in rat liver (Shinozuka et al., 1994), a cytokine implicated in the suppression of constitutive expression of CYP1A2 mRNA in rat hepatocytes. Based on these findings, Degawa et al. (1996) concluded that the inhibition of constitutive and aromatic amine-induced expression of CYP1A2 in rat liver caused by Pb-nitrate may occur at least in part by TNF-α-associated mechanisms. Lead-nitrate (0.33 mg/kg body wt) pretreatment-mediated protection conferred against carbon tetrachloride (0.3 mL/kg)-induced hepatotoxicity as reported by Calabrese et al. (1995) may be due to the inhibition of CYP450 activities in liver by Pb.

Jover et al. (1996) investigated the effect of heme deficiency on Pb-induced hepatic P450 function and transcription. These authors concluded that the decrease in hepatic P450 resulting from Pb intoxication was mediated by two different mechanisms. One mechanism is involved inhibitory effects on P450 by Pb at the transcriptional level; the second was heme- dependent, as Pb-mediated inhibition of heme synthesis decreased the heme saturation of P450 and the apo-P450 ratio.

The effect of heavy metals (Cd, Co, Cu, Ni, Pb, and Zn) on 3-methylcholanthrene-induction of cytochrome P4501A and the activity of ethoxyresorufin-O-deethylase (EROD) were investigated in fish hepatoma cells (PLHC-1) by Brucshweiler et al. (1996). The authors reported that all the heavy metals tested had more pronounced effects on EROD activity compared to controls. The inhibitory potency of Pb was reported to be very low compared to cadmium or cobalt. A single treatment of Pb-acetate induced hepatic DT diaphorase activity (Sugiura et al., 1993). This induction of hepatic DT diaphorase by Pb-acetate has been reported to be decreased with concomitant administration of Dil, a calcium antagonist. Based on these observations, Arizono et al. (1996) suggested that DT diaphorase induction by Pb-acetate may occur de novo via protein synthesis mediated by increased cellular calcium. The potential interaction of metals, including Pb, on the induction of CYP1A1 and CYP1A2 by polycyclic aromatic hydrocarbons (PAHs) in human hepatocyte cultures was investigated by Vakharia et al. (2001). Lead-nitrate, like other metals such as Cd, Hg, and As, decreased the extent of CYP1A1 and CYP1A2 induction by five different PAHs. The authors concluded from these studies that Pb (5 μM) diminished the induction of CYP1A1 and CYP1A2 in human hepatocytes by ultimately decreasing the levels of CYP1A1 protein that was normally attainable through PAH induction. Korashy and El-Kadi (2004) also investigated similar interactions of metals with aryl hydrocarbon receptor (AHR)-regulated gene expression and enzyme activities in wild-type murine hepatoma cells (Hepa 1c1c7) and AHR-deficient cells (C12). These studies indicated that metals alone (including Pb) did not significantly alter CYP1A1 proteins or activity, or change AHR ligand-induced enzyme activity. There was no change in mRNA levels. Lead, in the presence or absence of AHR ligand, increased the activity of NAD(P)H:quinone oxidoreductase and its mRNA levels.

Phase II Enzymes

A single injection of Pb-nitrate (5-10 μM/100 g body wt) was found to increase GST activity levels (Roomi et al., 1986). Additional studies by the same group identified induction of a specific form GST-P by Pb-nitrate in rat liver (Roomi et al., 1987). Because a single injection of Pb-nitrate decreased phase I and increased phase II hepatic enzymes, these investigators concluded that Pb-nitrate treatment initiated a biochemical phenotype similar to carcinogen-induced hepatocyte nodules. Immunohistochemical analysis by the same group reported that Pb-nitrate administration resulted in the appearance of GST-P in most of the hepatocytes, an enzyme that is otherwise undetectable in normal rat liver (Columbano et al., 1988; Roomi et al., 1987). On the other hand, Nakagawa (1991) reported inhibition of GST on acute exposure to Pb and that the inhibition of GST followed a reduction in liver GSH levels. Nakagawa (1991) concluded that the depletion of GSH was not necessarily a critical factor in inhibiting GST.

Planas-Bohne and Elizdale (1992) reported that acute exposure to Pb-nitrate (100 μmol/kg) caused a significant increase in liver and kidney GST activity. Gel electrophoresis analysis to evaluate the contribution of various GST isoforms indicated that enhancement of liver GST activity was predominantly due to induction of GST isoform 7-7 in liver compared to all isoforms in kidney. Liver GST-P isoform was reported to be induced by both Pb-acetate and Pb-nitrate (Boyce and Mantle, 1993; Koo et al., 1994). This transient induction of GST-P has been regulated at transcription, post-transcription, and post-translational levels. Suzuki et al. (1996) utilized a transgenic approach to investigate the transcriptional regulation of GST-P induced by Pb and identified glutathione S-transferase P enhancer I (GPEI), an enhancer (whose core consists of two AP-1 site-like sequences) located at the 5' flanking region of this gene. The authors demonstrated that GPEI is an essential element in the activation of the GST-P by Pb and that the trans activating factor AP-1 is likely to be involved, at least in part, in the transcriptional activation of the GST-P gene by Pb via the GPEI sequence.

Daggett et al. (1997, 1998) investigated the effect of inorganic and organic Pb on liver GST expression and other phase II detoxifying enzymes in rat liver and kidney. Triethyl Pb chloride (TEL) injection (10 mg/kg body wt) decreased liver GST activity, as well as levels of various other GST isoforms (Daggett et al., 1997), in contrast to significant induction of kidney GST activity, suggesting that a single compound, TEL, had opposite effects on the expression of GST isozymes and indicated the complexity of GST regulation. Similarly, this group also

reported that a single injection of Pb-acetate (114 mg/kg body wt) reduced GSH levels, increased production of malondialdehyde (MDA), and did not change the expression of various GST isoforms analyzed, except GST-p1 on repeated injection (Daggett et al., 1998). Similar to studies with TEL, Pb-acetate also increased the expression of GST enzyme activity and expression of various isoforms without changing GSH and MDA levels, suggesting that oxidative stress may not be mediating the toxicity in kidney. On the other hand, TEL exposure was found to decrease microsomal estradiol metabolism (Odenbro and Rafter, 1988). The suppression of GST expression reported by Daggett et al. (1997, 1998) is in contrast to the induction of GST reported by various other groups discussed earlier. Other GSH-dependent enzymes (i.e., GSH peroxidase, GSH reductase) have been found to be suppressed with a simultaneous increase in oxidized GSH (GSSG) and a reduction in GSH/GSSG ratio (Sandhir and Gill, 1995). More detailed information on these and related studies is summarized in Table AX5-10.1.

5.10.1.2 Biochemical and Molecular Perturbations in Lead-Induced Liver Tissue Injury

Oskarsson and Hellström-Lindahl et al. (1989) studied the cellular transport of Pb (^{203}Pb), in rat hepatocytes using dithiocarbamate (DTC). Cells treated with Pb-acetate and Pb-DTC lipophylic complex demonstrated increased cytosolic Pb levels compared to Pb alone. This was further evaluated by measuring levels of ALAD. Cells treated with Pb-DTC complex showed rapid and stronger inhibition of ALAD compared to Pb-acetate, suggesting that this inhibition was due to increased mobilization of Pb into cells treated with Pb-DTC complex. Another report by the same group, Hellström-Lindahl and Oskarsson (1990), suggested that the increased inhibition of ALAD was due to the release of Pb from the Pb-DTC complex by decomposition. Using the mouse strain with a duplication of the ALAD gene (DBA), Claudio et al. (1997) reported increased accumulation of Pb in this strain by many fold as compared to mice with a single copy of the ALAD gene (C57).

A single injection of Pb-nitrate was reported to cause hepatic hyperplasia correlating with hepatic de novo synthesis of cholesterol along with alterations in glucose and lipid metabolism leading to altered serum lipid profiles (Dessi et al., 1984; Pani et al., 1984). Mobilization of hepatic glycogen and altered gluconeogenic enzymes, including differential expression of G6PD, have been reported following Pb exposure (Batetta et al., 1990; Hacker et al., 1990). Chronic Pb

intoxication has also been reported to inhibit gluconeogenic enzymes, alterations that were implicated in Pb bio-transformation rather than liver cell proliferation in Wistar rats (Calabrese and Baldwin, 1992). Increased levels of serum lipid peroxide (LPO) were also observed in rats given SC injection of Pb-acetate, supporting similar increased levels of serum LPO in humans exposed to Pb (Ito et al., 1985). These initial studies suggest that alterations in liver intermediary metabolism occur on exposure to Pb with a role for Pb-induced LPO in hepatotoxicity and potential involvement of oxidative stress in Pb toxicity.

Dessi et al. (1990) investigated the role of fasting on Pb-induced hepatic hyperplasia by monitoring the activities of enzymes involved in cholesterol synthesis and the hexose monophosphate shunt and reported that stimulation of these enzymes, even in Pb-acetate-treated fasting rats, supported the role of new endogenous synthesis of cholesterol and gluconeogenic mechanisms in Pb-induced hepatic cell proliferation. Chronic exposure to Pb was found to increase the arachidonate/linoleic acid ratio in liver and serum (Donaldson and Leeming, 1984; Donaldson et al., 1985) along with the GSG concentration (McGowan and Donaldson, 1987). As GSH and arachidonate are precursors for peptido-leukotrienes, Donaldson's group investigated the potential effects of dietary Pb on levels of fatty acids, peptido-leukotrienes, and arachidonate/linoleic ratios in chicken fed with diets low in calcium and methionine. These investigations found similar increases in arachidonate/linoelic acid ratio and in GSH levels without bearing on peptido-leukotriene levels. The authors also found the influence of a low calcium and methionine diet on Pb-induced serum fatty acid profiles (Knowles and Donaldson, 1990).

Chronic sublethal exposure (5 ppm Pb-nitrate for 30 days) has been found to alter liver lipid profiles in blood and liver tissue of the fresh water fish *Anabas testudineus* (Tulasi et al., 1992). These authors reported significant increases in liver total lipids, cholesterol, and free fatty acids. Tandon et al. (1994b) reported that iron deficiency enhanced the accumulation of Pb in liver and kidney and also increased liver calcium levels. Induced expression of metallothionein (MT) in renal and intestine was also observed in iron deficiency. Han et al. (1996) investigated the effect of Pb burden on weight loss using an energy restriction diet regimen on rats with prior Pb exposure. The authors reported that rats on a substantial weight loss regimen (40% of normal calories) exhibited a significant increase in the quantity and concentration of liver Pb and a decrease in the concentration of other metals (e.g., Ca, Cu, Mg, Zn). The authors concluded that

weight loss can increase the liver concentration of Pb, even in the absence of continued exposure. Combined exposure to Pb (70 mg/kg) and Cd (20 mg/kg) in Buffalo rats for 7 weeks was found to alter liver levels of Zn and Cu, with less accumulation of Pb and Cd, compared to individuals exposure to either Pb or Cd alone (Skoczynska et al., 1993). These authors also reported that a combined exposure regimen interfered with serum lipid profiles (Skoczynska and Smolik, 1994).

Liu et al. (1997) utilized rat primary hepatocyte cultures to explore the protective effect of Zn-induced expression of metallothionein (MT) in Pb toxicity. These authors found that, in the control cells without prior Zn exposure, most of the Pb was found bound to high-molecular weight proteins in the cytosol, while in the Zn pretreated cells, a majority of Pb bound to MT, indicating a MT-mediated protection against Pb toxicity to hepatocytes. More details about these and related studies are summarized in Table AX5-10.2.

5.10.1.3 Effects of Lead Exposure on Hepatic Cholesterol Metabolism

Lead-nitrate-induced hyperplasia or liver cell proliferation involves simultaneous increase in both liver and serum total cholesterol levels. Recent studies have reported various molecular events associated with this process. Induction of gene expression for CYP51 (Lanosterol 14α-demethylase), an essential enzyme for cholesterol biosynthesis, was reported in Pb-nitrate-induced liver hyperplasia, although other cytochrome P450 enzymes involved in drug metabolism have been reported as being suppressed, as discussed in earlier sections. This gene has various regulatory elements and its constitutive expression in liver is mediated by sterol regulatory element (SRE) and by the SRE binding proteins-1a, 2, and 1c. Kojima et al. (2002) reported that Pb-nitrate induced the expression of CYP51 in the livers of both immature (4-week-old) and mature (7-week-old) rats and that this induction appeared to be mediated by the upregulation of SRE binding protein-2. However, this increased synthesis of cholesterol observed in rat liver was not mediated by endogenous feedback regulation by sterols, as no decrease in serum total cholesterol was observed. To understand the molecular mechanisms involved in the Pb-nitrate-mediated development of hepatic hypercholesterolemia, Kojima et al. (2004) investigated the expression of various enzymes involved in cholesterol homeostasis, including some of the associated transcription factors in male rats exposed to Pb-nitrate (100 μmol/kg body wt). The authors reported that Pb-nitrate exposure caused a significant

increase in liver and serum total cholesterol levels at 3-72 h and 12-72 h, respectively. The enzymes involved in cholesterol biosynthesis viz. (i.e., 3-hydroxy-3methyglutaryl-CoA reductase, farnesyl diphosphate synthase, squalene synthase, CYP51) were all activated (3-24 h), while the enzymes involved in cholesterol catabolism such as 7α-hydroxylase were remarkably suppressed 3-72 h. Figure 5-10.1 shows the involvement of Pb at various stages of the cholesterol synthesis pathway. The induction of the cytokines interleukin-1α and TNF-α in rat liver prior to the induction of the genes for these synthesis enzymes suggested that Pb-nitrate-induced cholesterol synthesis is independent of sterol homeostasis regulation. Following gestational and lactational exposure to Pb-acetate (0.05 mg/kg body wt), Pillai and Gupta (2005) reported that the activities of the hepatic steroid metabolizing enzyme 17-β-hydroxy steroid reductase, UDP glucouronyl transferase, and CYP450 levels decreased in rat pups on PND21.

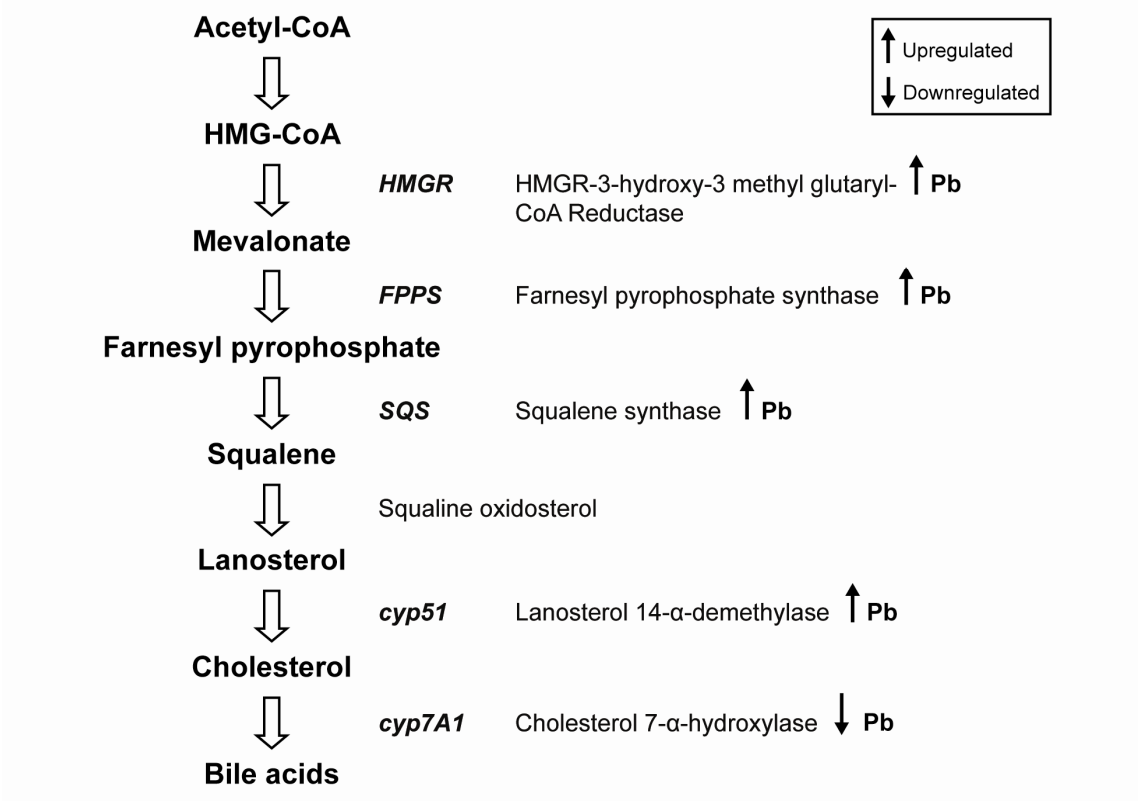


Figure 5-10.1. Flow diagram indicating the Pb effects on the cholesterol synthesis pathway.

Alterations in the hepatic system of neonates and pups (at PND12 and PND21) after gestational and lactational exposure to Pb-acetate (300 mg/L) have been reported by Corpas et al. (2002). The authors found significant reductions in the liver weight of pups and in hepatic glycogen that correlated with increased blood glucose levels. The authors also reported reductions in liver protein, lipid levels, and alkaline and acid phosphatase activities but did not find any gross structural alterations in liver tissue. These and other studies are summarized in Table AX5-10.3.

5.10.1.4 Effect of Chelation Therapy on Lead-Induced Hepatic Oxidative Stress

Although several mechanisms have been proposed to explain Pb toxicity, no mechanism has been defined explicitly. Recent literature on Pb toxicity suggests oxidative stress as one of the important mechanisms of toxic effects of Pb in liver, kidneys, brain, and other organs.

Schematic representation of the various mechanisms by which Pb induces lipid peroxidation is shown Figure 5-10.2. Lead toxicity to the liver has been found to be associated with significant accumulation of Pb in the liver. This results in the accentuation of lipid peroxidation with concomitant inhibition of antioxidant enzymes (i.e., SOD, catalase, GSH peroxidase, GSH reductase) and a simultaneous increase in GSSG with a reduction in GSH/GSSG ratio (Sandhir and Gill, 1995; Aykin-Burns et al., 2003). However, Furono et al. (1996) studied the potential of various redox-active metals to induce LPO in normal and alpha-linolenic acid-loaded rat hepatocytes and suggested that Pb ions were not capable of inducing lipid peroxidation in such hepatocytes.

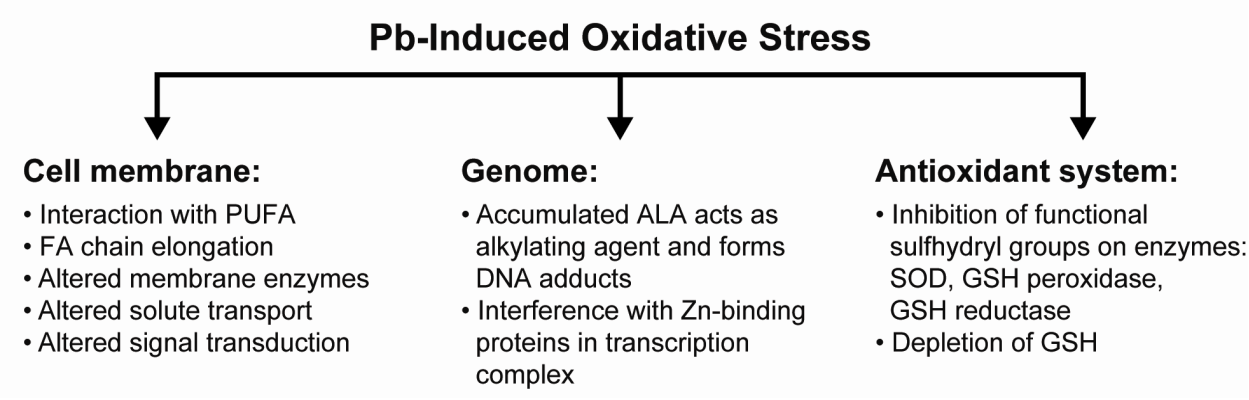


Figure 5-10.2. Schematic diagram illustrating the mode of Pb-induced lipid peroxidation.

The currently approved clinical intervention method is to give chelating agents that form an insoluble complex with Pb and remove the same from Pb-burdened tissues. The efficacy of various chelating agents and antioxidants studied in experimental animals on Pb induced liver toxicity is discussed below.

Chelation therapy with mono-3-methylbutane-1-yl (monoisomyl) ester of meso-2,3-dimercaptosuccinic acid (Mi-DMSA) and meso-DMSA (meso-2,3-dimercaptosuccinic acid) was found to offer no protection to suckling rat pups as measured by liver Pb levels (Cory-Slechta, 1988; Blanusa et al., 1995; Pappas et al., 1995; Smith et al., 2000). Similar studies by Kostial et al. (1999), using various isoforms of DMSA, EDTA, and combined therapy, did not find a chelator-mediated reduction in liver Pb levels except for meso-DMSA (0.5 mmol/kg), which caused significant reduction in Pb levels in kidney and brain. On the other hand, it decreased liver zinc and copper levels. The authors concluded that combined therapy may not be the best choice at this age, because infants are more sensitive to trace metal deficiency. Flora and Seth (1999) investigated the protective role of S-adenosyl-L-methionine (SAM) on acute Pb and Pb + thanol-induced hepatic toxicity in mice by monitoring hepatic GSH and MDA levels. The authors concluded that bioaccumulation of Pb in liver in both Pb- and Pb + ethanol-exposed groups were significantly decreased by SAM.

To identify the efficacy of chelation therapy (mono or combined therapy) for acute Pb poisoning in infants, Kostial et al. (1999) utilized suckling rat pups and monitored tissue Pb levels. Monotherapy of either EDTA (0.3 mmol/kg), meso-DMSA (0.5 mmol/kg), rac-DMSA (racemic-2,3-meso-2,3-dimercaptosuccinic acid, 0.5 mmol/kg), or a combined therapy of EDTA + meso-DMSA, EDTA + rac-DMSO indicated differential effects on liver tissue Pb and other trace metal levels. The authors concluded that meso-DMSA was the more potent therapy for acute Pb poisoning in infants and suggested that combined therapy may not be the best choice, as at this age the infants are more sensitive to trace metal deficiency.

Supplementation with sodium molybdate (1 mg/kg body wt) during the course of Pb exposure (0.1% Pb-acetate in water for 4 weeks) was found to provide significant protection from the uptake of Pb by blood, liver and kidneys and also from hepatic LPO (Flora et al., 1993). Similarly, supplementation with antioxidants and vitamins were explored to reduce the toxic effects of Pb on liver function and activity. Oral supplementation of vitamin C (100 mg/kg for 3 days) has been reported to provide significant protection against Pb-induced declines in liver

heme synthesis, drug metabolism, tissue thiols, and vitamin C levels along with reduction in liver Pb levels (Vij et al., 1998). Similarly, simultaneous administration of vitamin E (5 mg/kg body wt) was reported to confer protection against Pb-induced decline in hepatic type-1 iodothyronine 5'-monodeiodinase activity, inhibition of SOD and catalase activities, and increased lipid peroxidation (Chaurasia and Kar, 1997). Studies by Tandon et al. (1997) also suggested that Pb and Pb + ethanol-induced biochemical changes in mouse liver can be prevented by the simultaneous administration of lysine and zinc. This regimen was also reported to prevent the Pb-induced depletion of endogenous calcium and magnesium in liver. Two well-known antioxidants, N-acetylcysteine and lipoic acid, have been reported to reduce Pb-induced oxidative stress (OS) both in vitro in Chinese hamster ovary cells and in vivo in F344 rats (Ercal et al., 1996; Gurer et al., 1998, 1999b). The same group also investigated the protective effects of another antioxidant, taurine, against Pb-induced OS in the same systems both in vitro and in vivo. These authors reported that taurine was effective by increasing cellular GSH while simultaneously reducing malondiablehde (MAD) and catalase activity levels, offering protection against Pb-acetate-induced OS, without decreasing the liver or blood Pb levels (Gurer et al., 2001). Patra et al. (2001) studied the ameliorative effects of antioxidants (i.e., ascorbic acid, vitamin E, L-methionine) alone and vitamin E + EDTA on Pb-induced OS in liver, kidney, and brain tissues of rats exposed to Pb-acetate (1 mg/kg body wt, 4 weeks) and found that all the antioxidants used conferred protection against OS without a significant decline in tissue Pb burden. The level of protection conferred exhibited tissue-specific differences. L-Methionine was also found to offer similar protection in mice exposed to Pb (Xie et al., 2003). Othman and El Missiry (1998) reported that administration of selenium (sodium selinite, 10 μM/kg body wt) prior to Pb-acetate (100 μM/kg body wt) produced pronounced prophylactic action against Pb-induced LPO in liver and kidney of male albino rats.

In earlier combination chelation therapy using thiamine and Ca^{2+}-EDTA, Kim et al. (1992) reported that regardless of the route of exposure, reduction in liver tissue retention of ^{203}Pb occurred, while thiamine alone reduced only the Pb content of kidney. Recent studies used a combination of chelators with antioxidants to reduce Pb-induced OS in liver and other tissues (i.e., kidney and brain). α-Lipoic acid, meso-DMSA, and their combination was found to reduce OS by increasing hepatic GSH levels and reducing GSSG and thiobarbituric acid reactive substances (Pande and Flora, 2002). The same group also studied the protective effect of the

combination of ascorbic acid, vitamin E, meso-DMSA, and miADMSA and found a significant reduction in hepatic OS by the combination therapy of ascorbic acid and thiol chelators (i.e., DMSA, miADMSA) in rat. The combination therapy also produced similar reduction in renal OS (Flora et al., 2003). Studies reported by Varnai et al., (2003) suggested that ascorbic acid supplementation did not improve the efficiency of meso-DMSA in reducing Pb-induced OS in suckling rats. On the other hand, combined treatment of ascorbic acid (1 mg/100 g body wt) and silymarian (1 mg/100 g body wt) has been reported (Shalan et al., 2005) to cause marked improvement of the biochemical, molecular and histopathological changes caused by Pb-acetate (500 mg/kg body wt). Similarly, combined treatment with lipoic acid + DMSA has been found to completely ameliorate Pb-acetate-induced oxidative damage. However, either lipoic acid or DMSA alone conferred partial protection against Pb-induced hepatic damage (Sivaprasad et al., 2004). These and related studies are summarized in Table AX5-10.4.

5.10.1.5 Lead-Induced Liver Hyperplasia: Mediators and Molecular Mechanisms

The biochemical and molecular events associated with Pb-induced hyperplasia has been accumulating in the scientific literature. Lead-nitrate, a known mitogen, is also considered to be a carcinogen that induces liver cell proliferation in rats without any accompanying liver cell necrosis. It has been recognized that this proliferation is a transient process and that apoptosis plays a major role in the regression of Pb-nitrate-induced hepatic hyperplasia (Nakajima et al., 1995). Columbano et al. (1996) studied the cell proliferation and regression phases by apoptosis in Wistar male rat liver by monitoring the incorporation of tritiated thymidine as a marker for increased DNA synthesis. These studies demonstrated the production of Pb-induced proliferation 3 days after a single injection of Pb-nitrate with complete regression of hyperplasia seen after 15 days. The authors suggested that the apoptosis process observed in the regression phase also involved newly initiated hepatocytes. On the other hand, Dini et al. (1999) reported the regressive or involutive phase as beginning 5 days post single injection of Pb-nitrate. Apostoli et al. (2000) evaluated the proliferative effects of various Pb salts (i.e., Pb-acetate, Pb-chloride, Pb-monoxide, Pb-sulfate) using liver-derived REL cells. These authors reported that all the Pb compounds tested showed dose- and time-dependent effects on the proliferation of REL cells. Unlike other tumor promoters, Pb compounds did not exhibit effects on cell junctional coupling. Liver hyperplasia induced by Pb-nitrate has been shown to demonstrate

sexual dimorphism in all phases of the proliferation as well as in apoptosis (Tessitore et al., 1995). Biochemical changes associated with liver hyperplasia in the intermediary metabolic pathways were discussed in earlier sections of this chapter; the present discussion focuses on other molecular characteristics of this process. As the numerous molecular networks involved in both the proliferation and apoptosis processes have many common mediators and pathways, it is very difficult to provide a discussion without an overlap.

DNA hypomethylation has been recognized to play a major role in the proliferation of cells in regenerating and in hepatic pre-malignant lesions when compared to normal non-dividing liver cells. A single dose of Pb-nitrate (75 μM/kg body wt) has been found to cause extensive hypomethylation in rat liver (Kanduc et al., 1991). Additional investigations from the same group reported that this hypomethylation status of liver DNA by Pb-nitrate changed significantly with age and exhibited liver cell specificity (Kanduc and Prisco, 1992).

Investigations of cell cycle-dependent expression of proto-oncogenes in Pb-nitrate (10 μM/100 g body wt)-induced liver cell proliferation by Coni et al. (1989) showed that peak DNA synthesis occurred at 36 h after a single injection of Pb-nitrate. In addition to DNA synthesis, induced expression of c-fos, c-myc, and c-Ha-ras oncogenes was also observed in rat liver tissue. Additional studies by the same group reported that Pb-nitrate-induced liver hyperplasia involved an increased expression of c-jun in the absence of c-fos expression (Coni et al., 1993). The induced expression of c-myc persisted up to 40 h post Pb-nitrate exposure. Pb-nitrate-induced liver proliferation and DNA synthesis, as monitored by 5-bromo-2-deoxyuridine immunohistochemistry, lead to DNA labeling in a few hepatocytes (Rijhsinghani et al., 1993). The observed DNA synthesis appeared to be due to the increased activity and expression of DNA polymerase-α observed at 8 h postexposure to a single injection of Pb-nitrate (Menegazzi et al., 1992). Along with DNA synthesis, poly (ADP-ribose) polymerase was also induced by Pb-nitrate (Menegazzi et al., 1990). Differential activation of various PKC isoforms, downregulation of PKC-α, and marked activation of PKC-ϵ in Pb-nitrate-mediated liver hyperplasia suggested the involvement of these PKC enzymes in DNA synthesis and related signal transduction pathways (Tessitore et al., 1994; Liu et al., 1997).

Coni et al. (1992) reported the proliferation of normal and pre-neoplastic hepatic cells treated with the plasma derived from male Wistar rats treated with a single injection of Pb-nitrate; this was the first report on the secretion of biological cell proliferation signals in the liver

after Pb-nitrate treatment. These authors reported that DNA synthesis was detected as early as 30 min and persisted up to 5 days after Pb-nitrate exposure. This observation has opened up the inquiry into the involvement of various growth factors and other biological mediators in hepatic hyperplasia. Shinozuka et al. (1994) investigated the expression of various growth factors (i.e., hepatocyte growth factor, TGF-α, TGF-β) in rat liver after a single injection of Pb-nitrate (100 μM/kg body wt) and reported the involvement of these growth factors in liver cell proliferation. Additional studies by this group to observe LPS sensitivity in rats given Pb nitrate reported that animals given a single injection of LPS up to 100 μg survived, whereas in the presence of Pb-nitrate, they tolerated only 6 μg of LPS, indicating that Pb-nitrate may sensitize the animals for LPS toxicity.

Earlier studies by Honchel et al. (1991) reported that coexposure of rats to Pb-acetate (15 mg/kg) and LPS or TNF showed markedly increased serum levels for various liver injury parameters. They concluded that Pb may potentiate liver toxicity by LPS via a TNF-mediated pathway. The role of TNF-α in Pb-nitrate-induced liver cell proliferation was further investigated by (Ledda-Columbano et al., 1994) who demonstrated the inhibition of Pb-nitrate-induced cell proliferation by pretreatment with dexamethasone, an inhibitor of TNF-α expression. Additional studies by the same group evaluated the liver cell specificity in Pb-nitrate-induced cell proliferation (Shinozuka et al., 1996). They monitored the incorporation of 5-bromo-2-deoxyuridine by immunohistochemical analysis on rat liver as induced by Pb-nitrate and TNF-α and observed 5-bromo-2-deoxyuridine incorporation in hepatocytes and non-parenchymal cells (i.e., Kupffer cells, endothelial cells, periportal nondescript cells), confirming that Pb-induced liver cell proliferation was mediated by TNF-α. Kubo et al. (1996) used various TNF-α inhibitors to further confirm the role of TNF-α in Pb-nitrate-induced hepatocyte proliferation. Menegazzi et al. (1997) reported that Pb-nitrate induced proliferation involved the induction of iNOS along with TNF-α and that appeared to be mediated by a strong, prolonged activation of NFκB but not activator protein-1 (AP-1). Nemoto et al. (2000) investigated the potential role of neurotrophins and their receptors in Pb-nitrate-induced hepatic hyperplasia. The expression profile of TNF-α, neurotrophins (i.e., nerve growth factor, brain-derived neurotrophic factor neurotrophin-3 and (their receptors), tyrosine kinase receptor (Trk) and neurotrophin receptor (p75NTR) were investigated in liver tissue after a single injection of Pb-nitrate (100 μM/kg body wt). The Pb-nitrate induced increased expression of TNF-α preceded the

expression of the neurotrophins and their receptors. Based on these results, the author's suggested that neurotrophins and neurotrophin receptors are involved in mediating mitogenic signals related to hepatic hyperplasia.

The regression phase of Pb-induced liver hyperplasia appears to be mediated by OS. As discussed earlier, this process involves LPO and other cytokine mediators, including TNF-α. Sieg and Billings (1997) reported that Pb potentiated cytokine-induced OS, producing a significant decline in intracellular ATP concentration in mouse hepatocyte culture studies. The authors suggested that cytotoxic interaction between Pb and cytokines (e.g., TNF-α and IFN) may be mediated by oxidative DNA damage resulting from OS. The potential role OS along with TNF-α has been implicated in the apoptosis of hepatocytes by Milosevic and Maier (2000). Using freshly isolated cultures of hepatocytes and Kupffer cells and their co-culture system exposed to Pb-acetate (2-50 μM) and LPS (0.1-1000 ng/mL), the authors reported that, in the co-culture system, the Pb-LPS-induced release of TNF-α from the Kupffer cells, increased nitric oxide levels by 6-fold and downregulated the acute phase protein, albumin, in hepatocytes. From these observations the authors concluded that Pb-induced Kupffer cell-derived signals promoted the toxicity of Pb in hepatocytes, resulting in hepatocyte death by proteolysis. The importance of the Kupffer cells role in Pb-nitrate-induced heptatocyte apoptosis was further demonstrated (Pagliara et al., 2003a,b). These authors reported that in vivo hepatic apoptosis including oxidative response induced by Pb-nitrate, was prevented by pretreatment with gadolinium chloride, a Kupffer cell toxicant that specifically suppresses Kupffer cell activity. When treated hepatocytes were exposed in vitro to Pb-nitrate, hepatocyte apoptosis was not observed. On the other hand, hepatocyte apoptosis was evident when the hepatocytes were incubated with culture medium derived from Kupffer cells that had been exposed to Pb-nitrate. Based on these studies, the authors concluded that heptocyte apoptosis was potentiated by soluble factors secreted by Pb-exposed Kupffer cells. The role of activated Kupffer cells, macrophages, and TNF-α in chemical-induced hepatotoxicity is presented schematically in Figure 5-10.3.

Dini et al. (1993) investigated the expression of asialoglycoprotein receptors on the surface of hepatocytes and galactose-specific receptors of non-parenchymal cells during the apoptic phase of Pb-induced hepatic hyperplasia. A significant increase in asialoglycoprotein

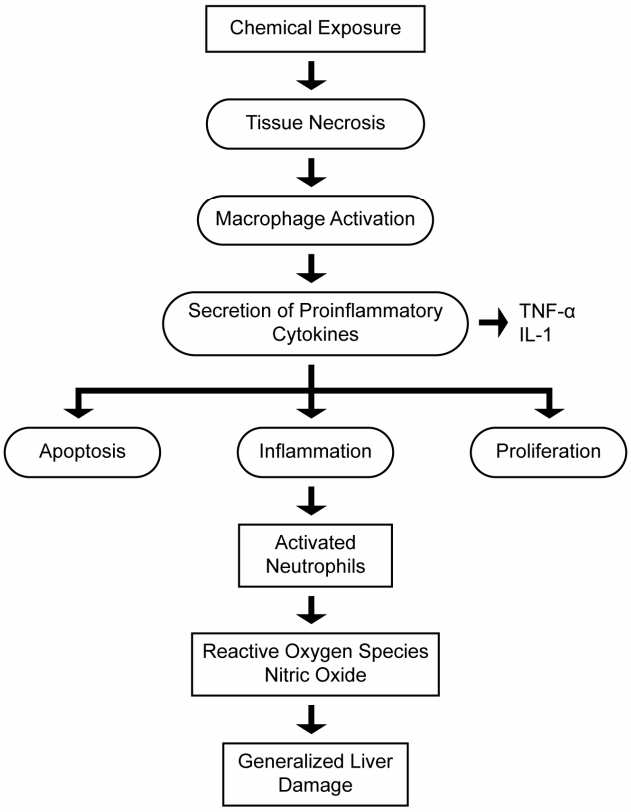


Figure 5-10.3. Hypothesis of chemical-induced liver injury generated primarily on the basis of different types of inhibitors.

receptor expression in hepatocytes coincided with massive apoptosis. Later studies from this group demonstrated that sinusoidal liver cells predominantly phagocytosed the Pb-nitrate-induced apoptic hepatic cells and concluded that this process appeared to be mediated by the cell surface carbohydrate receptors (i.e., mannose and galactose receptors) (Ruzittu et al., 1999). Pretreatment of rats with gadolinium chloride, a kupffer cell toxicant, was also found to abolish the altered expression of galactose receptors (Pagliara et al., 2003b).

The role of glucocorticoid-mediated signal transduction in the hepatotoxicity of Pb was evaluated by Heiman and Tonner (1995), using H4-IIE-C3 hepatoma cells (HTC). Acute exposure of cells to Pb (300 nM^{-1} or 10 μM) was found to inhibit processes involved in glucocorticoid-mediated enzyme induction (e.g., tyrosine aminotransferase activity) in a dose-dependent manner both at the transcriptional and translational level, without altering glucocorticoid receptor binding characteristics. Tonner and Heiman (1997) also reported Pb-induced hepatotoxicity by glucocorticoid-mediated signaling and its involvement in the

interference with calcium-mediated events as well as the differential modulation and translocation of protein kinase isoforms α and β into the nucleus. More information on these and other related studies is summarized in Table AX5-10.5.

5.10.1.6 Effects of Lead on Liver Heme Synthesis

Effects of Pb on heme metabolism have been extensively investigated in major target tissues such as liver and erythrocytes. Section 5.2 described Pb effects on heme synthesis, with particular relevance to erythrocytes. The effects of Pb on heme synthesis in the liver and the role of chelation therapy in this process are discussed in this section.

Fifteen percent of heme is produced in the liver. Heme metabolism in the liver is an essential component of various cytochrome P450s that participate in cellular redox reactions and xenobiotic detoxification pathways in the liver tissue and, hence, heme plays a vital role in liver function (Jover et al., 1996). Due to the important and critical role of heme in liver function, Pb-induced effects on hepatic heme metabolism are discussed below.

Initial studies on the effects of Pb-nitrate on hepatic heme biosynthesis were reported by Lake and Gerschenson (1978) using the rat liver cell line (RLC-GAI). The effects of various organic metal compounds on ALAD activity have been studied by Bondy (1986). The authors reported that triethyl Pb-chloride has the same potency as Pb-nitrate in inhibiting ALAD both in vitro and in vivo, with liver and blood ALAD exhibiting similar sensitivities to Pb compounds. By measuring the conversion of ALA into heme, these authors showed that heme biosynthesis was inhibited by Pb in a dose dependent manner. Using a lipophilic complex of Pb-acetate + DTC to increase the cellular uptake of Pb, Osksarsson et al. (1989) demonstrated the inhibition of ALAD activity in primary rat hepatocytes cultures. Lead-acetate has been reported to inhibit ALAD activity in rabbit liver tissue without any effect on delta-aminolevulinic acid synthase (ALA-synthase) activity (Zereba and Chemielnicka, 1992). Exposure to Pb (500 ppm) in drinking water did not inhibit hepatic ALA-synthase, but did inhibit ALA-dehydratase activity in mice (Tomokuni et al., 1991). Exposure to Pb-acetate (20 mg/kg body wt for 3 days) has been reported to decrease hepatic ALAD and uroporphyrinogen activity (Satija and Vij, 1995). These authors also reported that IP injection of zinc (5 mg/kg body wt for 3 days) conferred protection against Pb-acetate effects in liver tissue.

Effects of Pb on hepatic porphyrins, intermediate metabolites of heme metabolism, were investigated by few researchers. Quntanilla-Vega et al. (1995) reported that 3T3-hepatocyte cultures, when incubated with a micromolar concentration of Pb-acetate increased cellular porphyrin content and excretion. This increased porphyrin production may have been due to an accumulation of protoporphyrin and coproporphyrin, as in coproporphyrinuria, a well-characterized sign of Pb intoxication (Ichiba and Tomokuni, 1987; Zereba and Chemielnicka, 1992). Dietary supplementation of selenium and monensin increased Pb-induced accumulation of prophyrins in chicken liver (Khan and Szarek, 1994). Species-specific differences in the effects of Pb on protoporphyrins were reported by Jacobs et al. (1998). These authors investigated the effect of Pb on zinc protoporphyrin synthesis in cultured chick and rat hepatocytes and observed decreased levels of protoporphyrin in rat hepatocytes, but no effect on chick hepatocytes. Santos et al. (1999) also reported Pb-induced derangements (including porphyrin metabolism) in rat liver heme metabolism, but these effects were far less severe than those observed in erythrocytes. Their investigations on the effect of chronic alcoholism on Pb effects in hepatic heme metabolism suggested no potentiation by alcohol.

Transferrin (TF) is the major iron-transport protein in serum and other biological fluids. Transferrin can also has the capacity to transport other metals. Lead was found to inhibit TF endocytosis and transport of iron across the cell membrane of rabbit reticulocytes (Qian and Morgan, 1990). The effect of Pb on TF gene expression was investigated by Adrian et al. (1993) using a transgenic mouse with the human TF gene. They found that Pb suppressed the expression of TF transgene in mouse liver at the transcriptional level; however, the same dose of Pb did not inhibit mouse endogenous hepatic TF gene expression. Lead exposure was also found to inhibit recombinant TF expression in human hepatoma hepG2 cells. Other studies by the same group found that Pb exposure suppressed the expression of endogenous TF in HepG2 cells (Barnum-Huckins et al., 1997). These authors further suggested that Pb effects on hepatic TF levels may also interfere with iron metabolism in humans. (See Annex Table AX5-10.6 for more information on these and related studies.)

5.10.1.7 Summary

Extensive in vivo and in vitro experimental evidence has accumulated over the past 20 years and increased our understanding of the potential toxic effects of Pb in the hepatic

system. These studies ranged from simple biochemical studies to molecular characterizations of the induction of drug-metabolizing enzymes, liver hyperplasia, and the protective effects of chelation therapy.

- Rat liver microsomal cytochrome P-450 levels were found to decrease with a single dose exposure of Pb nitrate. Inhibition of both constitutive and induced expression of microsomal P450 A1 and A2 activity occurred. Simultaneous induction of the activities of phase II drug metabolizing enzymes with decreased phase I enzymes with single exposure to Pb nitrate suggests biochemical properties similar to hepatic nodules.
- Newer studies examined the induction of GST-P at both transcriptional and translational levels using in vitro systems and indicated a role for Pb-nitrate and Pb-acetate in the induction process. On the other hand, triethyl Pb compounds have been found to suppress the activity of various GST isoforms.
- Studies on Pb-induced liver hyperplasia demonstrated de novo synthesis of cholesterol, alterations in the gluconeogenic mechanism, as well as DNA hypomethylation and subsequent changes in the expression of protooncogenes.
- Lead-induced alterations in cholesterol metabolism appear to be mediated by the induction of several enzymes related to cholesterol metabolism and the decrease of 7 α-hydroxylase, a cholesterol catabolizing enzyme. This regulation of cholesterol homeostasis is modulated by changes in cytokine expression and related signaling.
- Studies using an inhibitor to block TNF-α have clearly demonstrated TNF-α as one of the major mitogenic signals that mediate Pb-nitrate-induced liver hyperplasia. Lead-induced hyperplasia also appears to be modulated by neurotrophins and their receptors.
- In vitro co-culture systems with Kupffer cells and hepatocytes suggested liver cell apoptosis is mediated by Kupffer cell-derived signals and Pb-induced oxidative stress.
- Newer experimental evidence suggests that Pb-induced alterations in liver heme metabolism involves perturbations in ALAD activity, and porphyrin metabolism, alterations in Transferrin gene expression, and associated changes in iron metabolism.
- Limited experimental evidence on the role of weight loss on liver Pb burden in exposed animals indicate that liver Pb content increases even in the absence of prolonged continued exposure.
- Extensive scientific evidence has accumulated over these two decades on the role of chelation therapy, both individual and combined. Studies using a combination of therapy regimens with chelators such as DMSA, Mi-DMSA, or DMSA+ EDTA did not prove beneficial in ameliorating the Pb-induced oxidative stress in infant/neonatal rats as the combination therapy in young rats resulted in essential mineral deficiencies.
- Therapeutic intervention with S-adenosyl-L-methionine, L-acetyl cysteine, lipoic acid, and vitamin E conferred protection against Pb accumulation in the liver and Pb-induced lipid peroxidation. Intervention with ascorbic acid, on the other hand, has been found to confer protection against Pb-induced decrease in hepatic heme synthesis.

5.10.2 Gastrointestinal System and Lead Absorption

Lead enters the body by many routes, but primarily via the GI tract. The intestinal epithelium serves as one of the body's primary interfaces with the outside world. The transporting epithelia in the small intestine are characterized by layers of anatomically and biochemically polarized cells that are connected to each other by tight junctions and resting on a basement membrane. Classically, the intestinal epithelium is thought of primarily as a barrier, but it also is a highly reactive barrier. Even modest perturbations in its functions may lead to diarrhea, constipation, malnutrition, dehydration, and infectious diseases (i.e., ulcerative colitis, collectively referred as chronic intestinal inflammatory diseases) (Gewirtz et al., 2002). Abdominal colic and constipation are symptoms of Pb poisoning, but its mechanism is not fully understood. Studies have been carried out in the past decade to increase our understanding of the fundamental mechanism(s) in order to extrapolate the experimental observations to human health effects.

The intestinal absorption of Pb is influenced by a variety of factors, including the chemical and physical forms of the element, age at intake, and various nutritional factors. Gastrointestinal absorption of Pb is thought to occur primarily in the duodenum. In the isolated rat intestine, absorption, and, in particular, serosal Pb transfer activity (net transfer of Pb from the small intestine lumen across the epithelium and into the serosal space) is highest in the duodenum. The mechanisms of absorption may involve active transport and/or diffusion through the intestinal epithelial cells. Both saturable and non-saturable pathways of absorption have been inferred from the studies in different animal models, although the understanding of the former is slightly more robust (Diamond et al., 1998).

Transport of Pb as a complex with proteins via endocytosis or as a complex with amino acids are postulated as possible mechanisms. Direct evidence for transport of an organic Pb complex has not been provided, but it seems possible.

In the cell, Pb interacts with a variety of intracellular ligands, including calcium-binding proteins and high-affinity Pb-binding proteins. Transfer across the cell or basolateral membrane (or both) involves a mechanism(s) that may be sensitive to vitamin D and iron status. Alternate transport mechanisms via a Ca^{2+}-Na^{+} exchanger, independent of regulation by vitamin D, are also possible.

5.10.2.1 Lead and In vitro Cytotoxicity in Intestinal Cells

In vitro cytotoxicity of metal salts for 48 h was determined in the intestinal epithelial cell line I-407 by Keogh et al. (1994). The investigations identified rank order cytotoxicity in terms of LC_{50} values: $HgCl_2$ (32 μM)>$CdCl_2$ (53 μM) > $CuCl_2$ (156 μM) > Ti_2SO_4 (377 μM) > Pb $(NO_3)_2$ (1.99 mM). Further studies using a noncytotoxic concentration of butathione sulphoxamine pretreatment for GSH depletion revealed that the cytotoxicity of Pb was unaffected by GSH depletion (see Table AX5-10.7).

5.10.2.2 Alterations in Intestinal Physiology and Ultrastructure

Karmakar et al. (1986) investigated the pathologic alterations that occur in the intestine, liver, and kidney of Pb-intoxicated rats upon short-term exposure to sublethal doses of Pb (44 mg/Kg body wt) and reported degeneration of intestinal mucosal epithelium leading to potential malabsorption.

The effect of low-concentration Pb-acetate (0.1%) on the jejunal ultrastructure was studied by Tomczok et al. (1988) in young male rats. The studies revealed that the villi of jejunum of rats exposed to Pb for 30 days had a rough appearance on the surface, which could be associated with a distortion of glycocalyx layer. Areas of extensive degenerative lesions were also observed on the surface of most villi on the 60th day of exposure. All intestinal epithelial cells exhibited various degrees of glycocalyx disturbance, indicating that pronounced toxic effects of Pb were related to modifications of the biochemical properties of the surface coat of the cells. These authors also reported the appearance of goblet cells and of Pb deposition along the goblet cell membrane in blocks of tissue along the border between duodenum and jejunum. Continued treatment up to 60 days resulted in mucus droplets in the cytoplasm of goblet cells, along with deposition of silver salts indicative of Pb in these cells. These results demonstrated the significance of goblet cells in Pb detoxification.

In another study on the ultrastructure of rat jejunum exposed to Pb-acetate (100 mg/kg body wt/day), Tomczok et al. (1991) found that 30-day treatment resulted in numerous small, rough-membraned vesicles and dilated golgi complexes in the cytoplasm. Continued treatment for 60 days resulted in vacuolated cytoplasm associated with the golgi complexes, rough-membraned vesicles, and dilated cisternae. Also, the surface of the intestinal epithelial cell microvilli showed evidence of Pb deposition, as evidenced by Timm sulfide silver reaction sites.

5.10.2.3 Intestinal Uptake and Transport

Infants are a particularly susceptible population for Pb toxicity, possibly due to the immaturity of the digestive tract, feeding pattern, or source of Pb. To investigate these aspects, Henning's group (Beach and Henning, 1988; Henning and Cooper, 1988) carried out a series of experiments using suckling rat pups and reported that Pb in rat and bovine milk and infant milk formula was primarily associated with casein micelles. Casein-bound Pb may be the most common form of Pb presented to the small intestine (Beach and Henning, 1988). Other studies by this group investigated potential differences in the mechanisms when Pb was presented in ionic or milk-bound form, using ^{203}Pb as a tracer. These studies clearly showed that when ^{203}Pb was administered intragastrically as a soluble salt, it was primarily accumulated in the duodenum, regardless of dose or vehicle used. In contrast, substantial accumulation of ^{203}Pb was found in the ileal tissue following Pb administration in milk. These studies clearly indicated strikingly different patterns in the intestinal accumulation of ionic and milk-bound Pb and suggest a greater toxicity for Pb in drinking water compared to Pb ingestion via milk (Henning and Cooper, 1988).

Dekaney et al. (1997) investigated the uptake and transport of Pb using intestinal epithelial cells (IEC-6). The authors observed that Pb accumulation in Pb-exposed (5-10 μM) IEC-6 cells was time- and dose-dependent up to 1 h and that reduction of the incubation temperature significantly reduced the total cellular Pb content of IEC-6 cells. Simultaneous exposure to Zn resulted in decreased cellular Pb content compared to cells exposed to Pb only. Exposure of cells to ouabin or sodium azide has been found to increase Pb accumulation in the cells compared to cells treated with Pb (5 μM) alone. These studies clearly demonstrate that Pb transport in IEC-6 cells is time- and temperature-dependent, involves the presence of sulfydryl groups, and competes with the uptake of Zn.

Lead speciation and transport across intestinal epithelium in artificial human digestive fluid (chyme), both in vivo and in vitro, in Caco-2 cells were evaluated by Oomen et al. (2003). In vivo studies indicated that in chyme, Pb-phosphate and Pb-bile complexes are important fractions. The metal ions dissociated from these complexes can subsequently be transported across the intestinal epithelium or they may traverse the intestinal membrane. In vitro studies, on the transport of bioaccessible Pb across the intestinal epithelium in Caco-2 cells exposed to diluted artificial chyme for 24 h, indicated that 3% of the Pb was transported across the cell

monolayer. Lead associated with cells in a linear relationship to the total amount of Pb in the system. Bile levels were not found to affect the fraction of Pb associated with the cells. The free Pb^{2+} concentration in chyme was negligible. Extrapolating these results to the in vivo situation, the authors concluded that Pb species other than the free metal ion may have contributed to the Pb flux towards the cells, possibly involving the dissociation of labile Pb species, such as Pb-phosphate and Pb-labile complexes and the subsequent transport of the released free metal ions toward the intestinal membrane.

5.10.2.4 Alterations in Gastrointestinal Motility/Gastrointestinal Transit and Function

The effect of Pb on contractility of rat duodenum was determined in vivo in rats given an oral dose of Pb-acetate (44 mg/kg per day, Pb as 53 mM/L for 4 weeks) to investigate the possible mechanisms associated with Pb-induced abdominal colic and constipation (Karmakar and Anand, 1989). Deodenal motility and the amplitude of contractility of rat duodenum were decreased significantly in the Pb-exposed rats, leading the authors to conclude that there was a fundamental change in the contractility of the intestinal tract due to Pb intoxication.

Chronic Pb ingestion through drinking water (2-5 mg/mL, Pb-acetate for 55 days) caused a 20-fold increase in urinary excretion of D-ALA and an increase in blood Pb level (80 μg/dL), without any perturbations in propulsive motility of guinea pig colon (Rizzi et al., 1989). On the other hand, Lawrel et al. (1991) observed no changes in gastric contractions during ingestion in red-tailed hawks exposed to Pb-acetate (0.82 or 1.64 mg/kg body wt for 3 weeks). This low level of exposure has also been found to have no bearing on the regular passing of pellets of undigested material. Shraideh (1999) studied the effect of triethyl Pb-chloride on the rhythmic and peristaltic contractile activity of ileum isolated from Swiss mice. These authors observed no significant effect below 40 μM of TEL, while higher concentrations (40-120 μM) caused changes in contraction rhythm. These studies also reported that TEL above 120 μM induced irreversible changes in the ileal contractile activity. These and related studies are summarized in Table AX5-10.8.

5.10.2.5 Lead, Calcium, and Vitamin D Interactions in the Intestine

The complex biological interactions between Pb and calcium have been recognized and demonstrated in virtually every type of tissue. Studies of high-affinity Pb binding to intracellular

calcium receptors and transport proteins, as well as the involvement of Pb in calcium-activated and calcium-regulated processes, have added to our understanding of the effects of Pb on biological processes at the cellular level. The intestinal absorption of Pb is influenced by a variety of factors, including chemical and physical forms of the element, age at intake, and various nutritional factors. Work dating back to the 1940s established that the deposition of Pb in bone and soft tissue significantly increases under conditions of dietary calcium and phosphorus deprivation or by the administration of vitamin D to rachitic animals. Later, in the 1970s, it was demonstrated that dietary calcium status was a major contributing factor determining relative susceptibility to Pb intoxication.

Fullmer's group (Fullmer and Rosen, 1990; Fullmer, 1991, 1992, 1997) carried out a series of studies to investigate the potential interaction between calcium and Pb in the ingestion and intestinal absorption of Pb. Various parameters, such as absorption kinetics for Ca and Pb, activity of alkaline phosphatase, expression of the clabindin D gene, and the potential role of endocrine function in this interaction (as assessed by cholecalciferol and its active hormonal form, 1, 25-dihydroxycholecalciferol levels) were investigated. Fullmer and Rosen (1990) observed that chicks fed with low (0.5%) and adequate (1.2%) dietary calcium and exposed to Pb (0-0.8%) exhibited differential effects on intestinal Ca absorption depending on their dietary Ca status. In the chicks fed a low-calcium diet, Pb inhibited intestinal Ca absorption and calbindin D and alkaline phosphatase synthesis in a dose-dependent fashion. On the other hand, chicks fed the normal diet, showed no inhibition of Ca absorption. Based on these results, the authors postulated that Pb-induced alterations in intestinal Ca absorption may involve cholecalciferol and the endocrine system. In an extension of this study using young growing chicks, Fullmer (1991) observed similar results in 2-week Pb-exposed, but not in 1-week exposed, chicks.

As dietary Ca deficiency is associated with a marked increase in the body burden of Pb and in the susceptibility to Pb toxicity during chronic ingestion, Fullmer (1992) examined the effects of vitamin D supplementation on intestinal Pb and Ca absorption. When vitamin D-deficient chicks received physiologic amounts of vitamin D (0.1mg/day), intestinal ^{203}Pb and ^{47}Ca absorption rates were elevated by 4- and 8-fold, respectively. Along with this, calbindin D and alkaline phosphatase activities were also found to be significantly elevated. Ingestion of even the highest level of Pb (0.8 %) during the repletion phase had no effect on intestinal Ca absorption. To further understand the Pb-Ca interactions and the potential involvement of

vitamin D on intestinal absorption, Fullmer (1997) evaluated serum levels of 1, 25-dihydroxyvitamin D. Lead ingestion and Ca deficiency alone, or in combination, generally increased serum 1, 25-dihydroxyvitamin D levels over most of the ranges of Pb or Ca studied. However, in severe Ca deficiency, Pb ingestion resulted in marked decreases in serum 1, 25-dihydroxyvitamin D, intestinal Ca absorption, and calbindin D mRNA. From these studies using response surface models, Fullmer (1997) concluded that the interactions between Pb and Ca were mediated via changes in circulating 1, 25-dihydroxy vitamin D hormone, rather than via direct effects on the intestine.

Similar to Ca deficiency, iron deficiency has also been found to increase intestinal absorption of Pb, as indicated by increased blood and kidney Pb levels in iron-deficient rats exposed to dietary Pb; but the mechanistic details are not known (Crowe and Morgan, 1996). These and other related studies are summarized in Table AX5-10.9.

5.10.2.6 Lead and Intestinal Enzymes

Differential effects of Pb on intestinal brush border enzyme activity profiles were reported by Gupta et al. (1994). Across a concentration range of 0.5-6.0 mM, Pb-acetate was found to significantly inhibit Ca-Mg-ATpase, g-glutamyl transpeptidase, and acetylcholineesterase activities in a dose-dependent manner without effects on alkaline phosphatase.

Cremin et al. (2001) investigated the effects of oral succimer on the intestinal absorption of Pb in infant rhesus monkeys. These studies indicated that chelation therapy with DMSA for two successive 19-day periods significantly decreased GI absorption of Pb and increased urinary excretion of endogenous lead (see Table AX5-10.9).

5.10.2.7 Summary

- Gastrointestinal absorption of Pb is influenced by a variety of factors, including chemical and physical forms of the element, age at intake, and various nutritional factors. The degeneration of intestinal mucosal epithelium leading to potential malabsorption and alterations in the jejunal ultrastructure (possibly associated with distortion of glycocalyx layer) have been reported in the intestine of Pb-exposed rats.
- Lead in rat and bovine milk and, also, infant milk formula was demonstrated to be primarily associated with caseine micelles.
- Tracer studies using ^{203}Pb indicated that intragastric administration of Pb as a soluble salt resulted in Pb primarily accumulating in the deuodenum, regardless of dose or vehicle

used, whereas Pb from milk was found to be taken up by ileal tissue. Studies also suggested Pb ingestion through water was more toxic than ingestion through milk.

- Lead induced decreases in duodenal motility and amplitude of contractility of the intestinal tract has been reported for rats.
- Nutritional studies using various levels of Pb, Ca, and vitamin D in the diet indicate competition of Pb with Ca absorption. Supplementation with vitamin D has been reported to enhance intestinal absorption of Ca and lead. Physiological amounts of vitamin D administered to vitamin D-deficient rats resulted in elevated Pb and Ca levels. In the case of severe Ca deficiency, Pb ingestion results in a marked decrease in serum 1,25-hydroxy vitamin D.

Overall, our understanding of Pb effects on hepatic and gastro intestinal systems using in vitro cell culture models and in vivo animal models has increased greatly compared to the 1986 AQCD. Significant insights have emerged regarding the role of Pb in hepatic cholesterol synthesis, the role of inflammation in Pb-induced hepatotoxicity, and the contribution of newer chelation therapy in the amelioration of Pb-induced oxidative burden. Similarly, our knowledge has greatly enhanced as to the absorption, transport, and toxicity of Pb in the gastrointestinal tract.

5.11 LEAD-BINDING PROTEINS

Lead-binding proteins that are constitutively expressed within the cells and bind Pb can be classified into two types of protein. The first type of Pb-binding proteins are inducible, i.e., their concentration increases after exposure to Pb. The second type of Pb-binding proteins have binding sites that are saturable by Pb, but no discernible increase in protein content occurs after exposure to Pb. The second type is, perhaps, most pertinent to enzymes that can be inhibited by Pb.

The history of research on Pb-binding proteins dates back to 1936, when the presence of intranuclear inclusion bodies in the liver and kidney as manifestations of Pb poisoning was first described (Blackman, 1936). Later, detailed studies of the composition of renal tubular intranuclear Pb inclusion bodies and consequent alterations in mitochondrial structure and function followed.

5.11.1 Lead-Binding Proteins Within Intranuclear Inclusion Bodies in Kidney

Goyer (1968) examined the renal tubules of rats fed 1% Pb-acetate for up to 20 weeks, and found that dense, deeply staining intranuclear inclusions were located in the straight portion of the proximal tubules, accompanied by swollen, globular or ovoid, closely packed mitochondria with many marginated, irregular, or vesicular cristae. Accompanying these mitochondrial changes was the presence of generalized aminoaciduria. Goyer et al. (1968) also isolated mitochondria from Pb-exposed and control rats and demonstrated that mitochondria from the Pb-exposed rats showed reduced rates of respiration and oxidative phosphorylation.

Lead within the kidneys in Pb-poisoned rats was found to be concentrated in the nuclei and, within nuclei, in the nuclear inclusion body (Goyer et al., 1970a,b). Choie and Richter (1972) showed that rapid induction of inclusion bodies by injections of Pb salts in the rat resulted in cytoplasmic inclusions, suggesting that they were precursors to the intranuclear inclusions. Lead-containing nuclear inclusions were also found in organs other than the kidney, including liver and glial cells of the central nervous system (Goyer and Rhyne, 1973). Moore et al. (1973) dissolved the rat renal intranuclear inclusions in strong denaturing agents and found that the protein in the inclusions is acidic, with high levels of aspartic acid, glutamic acid, glycine, and cystine. Moore and Goyer (1974) later characterized the protein as a 27.5 kDa protein, which migrates as a single band on acrylamide gel electrophoresis. Repeated intraperitoneal injections of $CaNa_2EDTA$ resulted in the disappearance of the inclusion bodies in Pb-exposed rats, together with a marked decrease in kidney Pb levels (Goyer et al., 1978).

Shelton and co-workers have also explored the composition of Pb-binding proteins in the nuclear inclusion proteins of Pb-exposed rat kidneys. Shelton and Egle (1982) first described a 32 kDa protein with an isoelectric point of 6.3, which was isolated from the kidneys of rats treated with 1% Pb-acetate in rat chow or 0.75% Pb-acetate in drinking water for 13-17 weeks. In contrast to Goyer and co-workers, they used two-dimensional gel electrophoresis to isolate the protein from the nuclear inclusion bodies and demonstrated that it was present in Pb-exposed, but not control, kidneys (hence, inducible). This protein has been termed p32/6.3. Inhibitor studies with cycloheximide and actinomycin D (McLachlin et al., 1980; Choie et al., 1975) had indicated earlier that protein synthesis was required for induction of the nuclear and cytoplasmic inclusion bodies.

Egle and Shelton (1986) unexpectedly found that p32/6.3, now characterized by a monoclonal antibody, was constitutively present in the cerebral cortex, both in neurons and astrocytes. The protein was concentrated in the insoluble nuclear protein, findings similar as for the Pb-exposed kidney. Brain p32/6.3 was detected in rat, mouse, dog, man, and chicken. In rat brain, adult levels were achieved in 1 to 2 weeks after birth, whereas only trace amounts were found at 3 days. Brain p32/6.3 increased between postnatal days 10 to 12 in the guinea pig and days 15 to 21 in the rat, suggesting that the increase may be related in part to exposure to the external environment (Shelton et al., 1993). When neuroblastoma cells were cultured after 1- and 3-day exposure to Pb, the abundance of p32/6.3 increased. Simultaneous incubation with Pb and cycloheximide or actinomycin D increased in p32/6.3, suggesting that Pb selectively retards the degradation of the brain protein (Klann and Shelton, 1989). The amino acid composition of partially purified p32/6.3 revealed a high percentage of glycine, aspartic and glutamic acid (Shelton et al., 1990). Thus, the inducible protein, p32/6.3, can be extracted from nuclear inclusion bodies from the Pb-exposed rat kidney, and a similar or identical protein from adult rat brain. Whether the brain protein is constitutive or inducible by exposure to environmental Pb has yet to be determined.

Oskarsson and Fowler (1985) examined the influence of pretreatment with Pb by a single IP injection of Pb-acetate (50 mg Pb per kg) 1, 3, and 6 days before injecting ^{203}Pb. Rats were sacrificed 24 h later and the kidneys were examined both microscopically and for the distribution of ^{203}Pb. At 3 days, rat kidneys displayed fibrillar cytoplasmic inclusions, but at 6 days, these inclusions were less prominent and intranuclear inclusions were observed. ^{203}Pb uptake at 6 days was maximal in the purified nuclear fraction and in the nuclear inclusion bodies (7× and 20× control, respectively).

5.11.2 Cytoplasmic Lead-Binding Proteins in Kidney and Brain

The remaining studies of non-Pb-stimulated cytoplasmic kidney and brain Pb-binding proteins have been provided by Fowler and associates.

The first study (Oskarsson et al., 1982) reported on the Pb-binding proteins in kidney postmitochondrial cytosolic fractions. Binding of ^{203}Pb was found in two protein fractions of control kidneys with molecular weights of 11.5 and 63 kDa. Binding was markedly decreased after Pb pretreatment. The use of cadmium to stimulate metallothionein synthesis did not

increase ^{203}Pb binding to the 11.5 kDa protein. The two binding proteins were also present in brain, but not in liver or lung. Subsequently, Mistry et al. (1985) demonstrated three Pb-binding proteins (11.5, 63, and >200 kDa) in rat kidney cytosol, which had binding characteristics of high affinity, low capacity with respective K_d values of 13, 40, and 123 nM. The 11.5 kDa and, possibly, the 63 kDa proteins were capable of translocating Pb into the nucleus as shown by uptake of ^{203}Pb into nuclei incubated with tagged cytosolic proteins. Goering and Fowler (1984) showed that the 11.5 kDa protein, but not the 63 kDa protein was capable of reversing Pb-induced ALAD inhibition in liver homogenates. This effect was mediated both by chelation of Pb by the Pb-binding protein and by donation of zinc to ALAD (Goering and Fowler, 1985). Various divalent metal ions influence the binding of Pb to the rat kidney cytosolic binding proteins, with an order of displacement of $Cd^{2+}>Zn^{2+}>Pb^{2+}$. Ca^{2+} had no effect, while Fe^{2+} had a cooperative effect (Mistry et al., 1985). These observations may account for the previously demonstrated effect of concomitant Pb and cadmium administration in reducing total kidney Pb (Mahaffey et al., 1981) and preventing the development of intranuclear inclusion bodies (Mahaffey and Fowler, 1977).

Later studies by Fowler and Duval (1991) identified the rat renal Pb-binding protein as a cleavage product of α2-microglobulin, with a K_d of 10^{-8} M Pb. There are two forms of the protein in the kidney, differentiated by the cleavage of the first 9-N terminal residues from the higher-molecular weight form. Other studies by Smith et al. (1998) found two Pb-binding proteins in environmentally exposed human kidneys, identified as acyl-CoA binding protein (ACBP) or diazepam binding inhibitor (molecular weight 9 kDa) and thymosin β4 (molecular weight 5 kDa). These polypeptides have a high affinity for Pb (K_d~14 nM).

In rat brain, Goering et al. (1986) and Duval and Fowler (1989) explored the effects of environmental Pb on Pb-binding proteins and the ability of rat brain Pb-binding proteins to diminish the inhibition of hepatic ALAD by Pb (liver does not contain the Pb-binding protein). In the first study, a brain protein of 12 kDa was described, in comparison to the kidney Pb-binding protein of 9 kDa. Both competition of Pb binding between the brain Pb-binding protein and ALAD and donation of zinc by the brain protein (shown by ^{65}Zn uptake) were found to account for the decreased ALAD inhibition. In the second study the rat brain Pb-binding protein was described as having a molecular weight of 23 kDa, with significant levels of glutamic acid, aspartic acid, and cysteine. Polyclonal antibody to rat renal Pb-binding proteins

showed a lack of reactivity with the brain protein, indicating that the proteins are immunologically distinct.

Fowler et al. (1993) examined monkey kidney and brain from non-Pb-treated animals and isolated Pb-binding proteins that also had a relatively high content of aspartic and glutamic amino acid residues and were similar in size to the rat Pb-binding proteins. Polyclonal antibodies to α-2 microglobulin and metallothionein did not cross-react with either monkey kidney or brain proteins. Quintanilla-Vega et al. (1995) isolated a thymosin β4 and a second, as yet unidentified, protein with a molecular weight of 20 kDa and a pI of 5.9 from brains of environmentally Pb-exposed humans.

5.11.3 Lead-Binding Proteins in Erythrocytes

Intra-erythrocytic Pb-binding was initially attributed primarily to hemoglobin, molecular weight 64 kDa (Barltrop and Smith, 1972; Raghavan and Gonick, 1977; Ong and Lee, 1980; Lolin and O'Gorman, 1988), but more recent studies have ascribed the major Pb binding to ALAD, molecular weight 240–280 kDa. In contrast to this protein, several studies have focused on an inducible low molecular weight protein in workers chronically exposed to Pb and which seems to have a protective effect. The first recognition of this protein was by Raghavan and Gonick (1977) who found an approximately 10 kDa protein in Pb workers but not in controls, following Sephadex G-75 fractionation (Figure 5-11.1). Upon subsequent SDS-polyacrylamide gel electrophoresis, the protein split into two bands, only the uppermost of which contained Pb (Figure 5-11.2).

Raghavan et al. (1980) then went on to fractionate the erythrocyte Pb into a hemoglobin fraction, a 10 kDa fraction, free Pb, and a "residual Pb" fraction thought to be composed of membrane Pb and a high-molecular weight fraction. Lead workers manifesting toxicity at both high blood Pb and relatively low blood Pb levels showed high levels of residual Pb, attributed in the workers with toxicity at low blood leads to a very low quantity of the 10 kDa fraction. In a follow-up study, Raghavan et al. (1981) reported elevated levels of Pb in the high molecular weight fraction (pre-hemoglobin) and in the membrane fraction in workers with toxicity at both high and low BLLs. Again, those with toxicity at low blood Pb had low levels of the Pb bound to the 10 kDa protein. Membrane Pb was found to correlate inversely with membrane Na-K-ATPase; no correlation was seen with total blood Pb.

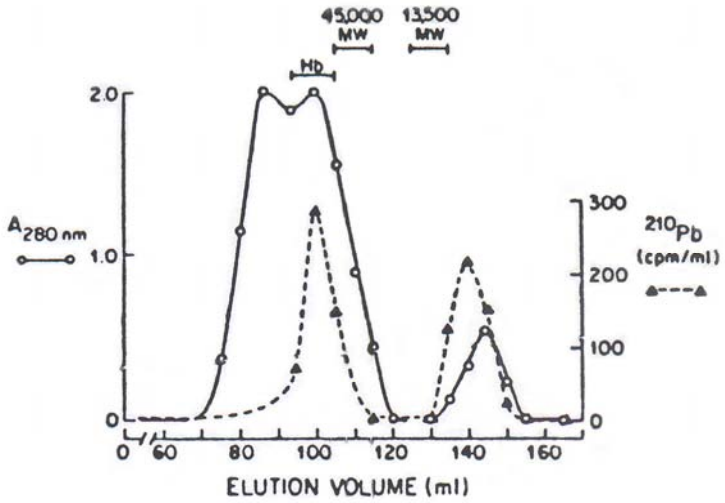


Figure 5-11.1. Sephadex G-75 gel filtration of RBC hemolysate from lead-exposed individual. Ultraviolet absorption and radioactivity of ^{210}Pb are plotted against elution volume. The column was calibrated with ovalbumin (mol wt 45,000) and ribonuclease (mol wt 13,700). Also indicated is the locus of hemoglobin (Hb). Hemolysates from normal control individuals showed no UV absorption or radioactivity in the volume eluting between 130 and 155 mL.

Source: Raghavan and Gonick (1977) with permission.

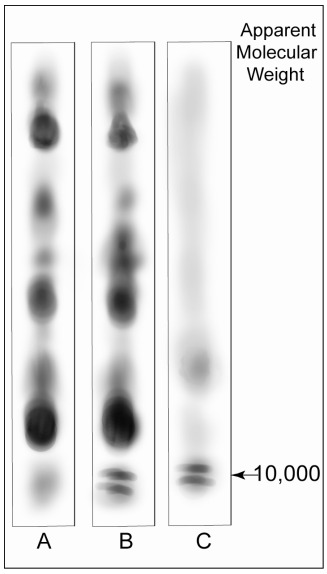


Figure 5-11.2. SDS-polyacrylamide gel electrophoresis of RBC hemolysates from normal control (A) and lead-exposed individuals (B), and of low-mol-wt. lead-binding protein (C). Stained with coomassie blue.

Source: Raghavan and Gonick (1977) with permission.

Gonick et al. (1985) partially purified the 10 kDa protein by HPLC using a protein I-125 column followed by isoelectric focusing on a sucrose gradient column. Three protein peaks resulted: one of 30 kDa, and two of 10 kDa. Only one of the latter peaks contained Pb. This peak had a pI of 5.3 and a molecular weight, determined by SDS-PAGE, of 12 kDa. The majority of Pb was found in this peak, which also contained calcium, zinc, and cadmium. Amino acid analysis showed a very high percentage of glycine (44%) and lower quantities of histidine, aspartic acid, and leucine.

Ong and Lee (1980) studied the distribution of ^{203}Pb in components of normal human blood. Ninety-four percent of ^{203}Pb was incorporated into the erythrocyte and 6% remained in the plasma. SDS-PAGE of plasma showed that 90% was present in the albumin fraction. Within the erythrocyte membrane, the most important binding site was the high molecular weight fraction, about 130–230 kDa. Within the erythrocytic cytoplasm, the protein band associated with ^{203}Pb had a molecular weight of 67 kDa as shown by the elution characteristics on G-75 chromatography. This was thought to be hemoglobin.

Lolin and O'Gorman (1988) and Church et al. (1993 a,b), following the same procedure as Raghavan and Gonick (1977), confirmed the findings of a low molecular weight protein in the erythrocytes of Pb workers, but not found in control patients. Lolin and O'Gorman (1988) quantitated the protein, which ranged from 8.2 to 52.2 mg/L RBC in Pb workers but found none in controls, again implying it to be an inducible protein. They found that the low molecular weight protein first appeared when the blood Pb concentration exceeded 39 µg/dL. A positive correlation was seen between the amount of the intra-erythocytic low molecular weight protein and dithiothreitol-activated ALAD activity but not the non-activated activity. Church et al. (1993a,b) also confirmed the findings of Raghavan et al. (1977). In 1993a, they described two patients with high blood Pb levels: an asymptomatic worker with a blood Pb of 180 µg/dL, and a symptomatic worker with a blood Pb of 161 µg/dL. In the first patient, approximately 67% of the erythrocyte Pb was bound to a low molecular weight protein of approximately 6–7 kDa. In the second patient, the protein only contained 22% of the total erythrocytic Pb. Church et al. (1993b) found that a sample of the low molecular weight protein purified from Pb workers, which they termed protein M, had characteristics of metallothionein, such as a molecular weight of 6.5 kDa, a pI between 4.7 and 4.9, and a greater UV absorbance at 254 nm than at 280 nm. Amino acid composition showed 33% cysteine but no aromatic amino acids. This composition

differed from that of the low molecular weight protein described by Gonick et al. (1985), which had a molecule weight of 12 kDa, a pI of 5.3, and amino acid analysis that showed no cysteine. This discrepancy might be explained by a combined Pb and cadmium exposure in the Church et al. (1993b) study, which may have produced a Pb-thionein.

Xie et al. (1998) used a Biogel A column instead of Sephadex G-75 to separate Pb-binding proteins from erythrocyte hemolysates from a control patient and from Pb-exposed workers. They clearly showed that the major Pb-binding was associated with a large molecular weight protein, consistent with ALAD, in both the controls and Pb workers. When they added increasing amounts of Pb to the blood of the control patient, a second low molecular weight protein peak occurred, in which Pb binding was larger than the ALAD peak (Figure 5-11.3). This second peak was also seen in a chronically Pb-exposed worker (Figure 5-11.4) and was estimated to be less than 30 kDa in molecular weight. Thus these results are consistent with the aforementioned studies.

5.11.4 Lead-Binding Proteins in Rat Liver

Sabbioni and Marafante (1976) explored the distribution of ^{203}Pb in rat whole tissue as well as in subcellular liver fractions. By far the largest quantity of Pb recovered was in the kidney, with lesser amounts in liver, spleen, and blood. Upon subcellular fractionation of the liver, the majority of ^{203}Pb was found in the nuclei, and most of the Pb was detected in the nuclear membrane fraction, bound exclusively to membrane proteins. The intranuclear Pb was associated with histone fractions. As reported by Oskarsson et al. (1982), Pb binding proteins were found in the cytoplasm of the liver.

5.11.5 Lead-Binding Proteins in Intestine

Fullmer et al. (1985) showed in the chick and cow that although Pb does not directly stimulate Pb-binding proteins in the intestine, Pb can displace calcium from calcium-binding proteins; and, thus, calcium-binding proteins may play a role in intestinal Pb transport. Purified calcium-binding protein from chick and cow, as well as calmodulin, troponin C, and oncomodulin were dialyzed against added labeled and unlabeled Pb or calcium. Results disclosed high affinity binding sites, with greater affinity for Pb than for calcium. Similar results

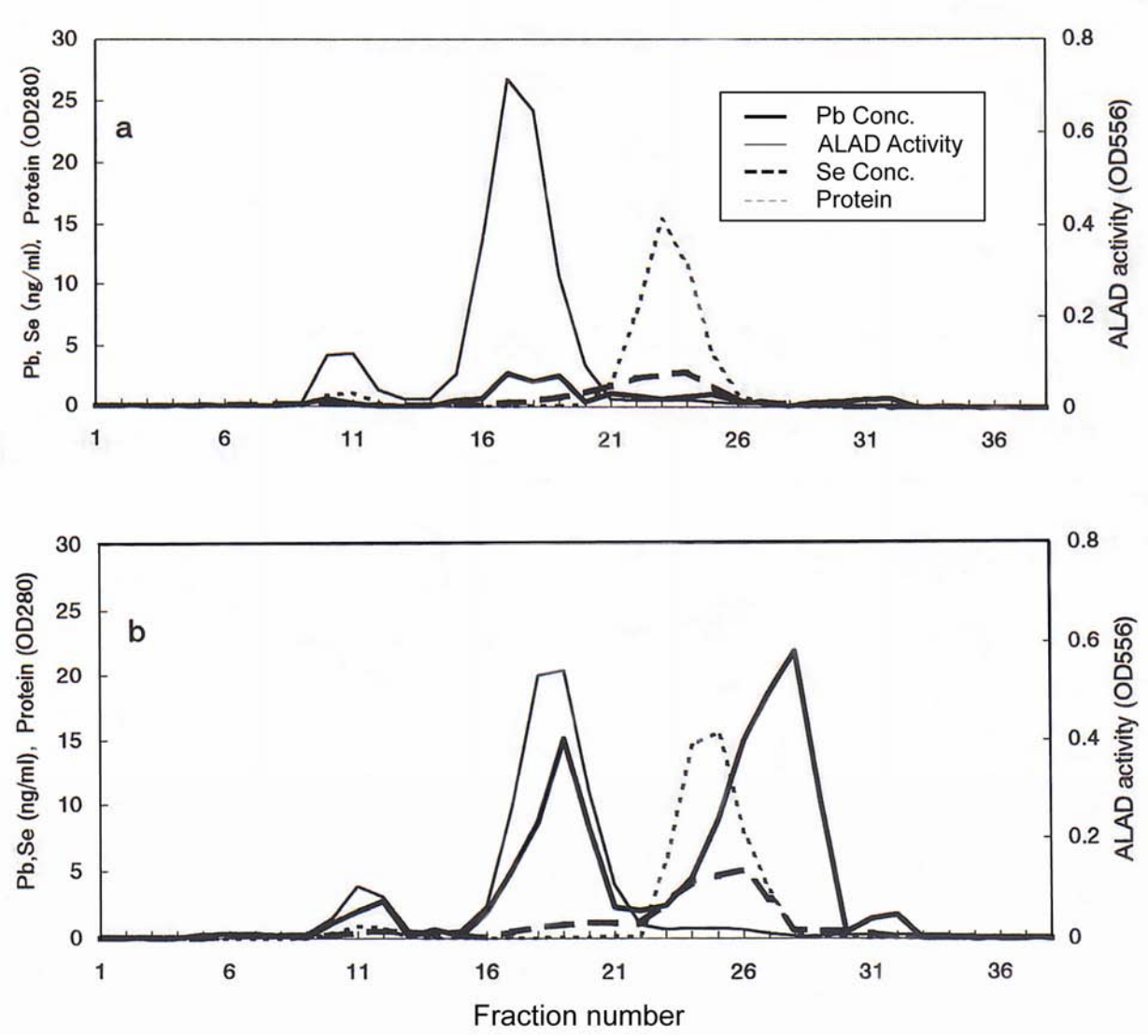


Figure 5-11.3. Chromatographic profiles of protein, ALAD activity and Pb in human erythrocytes incubated with 5% glucose solution containing Pb acetate. Blood was incubated (a) without Pb (b) 10 µM Pb (final concentrations).

Source: Adapted from Xie et al. (1998).

1 were obtained with calmodulin, troponin C, and oncomodulin, all members of the troponin C
2 superfamily of calcium-binding proteins.

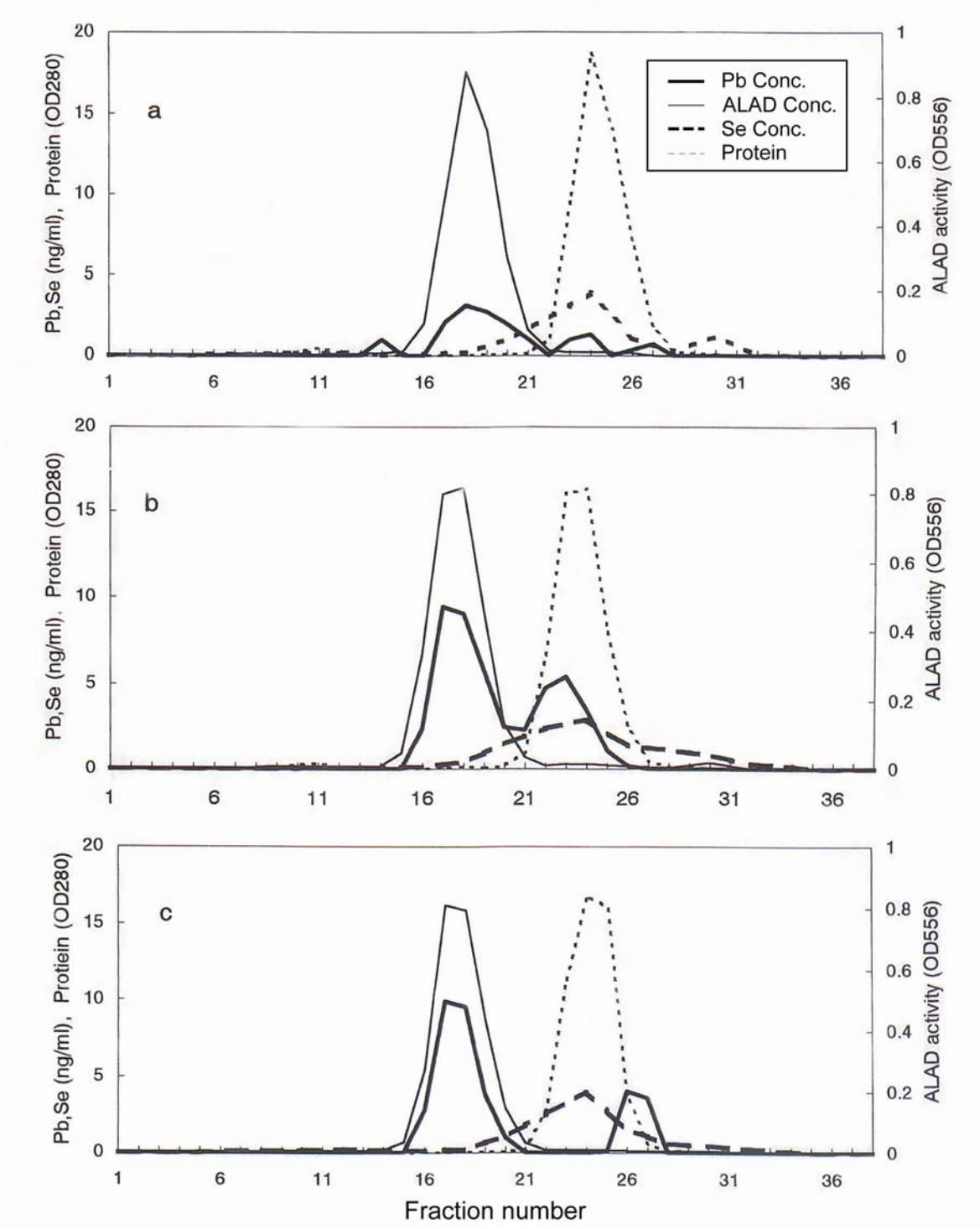


Figure 5-11.4. Chromatic profiles of protein, ALAD activity, Pb, and Se in the erythrocytes of lead-exposed workers. (a) control, (b) subacute exposure, (c) chronic exposure.

Source: Xie et al. (1998) with permission.

5.11.6 Relationship of Lead-Binding Protein to Metallothionein

Similarities of Pb-binding protein to metallothionein have been discussed earlier. Maitani et al. (1986) commented that hepatic zinc-metallothionein could be induced by intravenous and intraperitoneal injections of Pb into mice, but not by subcutaneous injection. Ikebuchi et al. (1986) found that a sublethal dose of Pb-acetate injected intraperitoneally into rats induced the synthesis of a Pb-metallothionein in addition to zinc-metallothionein. The Pb-metallothionein contained 28% half-cysteine and cross-reacted with an antibody against rat zinc-thionein II.

Goering and Fowler (1987 a,b) demonstrated that pretreatment of rats with zinc 48 and 24 h prior to injection of ^{203}Pb resulted in both zinc and Pb co-eluting with a zinc-thionein fraction on Sephadex G-75 filtration. In addition, both purified zinc-thionein-I and II bound ^{203}Pb in vitro. Gel filtration of incubates containing liver ALAD and ^{203}Pb demonstrated that the presence of zinc-thionein alters the cytosolic binding pattern of Pb, with less binding to ALAD. Zinc-thionein also donates zinc to activate ALAD. Goering and Fowler (1987b) found that pretreatment of rats with either cadmium or zinc affected liver ALAD activity when incubated with Pb. Liver and kidney zinc-thioneins, and to a lesser extent, cadmium, zinc-thionein decreased the free pool of Pb available to interact with ALAD, resulting in attenuated ALAD inhibition. Liu et al. (1991) further showed that zinc-induced metallothionein in primary hepatocyte cultures protects against Pb-induced cytotoxicity, as assessed by enzyme leakage and loss of intracellular potassium.

Qu et al. (2002) and Waalkes et al. (2004) have shown that metallothionein-null phenotypic mice are more susceptible to Pb injury over a 20-week period than wild type mice. Unlike the wild type mice, Pb-treated metallothionein-null mice showed nephromegaly and significantly decreased renal function after exposure to Pb. The metallothionein-null mice accumulated less renal Pb than wild type and formed no inclusion bodies. When the observations were extended to 104 weeks, renal proliferative lesions (adenoma and cystic tubular atypical hyperplasia) were more common and severe in metallothionein-null than in wild type mice. A metastatic renal cell carcinoma occurred in a metallothionein-null mouse, whereas none occurred in wild type mice. Such studies lend credence to the view that metallothinein, or a closely related gene, is involved in the formation of Pb-binding proteins in the kidney.

5.11.7 Is ALAD an Inducible Enzyme and is it the Principal Lead-Binding Protein in the Erythrocyte?

The enzyme ALAD has been found to be the most sensitive indicator of Pb exposure and toxicity (Granick et al., 1973, Buchet et al., 1976). In the 1980s, two articles were presented appearing to show that ALAD is inducible after Pb exposure in humans. By comparing a nonexposed control population of Pb workers and assaying ALAD by means of immunoassay or as 'restored' ALAD activity (i.e., incubation with heat, zinc and dithiothreitol) both articles indicated that the amount of ALAD, as contrasted to ALAD activity, was increased by Pb exposure (Fujita et al., 1982; Boudene et al., 1984). Similar findings were reported for the rat (Fujita et al., 1981). Subsequent studies have focused on the effect of ALAD polymorphism on the susceptibility to Pb intoxication. ALAD is a zinc-containing enzyme, which catalyzes the second step of heme synthesis, i.e., catalyzes the condensation of two delta-aminolevulinic acid molecules into one molecule of porphobilinogen (Boudene et al., 1984). It is a polymorphic protein with three isoforms: ALAD-1, ALAD 1-2, and ALAD 2-2. Several studies have shown that, with the same exposure to Pb, individuals with the ALAD-2 gene have higher blood Pb levels (Astrin et al., 1987; Wetmur, 1994; Wetmur et al., 1991; Smith et al., 1995a; Bergdahl et al., 1997; Perez-Bravo et al., 2004; Kim et al., 2004). Initially it was thought that these individuals might be more susceptible to Pb poisoning (Wetmur et al., 1991), but it is now appreciated that the ALAD-2 gene offers protection against Pb poisoning by binding Pb more securely (Kelada et al., 2001). In support of this statement, it can be cited that individuals with the ALAD 1-2/2-2 genotypes, in comparison to those with the ALAD 1-1 genotype, have not only higher blood Pb but also decreased plasma levulinic acid (Schwartz et al., 1997), lower zinc protopophyrin (Kim et al., 2004), lower cortical bone Pb (Smith et al., 1995b), and lower amounts of DMSA-chelatable Pb (Schwartz et al., 1997, 2000).

The significance of erythrocyte ALAD binding to Pb was initially confirmed by a study by Bergdahl et al. (1997) in which the authors used a FPLC Superdex 200 HR 10/30 chromatographic column coupled to ICP-MS (for determination of Pb) to examine erythrocytes from Pb workers and controls. They found the principal Pb-binding protein peak to be 240 kDa (rather than the presumed hemoglobin peak reported by Barltrop and Smith (1972) and Raghavan and Gonick (1977), using Sephadex G-75 chromatography). This was shown to be ALAD by binding to specific ALAD antibodies. Two additional smaller Pb-binding peaks of

45 kDA and 10 kDa were also seen, but not identified. Bergdahl et al. (1997) attributed the discrepancies in the studies to the fact that Sephadex G-75 separates proteins in the range of 3 to 80 kDa, making the separation of hemoglobin (molecular weight 64 kDa) from ALAD (molecular weight 240–280 kDa) very difficult. In addition, the earlier studies had utilized binding of ^{203}Pb or ^{210}Pb to identify the binding proteins, a technique which may have skewed the findings if ALAD were already saturated. ALAD binding capacity for Pb has been measured at 85 µg/dL in erythrocytes or 40 µg/dL in whole blood (Bergdahl et al., 1998), which would permit a greater degree of binding to the low molecular weight component when blood Pb exceeded 40 µg/dL. Bergdahl et al. (1998) have speculated that the low molecular weight component might be acyl-CoA-binding protein, identical to the kidney Pb-binding protein described by Smith et al. (1995b). Goering and Fowler (1987) had reported earlier that the presence of low molecular weight high affinity (K_d 10^{-8}M) Pb-binding proteins in kidney and brain served as protection against ALAD inhibition in those organs, whereas the absence of the low molecular weight proteins in liver contributed to the greater sensitivity to ALAD inhibition in that organ.

A summary of the findings on Pb-binding protein can be found in Table AX5-11.1.

5.11.8 Summary

- There appears to be a consensus that the enzyme, ALAD, a 280 kDa protein, is inducible and is the major Pb-binding protein within the erythrocyte. ALAD polymorphism influences the degree of Pb-binding as the ALAD-2 phenotype binds more Pb in a nontoxic fashion than ALAD-1. What is more confusing is the nature and importance of the low molecular weight erythrocytic Pb-binding protein. There is no doubt that it appears in Pb-exposed workers but not in controls and that its molecular weight is approximately 10 kDa. The in vitro addition of Pb to erythrocytes of controls results in progressively increasing Pb binding to a low molecular weight protein peak migrating in the same position as the low molecular weight protein from Pb workers. This confirms the fact that once the binding capacity of ALAD is saturated, Pb shifts to the low molecular weight protein. The nature of the low-molecular weight protein is also questionable, it has been variously identified as a 12 kDa protein with a high percentage of glycine plus histidine, aspartic acid, and leucine and as a 6.5 kDa molecule with a large percentage of cysteine and a greater UV absorbance at 254 than 280 nm. The latter findings suggest that the protein might be a metallothionein.

- Metallothionein is a protein that is mildly inducible by Pb but to a much greater degree by zinc and cadmium. What is more significant is that Pb binds to pre-formed metallothionein, stimulated by zinc or cadmium, so that under these conditions a

Pb-thionein forms. Thus, concomitant Pb and cadmium exposure occurred in Pb workers that could account for the finding of a metallothionein-like protein in those workers.

- Extensive studies of cytoplasmic Pb-binding proteins in non-Pb-treated rats, human, and monkeys have been reported. The Pb-binding protein in rat kidney has been identified as a cleavage product of α-2 microglobulin. The low molecular weight Pb-binding proteins in human kidney have been identified as thymosin β4 (molecular weight 5 kDa) and acyl-CoA binding protein (molecular weight 9 kDa). In human brain the Pb-binding proteins were thymosin β4 and an unidentified protein of 23 kDa. Antibodies to α-2 microglobulin and metallothionein did not cross-react with monkey kidney or brain Pb-binding proteins, suggesting species differences. Whether the low molecular weight human kidney and brain Pb-binding proteins are similar or identical to the low molecular weight Pb-binding proteins in erythrocytes is at present unknown. Perhaps some clarification would be provided were subsequent investigators to contrast normal with Pb-exposed rats and to measure the resting and inducible Pb-binding protein levels in kidney, brain, and erythrocyte.
- The possible role of metallothionein as a renal Pb-binding protein assumes greater importance because of the work showing that metallothionein-null mice failed to respond to Pb exposure by developing intranuclear Pb inclusion bodies or greatly increased Pb content of the kidneys.

5.12 REFERENCES

Abdollahi, M.; Dehpour, A. R.; Fooladgar, M. (1997) Alteration of rat submandibulary gland secretion of protein, calcium and *N*-acetyl-β-D-glucosaminidase activity by lead. Gen. Pharmacol. 29: 675-680.

Aboul-Ela, E. I. (2002) The protective effect of calcium against genotoxicity of lead acetate administration on bone marrow and spermatocyte cells of mice in vivo. Mutat. Res. 516: 1-9.

Acharya, U. R.; Acharya, S.; Mishra, M. (2003) Lead acetate induced cytotoxicity in male germinal cells of Swiss mice. Ind. Health 41: 291-294.

Ades, A. E.; Kazantzis, G. (1988) Lung cancer in a non-ferrous smelter: the role of cadmium. Br. J. Ind. Med. 45: 435-442.

Adhikari, N.; Sinha, N.; Saxena, D. K. (2000) Effect of lead on Sertoli-germ cell coculture of rat. Toxicol. Lett. 116: 45-49.

Adhikari, N.; Sinha, N.; Narayan, R.; Saxena, D. K. (2001) Lead-indued cell death in testes of young rats. J. Appl. Toxicol. 21: 275-277.

Adrian, G. S.; Rivera, E. V.; Adrian, E. K.; Lu, Y.; Buchanan, J.; Herbert, D. C.; Weaker, F. J.; Walter, C. A.; Bowman, B. H. (1993) Lead suppresses chimeric human transferrin gene expression in transgenic mouse liver. Neurotoxicology 14: 273-282.

Alber, S. A.; Strupp, B. J. (1996) An in-depth analysis of lead effects in a delayed spatial alternation task: assessment of mnemonic effects, side bias, and proactive interference. Neurotoxicol. Teratol. 18: 3-15.

Al-Hakkak, Z. S.; Zahid, Z. R.; Ibrahim, D. K.; Al-Jumaily, I. S.; Bazzaz, A. A. (1988) Effects of ingestion of lead monoxide alloy on male mouse reproduction. Arch. Toxicol. 62: 97-100.

Alkondon, M.; Costa, A. C. S.; Radhakrishnan, V.; Aronstam, R. S.; Albuquerque, E. X. (1990) Selective blockade of NMDA-activated channel currents may be implicated in learning deficits caused by lead. FEBS Lett. 261: 124-130.

Altmann, L.; Weinsberg, F.; Sveinsson, K.; Lilienthal, H.; Wiegand, H.; Winneke, G. (1993) Impairment of long-term potentiation and learning following chronic lead exposure. Toxicol. Lett. 66: 105-112.

Alvarez, J.; Garcia-Sancho, J.; Herreros, B. (1986) Inhibition of Ca2+-dependent K+ channels by lead in one-step inside-out vesicles from human red cell membranes. Biochim. Biophys. Acta 857: 291-294.

Amoruso, M. A.; Witz, G.; Goldstein, B. D. (1987) Alteration of erythrocyte membrane fluidity by heavy metal cations. Toxicol. Ind. Health 3: 135-144.

Angle, C. R.; Thomas, D. J.; Swanson, S. A. (1990) Lead inhibits the basal and stimulated responses of a rat osteoblast-like cell line ROS 17/2.8 to 1"alpha", 25-dihydroxyvitamin D3 and IGF-I. Toxicol Appl. Pharmacol. 103: 281-287.

Angle, C. R.; Thomas, D. J.; Swanson, S. A. (1993) Osteotoxicity of cadmium and lead in HOS TE 85 and ROS 17/2.8 cells: relation to metallothionein induction and mitochondrial binding. BioMetals 6: 179-184.

Antonowicz, J.; Andrzejak, R.; Smolik, R. (1990) Influence of heavy metal mixtures on erythrocyte metabolism. Int. Arch. Occup. Environ. Health 62: 195-198.

Anttila, A.; Heikkila, P.; Pukkala, E.; Nykyri, E.; Kauppinen, T.; Hernberg, S; Hemminki, K. (1995) Excess lung cancer among workers exposed to lead. Scand. J. Work Environ. Health. 21: 460-469.

Anttila, A.; Heikkila, P.; Nykyri, E.; Kauppinen, T.; Pukkala, E.; Hernberg, S.; Hemminki, K. (1996) Risk of nervous system cancer among workers exposed to lead. J. Occup. Environ. Med. 38: 131-136.

Apostoli, P.; Romeo, L.; De Matteis, M. C.; Menegazzi, M.; Faggionato, G.; Vettore, L. (1988) Effects of lead on red blood cell membrane proteins. Int. Arch. Occup. Environ. Health 61: 71-75.

Apostoli, P.; Huard, C.; Chaumontet, C.; Martel, P.; Allesio, L.; Mazzoleni, G. (2000) Effects of four inorganic lead compounds on the proliferation and junctional coupling of cultured REL liver cells. Am. J. Ind. Med. 38: 340-348.

Appleton, J. (1991) The effect of lead acetate on dentine formation in the rat. Arch. Oral Biol. 36: 377-382.

Appleton, J. (1992) Dentinogenesis and the calciotraumatic response to the injection of lead or fluoride ions. Scanning Microsc. 6: 1073-1081.

Arizono, K.; Sugiura, S.; Miyazato, S.; Takiguchi, M.; Ariyoshi, T. (1996) DT-diaphorase induction by lead acetate in the liver of rats. Bull. Environ. Contam. Toxicol. 57: 41-46.

Astrin, K. H.; Bishop, D. F.; Wetmur, J. G.; Kaul, B.; Davidow, B.; Desnick, R. J. (1987) Delta-aminolevulinic acid dehydratase isozymes and lead toxicity. Ann. N. Y. Acad. Sci. 514: 23-29.

Attri, J.; Dhawan, V.; Mahmood, S.; Pandhi, P.; Parwana, H. K.; Nath, R. (2003) Effect of vitamin C supplementation on oxidative DNA damage in an experimental model of lead-induced hypertension. Ann. Nutr. Metab. 47: 294-301.

Aykin-Burns, N.; Laegeler, A.; Kellogg, G.; Ercal, N. (2003) Oxidative effects of lead in young and adult Fisher 344 rats. Arch. Environ. Contam. Toxicol. 44: 417-420.

Baginski, B.; Grube, B. (1991) Einfluss von blei, zink, und cadmium auf die zelltoxische wirklund humaner polymorphkerniger leukozyten am beispiel von hefzellen. Zentralbl. Hyg. Umweltmed. 191: 28-35.

Ballew, C.; Khan, L. K.; Kaufmann, R.; Mokdad, A.; Miller, D. T.; Gunter, E. W. (1999) Blood lead concentration and children's anthropometric dimensions in the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. J. Pediatr. 134: 623-630.

Ban, M.; Hettich, D. (2005) Effect of Th2 cytokine antagonist treatments on chemical-induced allergic response in mice. J. Appl. Toxicol. 25: 239-247.

Bannon, D. I.; Olivi, L.; Bressler, J. (2000) The role of anion exchange in the uptake of Pb by human erythrocytes and Madin-Darby canine kidney cells. Toxicology 147: 101-107.

Baranowska-Bosiacka, I.; Hlynczak, A. J. (2003) The effect of lead ions on the energy metabolism of human erythrocytes in vitro. Comp. Biochem. Physiol. Part C: Toxicol. Pharmacol. 134: 403-416.

Baranowska-Bosiacka, I.; Hlynczak, A. J. (2004) Effect of lead ions on rat erythrocyte purine content. Biol. Trace Elem. Res. 100: 259-273.

Barbier, O.; Jacquillet, G.; Tauc, M.; Cougnon, M.; Poujeol, P. (2005) Effect of heavy metals on, and handling by, the kidney. Nephron. Physiol. 99: 105-110.

Barltrop, D.; Smith, A. (1972) Lead binding to human haemoglobin. Experientia 28: 76-77.

Barnett, J. B. (1996) Developmental immunotoxicology. In. Smialowicz, R. J.; Holsapple, M. P., ed. Experimental immunotoxicology. CRC Press, Inc. Boca Raton. 47-62.

Barnum-Huckins, K. M.; Martinez, A. O.; Rivera, E. V.; Adrian, E. K., Jr.; Herbert, D. C.; Weaker, F. J.; Walter, C. A.; Adrian, G. S. (1997) A comparison of the suppression of human transferrin synthesis by lead and lipopolysaccharide. Toxicology 118: 11-22.

Basaran, N.; Undeger, U. (2000) Effects of lead on immune parameters in occupationally exposed workers. Am. J. Ind. Med. 38: 349-354.

Batetta, B.; Dessi, S.; Pulisci, D.; Carrucciu, A.; Pani, P. (1990) Multiple molecular forms of rat liver glucose-6-phosphate dehydrogenase during liver hyperplasia induced by lead nitrate. Res. Commun. Chem. Pathol. Pharmacol. 67: 279-288.

Batra, N.; Nehru, B.; Bansal, M. P. (2001) Influence of lead and zinc on rat male reproduction at 'biochemical and histopathological levels'. J. Appl. Toxicol. 21: 507-512.

Baykov, B.; Gunova, M.; Stoyanov, M.; Neychev, H.; Stefanova, T.; Nicolova, N. (1996) Designing an artificial ecological mesocosm for the study of Cd and Pb impact on the immune system of experimental animals. Toxicol Lett. 89: 5-10.

Beach, J. R.; Henning, S. J. (1988) The distribution of lead in milk and the fate of milk lead in the gastrointestinal tract of suckling rats. Pediatr. Res. 23: 58-62.

Bellinger, D. C. (2004) What is an adverse effect? A possible resolution of clinical and epidemiological perspectives on neurobehavioral toxicity. Environ. Res. 95: 394-405.

Bellinger, D.; Sloman, J.; Leviton, A.; Rabinowitz, M.; Needleman, H. L.; Waternaux, C. (1991) Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics 87: 219-227.

Bellinger, D. C.; Stiles, K. M.; Needleman, H. L. (1992) Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics 90: 855-861.

Bellinger, D.; Hu, H.; Titlebaum, L.; Needleman, H. L. (1994) Attentional correlates of dentin and bone lead levels in adolescents. Arch. Environ. Health 49: 98-105.

Belloni-Olivi, L.; Annadata, M.; Goldstein, G. W.; Bressler, J. P. (1996) Phosphorylation of membrane proteins in erythrocytes treated with lead. Biochem. J. 315: 401-406.

Bergdahl, I. A.; Grubb, A.; Schutz, A.; Desnick, R. J.; Wetmur, J. G.; Sassa, S.; Skerfving, S. (1997) Lead binding to δ-aminolevulinic acid dehydratase (ALAD) in human erythrocytes. Pharmacol. Toxicol. 81: 153-158.

Bergdahl, I. A.; Sheveleva, M.; Schutz, A.; Artamonova, V. G.; Skerfving, S. (1998) Plasma and blood lead in humans: capacity-limited binding to "delta"-aminolevulinic acid dehydratase and other lead-binding components. Toxicol. Sci. 46: 247-253.

Bernard, A.; Lauwerys, R. (1987) Metal-induced alterations of δ aminolevulinic acid dehydratase. In: Silbergeld, E. K.; Fowler, B. A., eds. Mechanisms of chemical-induced porphyrinopathies. New York, NY: New York Academy of Sciences; pp. 41-47. [Annals of the New York Academy of Sciences: v. 514].

Bernard, S. M.; McGeehin, M. A. (2003) Prevalence of blood lead levels >/= 5 "mu"g/dL among US children 1 to 5 years of age and socioeconomic and demographic factors associated with blood of lead levels 5 to 10

"mu"g/dL, Third National Health and Nutrition Examination Survey, 1988-1994. Pediatrics 112: 1308-1313.

Berry, W. D., Jr.; Moriarty, C. M.; Lau, Y. S. (2002) Lead attenuation of episodic growth hormone secretion in male rats. Int. J. Toxicol. 21: 93-98.

Bhattacharya, A.; Shukla, R.; Dietrich, K. N.; Miller, J.; Bagchee, A.; Bornschein, R. L.; Cox, C.; Mitchell, T. (1993) Functional implications of postural disequilibrium due to lead exposure. Neurotoxicology 14: 179-189.

Biedermann, K. A.; Landolph, J. R. (1987) Induction of anchorage independence in human diploid foreskin fibroblasts by carcinogenic metal salts. Cancer Res. 47: 3815-3823.

Biedermann, K. A.; Landolph, J. R. (1990) Role of valence state and solubility of chromium compounds on induction of cytotoxicity, mutagenesis, and anchorage independence in diploid human fibroblasts. Cancer Res. 50: 7835-7842.

Bielarczyk, H.; Tian, X.; Suszkiw, J. B. (1996) Cholinergic denervation-like changes in rat hippocampus following developmental lead exposure. Brain Res. 708: 108-115.

Bilban, M. (1998) Influence of the work environment in a Pb-Zn mine on the incidence of cytogenetic damage in miners. Am. J. Ind. Med. 34: 455-463.

Bizarro, P.; Acevedok, S.; Nino-Cabrera, G.; Mussali-Galante, P.; Pasos, F.; Avila-Costa, M. R.; Fortoul, T. I. (2003) Ultrastructural modifications in the mitochondrion of mouse Sertoli cells after inhalation of lead, cadmium or lead-cadmium mixture. Reprod. Toxicol. 17: 561-566.

Blackman, S. S., Jr. (1936) Intranuclear inclusion bodies in the kidney and liver caused by lead poisoning. Bull. Johns Hopkins Hosp. 58: 384-402.

Blakley, B. R. (1987) The effect of lead on chemical- and viral-induced tumor production in mice. J. Appl. Toxicol. 7: 167-172.

Blakley, B. R.; Archer, D. L. (1981) The effect of lead acetate on the immune response in mice. Toxicol. Appl. Pharmacol. 61: 18-26.

Blakley, B. R.; Sisodia, C. S.; Mukkur, T. K. (1980) The effect of methylmercury, tetraethyl lead, and sodium arsenite on the humoral immune response in mice. Toxicol. Appl. Pharmacol. 52: 245-254.

Blankenship, L. J.; Carlisle, D. L.; Wise, J. P., Sr.; Orenstein, J. M.; Dye, L. E., III; Patierno, S. R. (1997) Induction of apoptotic cell death by particulate lead chromate: differential effects of vitamins C and E on genotoxicity and survival. Toxicol. Appl. Pharmacol. 146: 270-280.

Blanusa, M.; Kostial, K.; Piasek, M.; Jones, M. M.; Singh, P. K. (1995) Reduction of lead retention by mono-3-methylbutan-1-yl meso-2,3-dimercaptosuccinate in suckling rats. Analyst (Cambridge, U. K.) 120: 951-953.

Bogden, J. D.; Gertner, S. B.; Kemp, F. W.; McLeod, R.; Bruening, K. S.; Chung, H. R. (1991) Dietary lead and calcium: effects on blood pressure and renal neoplasia in Wistar rats. J. Nutr. 121: 718-728.

Bogden, J. D.; Kemp, F. W.; Han, S.; Murphy, M.; Fraiman, M.; Czerniach, D.; Flynn, C. J.; Banua, M. L.; Scimone, A.; Castrovilly, L.; Gertner, S. B. (1995) Dietary calcium and lead interact to modify maternal blood pressure, erythropoiesis, and fetal and neonatal growth in rats during pregnancy and lactation. J. Nutr. 125: 990-1002.

Bonacker, D.; Stoiber, T.; Bohm, K. J.; Prots, I.; Wang, M.; Unger E.; Thier, R.; Bolt, H. M.; Degen, G. H. (2005) Genotoxicity of inorganic lead salts and disturbance of microtubule function. Environ. Mol. Mutagen. 45: 346-353.

Bondy, S. C. (1986) Effect of triethyl lead chloride on "delta"-aminolevulinic acid dehydratase. J. Toxicol. Environ. Health 18: 639-649.

Borella, P.; Giardino, A. (1991) Lead and cadmium at very low doses affect in vitro immune response of human lymphocytes. Environ. Res. 55: 165-177.

Borg, C.; Abdelali, J.; Laderach, D.; Maruyama, K.; Wakasugi, H.; Charrier, S.; Ryffel, B.; Vainchenker, W.; Galy, A.; Caignard, A.; Zitvogel, L.; Cambi, A.; Figdor, C. (2004) NK cell activation by dendritic cells (DC) require the formation of a synapse leading to IL-12 polarization in DC. Blood 104: 3267-3275.

Boudene, C.; Despaux-Pages, N.; Comoy, E.; Bohuon, C. (1984) Immunological and enzymatic studies of erythrocytic delta-aminolevulinate dehydratase. Comparison of results obtained in normal and lead-exposed subjects. Int. Arch. Occup. Environ. Health 55: 87-96.

Bouley, G.; Dubreuil, A.; Arsac, F.; Boudene, C. (1977) Effet du plomb microparticulaire, introduit dans l'appareil respiratoire, sur la sensibilite de la souris a l'infection par aerosol de Pasteurella multocida [Effect of microparticulate lead, introduced through respiratory apparatus, on the resistance of mice to infection by aerosolized Pasteurella multocida]. C. R. Hebd. Seances Acad. Sci. Ser. D 285: 1553-1556.

Bourjeily, N.; Suszkiw, J. B. (1997) Developmental cholinotoxicity of lead: loss of septal cholinergic neurons and long-term changes in cholinergic innervation of the hippocampus in perinatally lead-exposed rats. Brain Res. 771: 319-328.

Bowen, W. H. (2001) Exposure to metal ions and susceptibility to dental caries. J. Dent. Ed. 65: 1046-1053.

Boyce, S. J.; Mantle, T. J. (1993) Effect of lead acetate and carbon particles on the expression of glutathione S-transferase YfYf in rat liver. Biochem. J. 294: 301-304.

Bradman, A.; Eskenazi, B.; Sutton, P.; Athanasoulis, M.; Goldman, L. R. (2001) Iron deficiency associated with higher blood lead in children living in contaminated environments. Environ. Health Perspect. 109: 1079-1084.

Braga, M. F. M; Pereira, E. F. R.; Albuquerque, E. X. (1999a) Nanomolar concentrations of lead inhibit glutamatergic and GABAergic transmission in hippocampal neurons. Brain Res. 826: 22-34.

Braga, M. F. M.; Pereira, E. F. R.; Marchioro, M.; Albuquerque, E. X. (1999b) Lead increases tetrodotoxin-insensitive spontaneous release of glutamate and GABA from hippocampal neurons. Brain Res. 826: 10-21.

Braga, M. F.; Pereira, E. F.; Mike, A.; Albuquerque, E. X. (2004) Pb2+ via protein kinase C inhibits nicotinic cholinergic modulation of synaptic transmission in the hippocampus. J. Pharmacol. Exp. Ther. 311: 700-710.

Bratton, G. R.; Hiney, J. K.; Dees, W. L. (1994) Lead (Pb) alters the norepinephrine-induced secretion of luteinizing hormone releasing hormone from the medium eminence of adult male rats in vitro. Life Sci. 55: 563-571.

Breslau, N.; Chilcoat, H. D.; Susser, E. S.; Matte, T.; Liang, K.-Y.; Peterson, E. L. (2001) Stability and change in children's intelligence quotient scores: a comparison of two socioeconomically disparate communities. Am. J. Epidemiol. 154: 711-717.

Bressler, J. P.; Goldstein, G. W. (1991) Mechanisms of lead neurotoxicity. Biochem. Pharmacol. 41: 479-484.

Bressler, J.; Kim, K.-A.; Chakraborti, T.; Goldstein, G. (1999) Molecular mechanisms of lead neurotoxicity. Neurochem. Res. 24: 595-600.

Brody, D. J.; Pirkle, J. L.; Kramer, R. A.; Flegal, K. M.; Matte, T. D.; Gunter, E. W.; Paschal, D. C. (1994) Blood lead levels in the US population: phase 1 of the third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991). JAMA J. Am. Med. Assoc. 272: 277-283.

Bruschweiler, B. J.; Wurgler, F. E.; Fent, K. (1996) Inhibitory effects of heavy metals on cytochrome P4501A induction in permanent fish hepatoma cells. Arch. Environ. Contam. Toxicol. 31: 475-482.

Buchet, J.-P.; Roels, H. E.; Hubermont, G.; Lauwerys, R. (1976) Effect of lead on some parameters of the heme biosynthetic pathway in rat tissues in vivo. Toxicology 6: 21-34.

Buckley, J. D.; Robison, L. L.; Swotinsky, R.; Garabrant, D. H.; LeBeau, M.; Manchester, P.; Nesbit, M. E.; Odom, L.; Peters, J. M.; Woods, W. G.; Hammond, G. D. (1989) Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the children's cancer study group. Cancer Res. 49: 4030-4037.

Bunn, T. L.; Marsh, J. A.; Dietert, R. R. (2000) Gender differences in developmental immunotoxicity to lead in a chicken: analysis following a single early low-level exposure in ovo. J. Toxicol. Environ. Health A 61: 677-693.

Bunn, T. L.; Parsons, P. J.; Kao, E.; Dietert, R. R. (2001a) Gender-based profiles of developmental immunotoxicity to lead in the rat: assessment in juveniles and adults. J. Toxicol. Environ. Health A 64: 223-240.

Bunn, T. L.; Ladics, G. S.; Holsapple, M. P.; Dietert, R. R. (2001b) Developmental immunotoxicology assessment in the rat: age, gender and strain comparisons after exposure to Pb. Toxicol. Methods 11: 41-58.

Bunn, T. L.; Parsons, P. J.; Kao, E.; Dietert, R. R. (2001c) Exposure to lead during critical windows of embryonic development: differential immunotoxic outcome based on stage of exposure and gender. Toxicol. Sci. 64: 57-66.

Burchfiel, J. L.; Durry, F. H.; Bartels, P. H.; Needleman, H. L. (1992) Low-level lead exposure: effect on quantitative electroencephalography and correlation with neuropsychologic measures. In: Needleman, H. L., ed. Human lead exposure. Boca Raton, FL: CRC Press; pp. 209-222.

Burkey, R. T.; Nation, J. R. (1994) Brain stimulation reward following chronic lead exposure in rats. Behav. Neurosci. 108: 532-536.

Burstein, H. J.; Tepper, R. I.; Leder, P.; Abbas, A. K. (1991) Humoral immune functions in IL-4 transgenic mice. J. Immunol. 147: 2950-2956.

Cai, M. Y.; Arenaz, P. (1998) Antimutagenic effect of crown ethers on heavy metal-induced sister chromatid exchanges. Mutagenesis 13: 27-32.

Calabrese, E. J.; Baldwin, L. A. (1992) Lead-induced cell proliferation and organ-specific tumorigenicity. Drug Metab. Rev. 24: 409-416.

Calabrese, E. J.; Baldwin, L. A.; Leonard, D. A.; Zhao, X. Q. (1995) Decrease in hepatotoxicity by lead exposure is not explained by its mitogenic response. J. Appl. Toxicol. 15: 129-132.

Calderon-Salinas, J. V.; Quintanar-Escorza, M. A.; Hernandez-Luna, C. E.; Gonzalez-Martinez, M. T. (1999a) Effect of lead on the calcium transport in human erythrocyte. Hum. Exp. Toxicol. 18: 146-153.

Calderon-Salinas, J. V.; Quintanar-Escorcia, M. A.; Gonzalez-Martinez, M. T.; Hernandez-Luna, C. E. (1999b) Lead and calcium transport in human erythrocyte. Hum. Exp. Toxicol. 18: 327-332.

Camoratto, A. M.; White, L. M.; Lau, Y.-S.; Ware, G. O.; Berry, W. D.; Moriarty, C. M. (1993) Effect of exposure to low level lead on growth and growth hormone release in rats. Toxicology 83: 101-114.

Campbell, T. F.; Needleman, H. L.; Riess, J. A.; Tobin, M. J. (2000) Bone lead levels and language processing performance. Dev. Neuropsychol. 18: 171-186.

Canfield, R. L.; Henderson, C. R., Jr.; Cory-Slechta, D. A.; Cox, C.; Jusko, T. A.; Lanphear, B. P. (2003) Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. N. Engl. J. Med. 348: 1517-1526.

Canfield, R. L.; Gendle, M. H.; Cory-Slechta, D. A. (2004) Impaired neuropsychological functioning in lead-exposed children. Dev. Neuropsychol. 26: 513-540.

Carballido, J. M.; Schols, D.; Namikawa, R.; Zurawski, S.; Zurawski, Z.; Roncarolo, M. G.; de Vries, J. E. (1995) IL-4 induces human B cell maturation and IgE synthesis in SCID-hu mice. Inhibition of ongoing IgE production by in vivo treatment with an IL-4/IL-13 receptor antagonist. J. Immunol. 155: 4162-4170.

Cardenas, A.; Roels, H.; Bernard, A. M.; Barbon, R.; Buchet, J. P.; Lauwerys, R. R.; Rosello, J.; Ramis, I.; Mutti, A.; Franchini, I.; Fels, L. M.; Stolte, H.; De Broe, M. E.; Nuyts, G. D.; Taylor, S. A.; Price, R. G. (1993) Markers of early renal changes induced by industrial pollutants. II. Application to workers exposed to lead. Br. J. Ind. Med. 50: 28-36.

Cardinale, F.; de Benedictis, F. M.; Muggeo, V.; Giordana, P.; Loffredo, M. S.; Iacoviello, G.; Armenio, L. (2005) Exhaled nitric oxide, total serum IgE and allergic sensitization in childhood asthma and allergic rhinitis. Pediatr. Allergy Immunol. 16: 236-242.

Carmignani, M.; Boscolo, P.; Poma, A.; Volpe, A. R. (1999) Kininergic system and arterial hypertension following chronic exposure to inorganic lead. Immunopharmacology 44: 105-110.

Carmignani, M.; Volpe, A. R.; Boscolo, P.; Qiao, N.; Gioacchino, M. Di; Grilli, A.; Felaco, M. (2000) Catcholamine and nitric oxide systems as targets of chronic lead exposure in inducing selective functional impairment. Life Sci. 68: 401-415.

Carsia, R. V.; Forman, D.; Hock, C. E.; Nagele, R. G.; McIlroy, P. J. (1995) Lead alters growth and reduces angiotensin II receptor density of rat aortic smooth muscle cells. Proc. Soc. Exp. Biol. Med. 210: 180-190.

Castranova, V.; Bowman, L.; Reasor, M. J.; Miles, P. R. (1980) Effects of heavy metal ions on selected oxidative metabolic processes in rat alveolar macrophages. Toxicol. Appl. Pharmacol. 53: 14-23.

Chai, S.; Webb, R. C. (1988) Effects of lead on vascular reactivity. Environ. Health Perspect. 78: 85-89.

Chakraborty, I.; Sharma, A.; Talukder, G. (1987) Antagonistic and synergistic effects of lead and selenium in Rattus norvegicus. Toxicol. Lett. 37: 21-26.

Chang, H.-R.; Chen, S.-S.; Chen, T.-J.; Ho, C.-K.; Chiang, H.-C.; Yu, H.-S. (1996) Lymphocyte β2-adrenergic receptors and plasma catecholamine levels in lead-exposed workers. Toxicol. Appl. Pharmacol. 139: 1-5.

Chang, H.-R.; Chen, S.-S.; Tsao, D.-A.; Cheng, J.-T.; Ho, C.-K.; Yu, H.-S. (1997) Change of cardiac β-adrenoceptors in lead-exposed rats. Toxicology 123: 27-32.

Chang, H.-R.; Tsao, D.-A.; Yu, H.-S.; Ho, C.-K. (2005) The change of "beta"-adrenergic system after cessation of lead exposure. Toxicology 207: 73-80.

Chaurasia, S. S.; Kar, A. (1997) Protective effects of vitamin E against lead-induced deterioration of membrane associated type-I iodothyronine 5'-monodeiodinase (5'D-I) activity in male mice. Toxicology 124: 203-209.

Chavez, E.; Jay, D.; Bravo, C. (1987) The mechanism of lead-induced mitochondrial Ca2+ efflux. J. Bioenerg. Biomembrane 19: 285-295.

Chen, S.; Miller, T. E.; Golemboski, K. A.; Dietert, R. R. (1997) Suppression of macrophage metabolite production by lead glutamate in vitro is reversed by meso-2, 3-dimercaptosuccinic acid (DMSA). In Vitro Toxicology. 10: 351-357.

Chen, S.; Golemboski, K. A.; Sanders, F. S.; Dietert, R. R. (1999) Persistent effect of in utero meso-2,3-dimercaptosuccinic acid (DMSA) on immune function and lead-induced immunotoxicity. Toxicology 132: 67-79.

Chen, S. C.; Golemboski, K. A.; Piepenbrink, M.; Dietert, R. R. (2004) Developmental immunotoxicity of lead in the rat: influence of maternal diet. J. Toxicol. Environ. Health Part A 67: 495-511.

Chen, A.; Dietrich, K. N.; Ware, J. H.; Radcliffe, J.; Rogan, W. J. (2005) IQ and blood lead from 2 to 7 years of age: are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environ. Health Perspect. 113: 597-601.

Cheng, Y.; Willett, W. C.; Schwartz, J.; Sparrow, D.; Weiss, S.; Hu, H. (1998) Relation of nutrition to bone lead and blood lead levels in middle-aged to elderly men. The Normative Aging Study. Am. J. Epidemiol. 147: 1162-1174.

Chia, K. S.; Mutti, A.; Tan, C.; Ong, H. Y.; Jeyaratnam, J.; Ong, C. N.; Lee, E. (1994) Urinary N-acetyl-"beta"-D-glucosaminidase activity in workers exposed to inorganic lead. Occup. Environ. Med. 51: 125-129.

Choie, D. D.; Richter, G. W. (1972) Lead poisoning: rapid formation of intranuclear inclusions. Science (Washington, DC) 177: 1194-1195.

Choie, D. D.; Richter, G. W.; Young, L. B. (1975) Biogenesis of intranuclear lead-protein inclusions in mouse kidney. Beitr. Pathol. 155: 197-203.

Chowdhuri, D. K.; Narayan, R.; Saxena, D. K. (2001) Effect of lead and chromium on nucleic acid and protein synthesis during sperm-zona binding in mice. Toxicol. In Vitro 15: 605-613.

Chowdhury, A. R.; Dewan, A.; Gandhi, D. N. (1984) Toxic effect of lead on the testes of rat. Biomed. Biochim. Acta 43: 95-100.

Chowdhury, A. R.; Rao, R. V.; Gautam, A. K. (1986) Histochemical changes in the testes of lead induced experimental rats. Folia Histochem. Cytobiol. 24: 233-237.

Chowdhury, A. R.; Rao, R. V.; Gautam, A. K.; Kashyap, S. K. (1987) Functional changes of testes in lead intoxicated rats. Ind. Health 25: 55-62.

Church, H. J.; Day, J. P.; Braithwaite, R. A.; Brown, S. S. (1993a) Binding of lead to a metallothionein-like protein in human erythrocytes. J. Inorg. Biochem. 49: 55-68.

Church, H. J.; Day, J. P.; Braithwaite, R. A.; Brown, S. S. (1993b) The speciation of lead in erythrocytes in relation to lead toxicity: case studies of two lead-exposed workers. Neurotoxicology 14: 359-364.

Claudio, L.; Lee, T.; Wolff, M. S.; Wetmur, J. G. (1997) A murine model of genetic susceptibility to lead bioaccumulation. Fundam. Appl. Toxicol. 35: 84-90.

Cline, H. T.; Witte, S.; Jones, K. W. (1996) Low lead levels stunt neuronal growth in a reversible manner. Proc. Natl. Acad. Sci. U. S. A. 93: 9915-9920.

Cocco, P.; Carta, P.; Flore, C.; Congia, P.; Manca, M. B.; Saba, G.; Salis, S. (1996) Mortality of lead smelter workers with the glucose-6-phosphate dehydrogenase-deficient phenotype. Cancer Epidemiol. Biomarkers Prev. 5: 223-225.

Cocco, P.; Dosemeci, M.; Heineman, E. F. (1998) Brain cancer and occupational exposure to lead. J. Occup. Environ. Med. 40: 937-942.

Cohn, J.; Cory-Slechta, D. A. (1993) Subsensitivity of lead-exposed rats to the accuracy-impairing and rate-altering effects of MK-801 on a multiple schedule of repeated learning and performance. Brain Res. 600: 208-218.

Cohn, J.; Cory-Slechta, D. A. (1994a) Assessment of the role of dopaminergic systems in lead-induced learning impairments using a repeated acquisition and performance baseline. Neurotoxicology 15: 913-926.

Cohn, J.; Cory-Slechta, D. A. (1994b) Lead exposure potentiates the effects of NMDA on repeated learning. Neurotoxicol. Teratol. 16: 455-465.

Cohn, J.; Cox, C.; Cory-Slechta, D. A. (1993) The effects of lead exposure on learning in a multiple repeated acquisition and performance schedule. Presented at: Ninth international neurotoxicology conference; October 1991; Little Rock, AR. Neurotoxicology 14(2-3): 329-346.

Cole, L. J.; Bachhuber, L. J. (1915) The effect of lead on the germ cells of the male rabbit and fowl as indicated by their progeny. Proc. Soc. Exp. Biol. Med. 12: 24-29.

Columbano, A.; Ledda-Columbano, G. M.; Ennas, M. G.; Curto, M.; de Montis, M. G.; Roomi, M. W.; Pani, P.; Sarma, D. S. R. (1988) Modulation of the activity of hepatic gamma-glutamyl transpeptidase, adenosine triphosphatase, placental glutathione S-transferase and adenylate cyclase by acute administration of lead nitrate. Basic Appl. Histochem. 32: 501-510.

Columbano, A.; Endoh, T.; Denda, A.; Noguchi, O.; Nakae, D.; Hasegawa, K.; Ledda-Columbano, G. M.; Zedda, A. I.; Konishi, Y. (1996) Effects of cell proliferation and cell death (apoptosis and necrosis) on the early stages of rat hepatocarcinogenesis. Carcinogenesis 17: 395-400.

Coni, P.; Bignone, F. A.; Pichiri, G.; Ledda-Columbano, G. M.; Columbano, A.; Rao, P. M.; Rajalakhmi, S.; Sarma, D. S. (1989) Studies on the kinetics of expression of cell cycle dependent proto-oncogenes during mitogen-induced liver cell proliferation. Cancer Lett. (Shannon, Irel.) 47: 115-119.

Coni, P.; Pichiri-Coni, G.; Ledda-Columbano, G. M.; Semple, E.; Rajalakshmi, S.; Rao, P. M.; Sarma, D. S. R.; Columbano, A. (1992) Stimulation of DNA synthesis by rat plasma following in vivo treatment with three liver mitogens. Cancer Lett. 61: 233-238.

Coni, P.; Simbula, G.; De Prati, A. C.; Menegazzi, M.; Suzuki, H.; Sarma, D. S. R.; Ledda-Columbano, G. M.; Columbano, A. (1993) Differences in the steady-state levels of c-fos, c-jun and c-myc messenger RNA during mitogen-induced liver growth and compensatory regeneration. Hepatology (Baltimore) 17: 1109-1116.

Cook, J. A.; Hoffmann, E. O.; Di Luzio, N. R. (1975) Influence of lead and cadmium on the susceptibility of rats to bacterial challenge. Proc. Soc. Exp. Biol. Med. 150: 741-747.

Cook, L. R.; Stohs, S. J.; Angle, C. R.; Hickman, T. I.; Maxell, R. C. (1987) Erythrocyte membrane microviscosity and phospholipid composition in lead workers. Br. J. Ind. Med. 44: 841-844.

Cooper, G. P.; Manalis, R. S. (1984) Interactions of lead and cadmium on acetylcholine release at the frog neuromuscular junction. Toxicol. Appl. Pharmacol. 74: 411-416.

Corchs, J.; Gioia, I. A.; Serrani, R. E.; Taborda, D. (2001) Lead ions but not other metallic ions increase resistance to hypotonic lysis in prenatal hemopoiesis red blood cells. Biocell 25: 287-289.

Corpas, I.; Gaspar, I.; Martinez, S.; Codesal, J.; Candelas, S.; Antonio, M. T. (1995) Testicular alterations in rats due to gestational and early lactational administration of lead. Reprod. Toxicol. 9: 307-313.

Corpas, I.; Benito, M. J.; Marquina, D.; Castillo, M.; Lopez, N.; Antonio, M. T. (2002) Gestational and lactational lead intoxication produces alterations in the hepatic system of rat pups. Ecotoxicol. Environ. Saf. 51: 35-43.

Cory-Slechta, D. A. (1988) Mobilization of lead over the course of DMSA chelation therapy and long-term efficacy. J. Pharmacol. Exp. Ther. 246: 84-91.

Cory-Slechta, D. A. (1990a) Alterations in tissue Pb distribution and hematopoietic indices during advanced age. Arch. Toxicol. 64: 31-37.

Cory-Slechta, D. A. (1990b) Lead exposure during advanced age: alterations in kinetics and biochemical effects. Toxicol. Appl. Pharmacol. 104: 67-78.

Cory-Slechta, D. A. (1995) MK-801 subsensitivity following postweaning lead exposure. Neurotoxicology 16: 83-95.

Cory-Slechta, D. A. (1997a) Postnatal lead exposure and MK-801 sensitivity. Neurotoxicology 18: 209-220.

Cory-Slechta, D. A. (1997b) Relationships between Pb-induced changes in neurotransmitter system function and behavioral toxicity. Neurotoxicology 18: 673-688.

Cory-Slechta, D. A. (2003) Lead-induced impairments in complex cognitive function: offerings from experimental studies. Child Neuropsychol. 9: 54-75.

Cory-Slechta, D. A.; Pokora, M. J. (1995) Lead-induced changes in muscarinic cholinergic sensitivity. Neurotoxicology 16: 337-347.

Cory-Slechta, D. A.; Widzowski, D. V. (1991) Low level lead exposure increases sensitivity to the stimulus properties of dopamine D1 and D2 agonists. Brain Res. 553: 65-74.

Cory-Slechta, D. A.; Weiss, B.; Cox, C. (1989) Tissue distribution of Pb in adult vs. old rats: a pilot study. Toxicology 59: 139-149.

Cory-Slechta, D. A.; Pokora, M. J.; Widzowski, D. V. (1992) Postnatal lead exposure induces supersensitivity to the stimulus properties of D2-D3 agonist. Brain Res. 598: 162-172.

Cory-Slechta, D. A.; Pokora, M. J.; Fox, R. A. V.; O'Mara, D. J. (1996a) Lead-induced changes in dopamine D1 sensitivity: modulation by drug discrimination training. Neurotoxicology. 17: 445-457.

Cory-Slechta, D. A.; Pokora, M. J.; Johnson, J. L. (1996b) Postweaning lead exposure enhances the stimulus properties of N-methyl-D-aspartate: possible dopaminergic involvement? Neurotoxicology 17: 509-521.

Cory-Slechta, D. A.; McCoy, L.; Richfield, E. K. (1997) Time course and regional basis of Pb-induced changes in MK-801 binding: reversal by chronic treatment with the dopamine agonist apomorphine but not the D1 agonist SKF-82958. J. Neurochem. 68: 2012-2023.

Cory-Slechta, D. A.; Virgolini, M. B.; Thiruchelvam, M.; Weston, D. D.; Bauter, M. R. (2004) Maternal stress modulates the effects of developmental lead exposure. Environ. Health Perspect. 112: 717-730.

Costa, M.; Zhitkovich, A.; Gargas, M.; Paustenbach, D.; Finley, B.; Kuykendall, J.; Billings, R.; Carlson, T. J.; Wetterhahn, K.; Xu, J.; Patierno, S.; Bogdanffy, M. (1996) Interlaboratory validation of a new assay for DNA-protein crosslinks. Mutat. Res. 369: 13-21.

Courtois, E.; Marques, M.; Barrientos, A.; Casado, S.; Lopez-Farre, A. (2003) Lead-induced downregulation of soluble guanylage cyclase in isolated rat aortic segments mediated by reactive oxygen species and cyclooxygenase-2. J. Am. Soc. Nephrol. 14: 1464-1470.

Craan, A. G.; Nadon, G.; P'an, A. Y. (1984) Lead flux through the kidney and salivary glands of rats. Am. J. Physiol. 247: F773-F783.

Cramer, K.; Goyer, R. A.; Jagenburg, R.; Wilson, M. H. (1974) Renal ultrastructure, renal function, and parameters of lead toxicity in workers with different periods of lead exposure. Br. J. Ind. Med. 31: 113-127.

Cremin, J. D., Jr.; Luck, M. L.; Laughlin, N. K.; Smith, D. R. (2001) Oral succimer decreases the gastrointestinal absorption of lead in juvenile monkeys. Environ. Health Perspect. 109: 613-619.

Crowe, A.; Morgan, E. H. (1996) Interactions between tissue uptake of lead and iron in normal and iron-deficient rats during development. Biol. Trace Elem. Res. 52: 249-261.

Curzon, M. E. J.; Bibby, B. G. (1970) Effect of heavy metals on dental caries and tooth eruption. J. Dent. Child. 37: 463-465.

Daggett, D. A.; Nuwaysir, E. F.; Nelson, S. A.; Wright, L. S.; Kornguth, S. E.; Siegel, F. L. (1997) Effects of triethyl lead administration on the expression of glutathione S-transferase isoenzymes and quinone reductase in rat kidney and liver. Toxicology 117: 61-71.

Daggett, D. A.; Oberley, T. D.; Nelson, S. A.; Wright, L. S.; Kornguth, S. E.; Siegel, F. L. (1998) Effects of lead on rat kidney and liver: GST expression and oxidative stress. Toxicology 128: 191-206.

Danadevi, K.; Rozati, R.; Saleha Banu, B.; Hanumanth R. P.; Grover, P. (2003) DNA damage in workers exposed to lead using comet assay. Toxicology 187: 183-193.

Dantzer, R.; Bluthe, R. M.; Gheusi, G.; Cremona, S.; Laye, S.; Parnet, P.; Kelley, K. W. (1998) Molecular basis of sickness behavior. Ann. N.Y. Acad. Sci. 856: 132-138.

De Guise, S.; Bernier, J.; Lapierre, P.; Dufresne, M. M.; Dubreuil, P.; Fornier, M. (2000) Immune function of bovine leukocytes after in vitro exposure to selected heavy metals. Am. J. Vet. Res. 61: 339-344.

De Vries, I.; Spaans, E.; Van Dijk, A.; Meulenbelt, J. (1998) Lead toxicokinetics. Development of a biokinetic model to understand and predict the outcome of treatment. Przegl. Lek. 55: 500-504.

De la Fuente, H.; Portales-Perez, D.; Diaz-Barriga, F.; Saavedra-Alanis, V.; Layseca, E.; Gonzalez-Amaro, R. (2002) Effect of arsenic, cadmium and lead on the induction of apoptosis of normal human mononuclear cells. Clin. Exp. Immunol. 129: 69-77.

De, M.; Ghosh, S.; Palit, S.; Ghosh, A.; Talukder, G.; Sharma, A. (1995) Clastogenic effects in human samples following prolonged exposure in metal industry. Bull. Environ. Contam. Toxicol. 54: 357-362.

Dearth, R. K.; Hiney, J. K.; Srivastava, V.; Burdick, S. B.; Bratton, G. R.; Dees, W. L. (2002) Effects of lead (Pb) exposure during gestation and lactation on female pubertal development in the rat. Reprod. Toxicol. 16: 343-352.

Dearth, R. K.; Hiney, J. K.; Srivastava, V.; Les Dees, W.; Bratton, G. R. (2004) Low level lead (Pb) exposure during gestation and lactation: assessment of effects on pubertal development in Fisher 344 and Sprague-Dawley female rats. Life Sci. 74: 1139-1148.

Degawa, M.; Arai, H.; Kubota, M.; Hashimoto, Y. (1994) Ionic lead, a unique metal ion as an inhibitor for cytochrome P450IA2 (CYP1A2) expression in the rat liver. Biochem. Biophys. Res. Commun. 200: 1086-1092.

Degawa, M.; Arai, H.; Kubota, M.; Hashimoto, Y. (1995) Ionic lead, but not other ionic metals (Ni2+, Co2+ and Cd2+), suppresses 2-methoxy-4-aminoazobenzene-mediated cytochrome P450IA2 (CYP1A2) induction in rat liver. Biol. Pharm. Bull. 18: 1215-1218.

Degawa, M.; Arai, H.; Miura, S.; Hashimoto, Y. (1993) Preferential inhibitions of hepatic P450IA2 expression and induction by lead nitrate in the rat. Carcinogenesis (London) 14: 1091-1094.

Degawa, M.; Matsuda, K.; Arai, H.; Hashimoto, Y. (1996) Lead nitrate inhibits the induction of CYP1A mRNAs by aromatic amines but not by aryl hydrocarbons in the rat liver. J. Biochem. (Tokyo, Jpn.) 120: 547-551.

Dehpour, A. R.; Essalat, M.; Ala, S.; Ghazi-Khansari, M.; Ghafourifar, P. (1999) Increase by NO synthase inhibitor of lead-induced release of N-acetyl-"beta"-D-glucosaminidase from perfused rat kidney. Toxicology 132: 119-125.

Dekaney, C. M.; Harris, E. D.; Bratton, G. R.; Jaeger, L. A. (1997) Lead transport in IEC-6 intestinal epithelial cells. Biol. Trace Elem. Res. 58: 13-24.

Delville, Y. (1999) Exposure to lead during development alters aggressive behavior in golden hamsters. Neurotoxicol. Teratol. 21: 445-449.

Deng, W.; Poretz, R. D. (2002) Protein kinase C activation is required for the lead-induced inhibition of proliferation and differentiation of cultured oligodendroglial progenitor cells. Brain Res. 929: 87-95.

Deng, W.; McKinnon, R. D.; Poretz, R. D. (2001) Lead exposure delays the differentiation of oligodendroglial progenitors in vitro. Toxicol. Appl. Pharmacol. 174: 235-244.

Dentener, M. A.; Greve, J. W.; Maessen, J. G.; Buurman, W. A. (1989) Role of tumour necrosis factor in the enhanced sensitivity of mice to endotoxin after exposure to lead. Immunopharmacol. Immunotoxicol. 11: 321-334.

Dessi, S.; Batetta, B.; Laconi, E.; Ennas, C.; Pani, P. (1984) Hepatic cholesterol in lead nitrate induced liver hyperplasia. Chem. Biol. Interact. 48: 271-279.

Dessi, S.; Batetta, B.; Pulisci, D.; Carrucciu, A.; Mura, E.; Ferreli, A.; Pani, P. (1990) Modifying influence of fasting on liver hyperplasia induced by lead nitrate. Res. Commun. Chem. Pathol. Pharmacol. 68: 103-116.

Devi KD, Banu BS, Grover P, Jamil K. (2000) Genotoxic effect of lead nitrate on mice using SCGE (comet assay). Toxicology. 2000 Apr 14;145(2-3):195-201.

Dey, S.; Arjun, J.; Das, M.; Bhattacharjee, C. R.; Dkhar, P. S. (2001) Effect of prenatal lead toxicity on surface ultrastructural features, elemental composition and infrared absorption characteristics of the skin of albino mice. Cytobios 106(suppl. 2): 245-254.

Dhir, H.; Roy, A. K.; Sharma, A.; Talukder, G. (1990) Modification of clastogenicity of lead and aluminium in mouse bone marrow cells by dietary ingestion of Phyllanthus emblica fruit extract. Mutat. Res. 241: 305-312.

Dhir, H.; Ghosh, S.; Sharma, A.; Talukder, G. (1992a) Interaction between two group IV metals: - lead and zirconium - in bone marrow cells of Mus musculus in vivo. Biometals 5: 81-86.

Dhir, H.; Sharma, A.; Talukder, G. (1992b) Modifying effect of iron on lead-induced clastogenicity in mouse bone marrow cells. Biol. Trace Elem. Res. 34: 279-286.

Dhir, H.; Roy, A. K.; Sharma, A. (1993) Relative efficiency of Phyllanthus emblica fruit extract and ascorbic acid in modifying lead and aluminium-induced sister-chromatid exchanges in mouse bone marrow. Environ. Mol. Mutagen. 21: 229-236.

Diamond, G. L.; Goodrum, P. E.; Felter, S. P.; Ruoff, W. L. (1998) Gastrointestinal absorption of metals. Drug Chem. Toxicol. 21: 223-251.

Dieter, M. P.; Matthews, H. B.; Jeffcoat, R. A.; Moseman, R. F. (1993) Comparison of lead bioavailability in F344 rats fed lead acetate, lead oxide, lead sulfide, or lead ore concentrate from Skagway, Alaska. J. Toxicol. Environ. Health 39: 79-93.

Dietert, R. R.; Etzel, R. A.; Chen, D.; Halonen, M.; Holladay, S. D.; Jarabek, A. M.; Landreth, K.; Peden, D. B.; Pinkerton, K.; Smialowicz, R. J.; Zoetis, T. (2000) Workshop to identify critical window of exposure for children's health: immune and respiratory systems work group summary. Environ. Health Perspect. Suppl. 108(3): 483-490.

Dietert, R. R.; Lee, J.-E.; Bunn, T. L. (2002) Developmental immunotoxicology: emerging issues. Hum. Exp. Toxicol. 21: 479-485.

Dietert, R. R.; Lee, J.-E.; Hussain, I.; Piepenbrink, M. (2004) Developmental immunotoxicology of lead. Toxicol. Appl. Pharmacol. 86-94.

Dietrich, K. N.; Succop, P. A.; Berger, O. G.; Keith, R. W. (1992) Lead exposure and the central auditory processing abilities and cognitive development of urban children: the Cincinnati lead study cohort at age 5 years. Neurotoxicol. Teratol. 14: 51-56.

Dietrich, K. N.; Berger, O. G.; Succop, P. A.; Hammond, P. B.; Bornschein, R. L. (1993) The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry. Neurotoxicol. Teratol. 15: 37-44.

Dietrich, K. N.; Ris, M. D.; Succop, P. A.; Berger, O. G.; Bornschein, R. L. (2001) Early exposure to lead and juvenile delinquency. Neurotoxicol. Teratol. 23: 511-518.

Dietrich, K. N.; Ware, J. H.; Salganik, M.; Radcliffe, J.; Rogan, W. J.; Rhoads, G. G.; Fay, M. E.; Davoli, C. T.; Denckla, M. B.; Bornschein, R. L.; Schwarz, D.; Dockery, D. W.; Adubato, S.; Jones, R. L.; for the Treatment of Lead-Exposed Children Clinical Trial Group. (2004) Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics 114: 19-26.

Ding, Y.; Vaziri, N. D.; Gonick, H. C. (1998) Lead-induced hypertension. II. Response to sequential infusions of L-arginine, superoxide dismutase, and nitroprusside. Environ. Res. 76: 107-113.

Ding, Y.; Gonick, H. C.; Vaziri, N. D. (2000) Lead promotes hydroxyl radical generation and lipid peroxidation in cultured aortic endothelial cells. Am. J. Hypertens. 13: 552-555.

Ding, Y.; Gonick, H. C.; Vaziri, N. D.; Liang, K.; Wei, L. (2001) Lead-induced hypertension. III. Increased hydroxyl radical production. Am. J. Hypertens. 14: 169-173.

Dini, L.; Falasca, L.; Lentini, A.; Mattioli, P.; Piacentini, M.; Piredda, L.; Autuori, F. (1993) Galactose-specific receptor modulation related to the onset of apoptosis in rat liver. Eur. J. Cell. Biol. 61: 329-337.

Dini, L.; Giudetti, A. M.; Ruzittu, M.; Gnoni, G. V.; Zara, V. (1999) Citrate carrier and lipogenic enzyme activities in lead nitrate-induced proliferative and apoptotic phase in rat liver. Biochem. Mol. Biol. Int. 47: 607-614.

Donaldson, W. E.; Leeming, T. K. (1984) Dietary lead: effects on hepatic fatty acid composition in chicks. Toxicol. Appl. Pharmacol. 73: 119-123.

Donaldson, J.; Hemming, R.; LaBella, F. (1985) Vanadium exposure enhances lipid peroxidation in the kidney of rats and mice. Can. J. Physiol. Pharmacol. 63: 196-199.

Dorman, R. V.; Freeman, E. J. (2002) Lead-dependent effects on arachidonic acid accumulation and the proliferation of vascular smooth muscle. J. Biochem. Mol. Toxicol. 16: 245-253.

Dorward, A.; Yagminas, A. P. (1994) Activity of erythrocyte "delta"-aminolevulinic acid dehydratase in the female cynomolgus monkey (Macaca fascicularis): kinetic analysis in control and lead-exposed animals. Comp. Biochem. Physiol. B: Biochem. Mol. Biol. 108: 241-252.

Dowd, T. L.; Rosen, J. F.; Gupta, R. K. (1990) 31P NMR and saturation transfer studies of the effect of PB2+ on cultured osteoblastic bone cells. J. Biol. Chem. 265: 20833-20838.

Dowd, T. L.; Rosen, J. F.; Gundberg, C. M.; Gupta, R. K. (1994) The displacement of calcium from osteocalcin at submicromolar concentrations of free lead. Biochim. Biophys. Acta 1226: 131-137.

Dowd, T. L.; Rosen, J. F.; Mints, L.; Gundberg, C. M. (2001) The effect of Pb2+ on the structure and hydroxyapatite binding properties of osteocalcin. Biochim. Biophys. Acta 1535: 153-163.

Driscoll, K. E. (2000) TNF alpha and MIP-2: Role in particle induced inflammation and regulation by oxidative stress. Toxicol. Lett. 112-113: 177-183.

Dunon, D.; Allioli, N.; Vainio, O.; Ody, C.; Imhof, B. A. (1998) Renewal of thymocyte progenitors and emigration of thymocytes during avian development. Dev. Comp. Immunol. 22: 279-287.

Dursun, N.; Arifoglu, C.; Suer, C.; Keskinol, L. (2005) Blood pressure relationship to nitric oxide, lipid peroxidation, renal function, and renal blood flow in rats exposed to low lead levels. Biol. Trace Elem. Res. 104: 141-150.

DuVal, G.; Fowler, B. A. (1989) Preliminary purification and characterization studies of a low molecular weight, high affinity cytosolic lead-binding protein in rat brain. Biochem. Biophys. Res. Commun. 159: 177-184.

Duydu, Y.; Suzen, H. S.; Aydin, A.; Cander, O.; Uysal, H.; Isimer, A.; Vural, N. (2001) Correlation between lead exposure indicators and sister chromatid exchange (SCE) frequencies in lymphocytes from inorganic lead exposed workers. Arch. Environ. Contam. Toxicol. 41: 241-246.

Dyatlov, V. A.; Lawrence, D. A. (2002) Neonatal lead exposure potentiates sickness behavior induced by Listeria monocytogenes infection of mice. Brain Behav. Immun. 16: 477-492.

Dyatlov, V. A.; Dyatlova, O. M.; Parsons, P. J.; Lawrence, D. A.; Carpenter, D. O. (1998a) Lipopolysaccharide and interleukin-6 enhance lead entry into cerebellar neurons: application of a new and sensitive flow cytometric technique to measure intracellular lead and calcium concentrations. Neurotoxicology 19: 293-302.

Dyatlov, V. A.; Platoshin, A. V.; Lawrence, D. A.; Carpenter, D. O. (1998b) Lead potentiates cytokine- and glutamate-mediated increases in permeability of the blood-brain barrier. Neurotoxicology 19: 283-292.

Eder, K.; Reichlmayr-Lais, A. M.; Kirchgessner, M. (1990) Activity of Na-K-ATPase and Ca-Mg-ATPase in red blood cell membranes of lead-depleted rats. J. Trace Elem. Electrolytes Health Dis. 4: 21-24.

Egle, P. M.; Shelton, K. R. (1986) Chronic lead intoxication causes a brain-specific nuclear protein to accumulate in the nuclei of cells lining kidney tubules. J. Biol. Chem. 261: 2294-2298.

Eisenmann, D. R.; Yaeger, J. A. (1969) Alterations in the formation of rat dentine and enamel induced by various ions. Arch. Oral Biol. 14: 1045-1064.

El-Fawal, H. A. N.; Waterman, S. J.; De Feo, A.; Shamy, M. Y. (1999) Neuroimmunotoxicology: humoral assessment of neurotoxicity and autoimmune mechanisms. Environ. Health Perspect. 107(suppl. 5): 767-775.

Elias, Z.; Poirot, O.; Pezerat, H.; Suquet, H.; Schneider, O.; Daniere, M. C.; Terzetti, F.; Baruthio, F.; Fournier, M.; Cavelier, C. (1989) Cytotoxic and neoplastic transforming effects of industrial hexavalent chromium pigments in Syrian hamster embryo cells. Carcinogenesis 10: 2043-2052.

Elias, Z.; Poirot, O.; Baruthio, F.; Daniere, M. C. (1991) Role of solubilized chromium in the induction of morphological transformation of Syrian hamster embryo (SHE) cells by particulate chromium(VI) compounds. Carcinogenesis 12: 1811-1816.

El-Missiry, M. A. (2000) Prophylactic effect of melatonin on lead-induced inhibition of heme biosynthesis and deterioration of antioxidant systems in male rats. J. Biochem. Mol. Toxicol. 14: 57-62.

Elreedy, S.; Krieger, N.; Ryan, P. B.; Sparrow, D.; Weiss, S. T.; Hu, H. (1999) Relations between individual and neighborhood-based measures of socioeconomic position and bone lead concentrations among community-exposed men: the Normative Aging Study. Am. J. Epidemiol. 150: 129-141.

Englyst, V.; Lundstrom, N. G.; Gerhardsson, L.; Rylander, L.; Nordberg, G. (2001) Lung cancer risks among lead smelter workers also exposed to arsenic. Sci. Total Environ. 273: 77-82.

Ercal, N.; Treeratphan, P.; Hammond, T. C.; Matthews, R. H.; Grannemann, N. H.; Spitz, D. R. (1996) In vivo indices of oxidative stress in lead-exposed C57BL/6 mice are reduced by treatment with meso-2,3-dimercaptosuccinic acid or N-acetylcysteine. Free Radical Biol. Med. 21: 157-161.

Eriksson, L. E. G.; Beving, H. (1993) Calcium- and lead-activated morphological changes in human erythrocytes: a spin label study of the cytoplasm. Arch. Biochem. Biophys. 303: 296-301.

Escribano, A.; Revilla, M.; Hernandez, E. R.; Seco, C.; Gonzalez-Riola, J.; Villa, L. F.; Rico, H. (1997) Effect of lead on bone development and bone mass: a morphometric, densitometric, and histomorphometric study in growing rats. Calcif. Tiss. Int. 60: 200-203.

Ewers, U.; Stiller-Winkler, R.; Idel, H. (1982) Serum immunoglobulin, complement C3, and salivary IgA levels in lead workers. Environ. Res. 29: 351-357.

Exon, J. H.; Koller, L. D.; Kerkvliet, N. I. (1979) Lead-cadmium interaction: effects on viral-induced mortality and tissue residues in mice. Arch. Environ. Health 34: 469-475.

Fahmy, M. A. (1999) Lead acetate genotoxicity in mice. Cytologia 64: 357-365.

Faith, R. E.; Luster, M. I.; Kimmel, C. A. (1979) Effect of chronic developmental lead exposure on cell-mediated immune functions. Clin. Exp. Immunol. 35: 413-420.

Fanning, D. (1988) A mortality study of lead workers, 1926-1985. Arch. Environ. Health 43: 247-251.

Farant, J.-P.; Wigfield, D. C. (1987) Interaction of divalent metal ions with normal and lead-inhibited human erythrocytic porphobilinogen synthase in vitro. Toxicol. Appl. Pharmacol. 89: 9-18.

Farant, J.-P.; Wigfield, D. C. (1990) The effects of copper, zinc, mercury, and cadmium on rabbit erythrocytic porphobilinogen synthase in vivo. J. Anal. Toxicol. 14: 222-226.

Farias, P.; Borja-Aburto, V. H.; Rios, C.; Hertz-Picciotto, I.; Rojas-Lopez, M.; Chavez-Ayala, R. (1996) Blood lead levels in pregnant women of high and low socioeconomic status in Mexico City. Environ. Health Perspect. 104: 1070-1074.

Farmand, F.; Ehdale, A.; Roberts, C. K.; Sindhu, R. K. (2005) Lead-induced dysregulation of superoxide dismutases, catalase, glutathione peroxidase, and guanylate cyclase. Environ. Res. 98: 33-39.

Faust, D.; Brown, J. (1987) Moderately elevated blood lead levels: effects on neuropsychologic functioning in children. Pediatrics 80: 623-629.

Faustman, E. M.; Silbernagel, S. M.; Fenske, R. A.; Burbacher, T. M.; Ponce, R. A. (2000) Mechanisms underlying children's susceptibility to environmental toxicants. Environ. Health Perspect. Suppl. 108(1): 13-21.

Favalli, L.; Chiari, M. C.; Piccinini, F.; Rozza, A. (1977) Experimental investigations on the contraction induced by lead in arterial smooth muscle. Acta Pharmacol. Toxicol. 41: 412-420.

Featherstone, J. D.; Goodman, P.; McLean, J. D. (1979) Electron microscope study of defect zones in dental enamel. J. Ultrastruct. Res. 67: 117-123.

Featherstone, J. D. B.; Nelson, D. G. A.; McLean, J. D. (1981) An electron microscope study of modifications to defect regions in dental enamel and synthetic apatites. Caries Res. 15: 278-288.

Federal Register. (2001) Lead and lead compounds; lowering of reporting thresholds; community right-to-know toxic chemicals release reporting: delay of effective date. F. R. 66 (February 16): 10585-10586.

Fehlau, R.; Grygorczyk, R.; Fuhrmann, G. F.; Schwarz, W. (1989) Modulation of the calcium or lead-activated potassium-selective channels in human red cells. II. Parallelisms to modulation of the activity of a membrane-bound oxidoreductase. Biochim. Biophys. Acta 978: 37-42.

Fels, L. M.; Herbort, C.; Pergande, M.; Jung, K.; Hotter, G.; Rosello, J.; Gelpi, E.; Mutti, A.; De Broe, M.; Stolte, H. (1994) Nephron target sites in chronic exposure to lead. Nephrol. Dial. Transplant. 9: 1740-1746.

Ferguson, C.; Kern, M.; Audesirk, G. (2000) Nanomolar concentrations of inorganic lead increase Ca2+ efflux and decrease intracellular free Ca2+ ion concentrations in cultured rat hippocampal neurons by a calmodulin-dependent mechanism. Neurotoxicology 21: 365-378.

Fergusson, D. M.; Horwood, L. J.; Lynskey, M. T. (1997) Early dentine lead levels and educational outcomes at 18 years. J. Child Psychol. Psychiatry 38: 471-478.

Ferm, V. H.; Carpenter, S. J. (1967) Developmental malformations resulting from the administration of lead salts. Exp. Mol. Pathol. 7: 208-213.

Fernandez-Cabezudo, M. J.; Hassan, M. Y.; Mustafa, N.; El-Sharkawy, R.; Fahim, M. A.; Al-Ramada, K. (2003) Alpha tocopherol protects against immunosuppressive and immunotoxic effects of lead. Free Radical Res. 37: 437-445.

Filkins, J. P.; Buchanan, B. J. (1973) Effects of lead acetate on sensitivity to shock, intravascular carbon and endotoxin clearances, and hepatic endotoxin detoxification. Proc. Soc. Exp. Biol. Med. 142: 471-475.

Finkelstein, Y.; Markowitz, M. E.; Rosen, J. F. (1998) Low-level lead-induced neurotoxicity in children: an update on central nervous system effects. Brain Res. Rev. 27: 168-176.

Flohe, S. B.; Bruggemann, J.; Herder, C.; Goebel, C.; Kolb, H. (2002) Enhanced proinflammatory response to endotoxin after priming of macrophages with lead ions. J. Leukoc. Biol. 71: 417-424.

Flora, G. J. S.; Seth, P. K. (1999) Beneficial effects of S-adenosyl-L-methionine on aminolevulinic acid dehydratase, glutathione, and lipid peroxidation during acute lead--ethanol administration in mice. Alcohol 18: 103-108.

Flora, S. J. S.; Tandon, S. K. (1987) Influence of calcium disodium edetate on the toxic effects of lead administration in pregnant rats. Indian J. Physiol. Pharmacol. 31: 267-272.

Flora, S. J. S.; Singh, S.; Tandon, S. K. (1989) Thiamine and zinc in prevention or therapy of lead intoxication. J. Int. Med. Res. 17: 68-75.

Flora, S. J. S.; Jeevaratnam, K.; Kumar, D. (1993) Preventive effects of sodium molybdate in lead intoxication in rats. Ecotoxicol. Environ. Saf. 26: 133-137.

Flora, S. J. S.; Bhattacharya, R.; Sachan, S. R. S. (1994) Dose-dependent effects of zinc supplementation during chelation of lead in rats. Pharmacol. Toxicol. 74: 330-333.

Flora, S. J. S.; Pande, M.; Mehta, A. (2003) Beneficial effect of combined administration of some naturally occurring antioxidants (vitamins) and thiol chelators in the treatment of chronic lead intoxication. Chem. Biol. Interact. 145: 267-280.

Fontanellas, A.; Navarro, S.; Moran-Jimenez, M.-J.; Sanchez-Fructuoso, A. I.; Vegh, I.; Barrientos, A.; De Salamanca, R. E. (2002) Erythrocyte aminolevulinate dehydratase activity as a lead marker in patients with chronic renal failure. Am. J. Kidney Dis. 40: 43-50.

Foote, R. H. (1999) Fertility of rabbit sperm exposed in vitro to cadmium and lead. Reprod. Toxicol. 13: 443-449.

Fortoul, T. I.; Moncada-Hernandez, S.; Saldivar-Osorio, L.; Espejel-Maya, G.; Mussali-Galante, P.; Del Carmen Avila-Casando, M.; Colin-Barenque, L.; Hernandez-Serrato, M. I.; Avila-Costa, M. R. (2005) Sex differences in brochiolar epithelium response after the inhalation of lead acetate (Pb). Toxicology 207: 323-330.

Foster, W. G. (1992) Reproductive toxicity of chronic lead exposure in the female cynomolgus monkey. Reprod. Toxicol. 6: 123-131.

Foster, W. G.; Stals, S. I.; McMahon, A. (1992) An ultrasound study of the effect of chronic lead exposure on endometrial cycle changes in the female cynomolgus monkey. J. Med. Primatol. 21: 353-356.

Foster, W. G.; McMahon, A.; YoungLai, E. V.; Hughes, E. G.; Rice, D. C. (1993) Reproductive endocrine effects of chronic lead exposure in the male cynomolgus monkey. Reprod. Toxicol. 7: 203-209.

Foster, W. G.; McMahon, A.; Rice, D. C. (1996a) Sperm chromatin structure is altered in cynomolgus monkeys with environmentally relevant blood lead levels. Toxicol. Ind. Health 12: 723-735.

Foster, W. G.; McMahon, A.; Rice, D. C. (1996b) Subclinical changes in luteal function in cynomolgus monkeys with moderate blood lead levels. J. Appl. Toxicol. 16: 159-163.

Foster, W. G.; Singh, A.; McMahon, A.; Rice, D. C. (1998) Chronic lead exposure effects in the cynomolgus monkey (Macaca fascicularis) testis. Ultrastruct. Pathol. 22: 63-71.

Fowler, B. A. (1992) Mechanisms of kidney cell injury from metals. Environ. Health Perspect. 100: 57-63.

Fowler, B. A.; DuVal, G. (1991) Effects of lead on the kidney: roles of high-affinity lead-binding proteins. Environ. Health Perspect. 91: 77-80.

Fowler, B. A.; Kimmel, C. A.; Woods, J. S.; McConnell, E. E.; Grant, L. D. (1980) Chronic low-level lead toxicity in the rat. III. An integrated assessment of long-term toxicity with special reference to the kidney. Toxicol. Appl. Pharmacol. 56: 59-77.

Fowler, B. A.; Kahng, M. W.; Smith, D. R.; Conner, E. A.; Laughlin, N. K. (1993) Implications of lead binding proteins for risk assessment of lead exposure. J. Exposure Anal. Environ. Epidemiol. 3: 441-448.

Fox, D. A.; Chu, L. W.-F. (1988) Rods are selectively altered by lead: II. ultrastructure and quantitative histology. Exp. Eye Res. 46: 613-625.

Fox, D. A.; Farber, D. B. (1988) Rods are selectively altered by lead: I. electrophysiology and biochemistry. Exp. Eye Res. 46: 597-611.

Fox, D. A.; Rubinstein, S. D. (1989) Age-related changes in retinal sensitivity, rhodopsin content and rod outer segment length in hooded rats following low-level lead exposure during development. Exp. Eye Res. 48: 237-249.

Fox, D. A.; Sillman, A. J. (1979) Heavy metals affect rod, but not cone, photoreceptors. Science (Washington, DC) 206: 78-80.

Fox, D. A.; Katz, L. M.; Farber, D. B. (1991a) Low level developmental lead exposure decreases the sensitivity, amplitude and temporal resolution of rods. Neurotoxicology 12: 641-654.

Fox, D. A.; Rubinstein, S. D.; Hsu, P. (1991b) Developmental lead exposure inhibits adult rat retinal, but not kidney, Na+,K+-ATPase. Toxicol. Appl. Pharmacol. 109: 482-493.

Fox, D. A.; Srivastava, D.; Hurwitz, R. L. (1994) Lead-induced alterations in rod-mediated visual functions and cGMP metabolism: new insights. Neurotoxicology 15: 503-512.

Fox, D. A.; Campbell, M. L.; Blocker, Y. S. (1997) Functional alterations and apoptotic cell death in the retina following developmental or adult lead exposure. Neurotoxicology 18: 645-664.

Fracasso, M. E.; Perbellini, L.; Solda, S.; Talamini, G.; Franceschetti, P. (2002) Lead induced DNA strand breaks in lymphocytes of exposed workers: role of reactive oxygen species and protein kinase C. Mutat. Res. 515: 159-169.

Franklin, C. A.; Inskip, M. J.; Baccanale, C. L.; Edwards, C. M.; Manton, W. I.; Edwards, E.; O'Flaherty, E. J. (1997) Use of sequentially administered stable lead isotopes to investigate changes in blood lead during pregnancy in a nonhuman primate (Macaca fascicularis). Fundam. Appl. Toxicol. 39: 109-119.

Franks, P. A.; Laughlin, N. K.; Dierschke, D. J.; Bowman, R. E.; Meller, P. A. (1989) Effects of lead on luteal function in rhesus monkeys. Biol. Reprod. 41: 1055-1062.

Fu, H.; Boffetta, P. (1995) Cancer and occupational exposure to inorganic lead compounds: a meta-analysis of published data. Occup. Environ. Med. 52: 73-81.

Fuentes, M.; Torregrosa, A.; Mora, R.; Gotzens, V.; Corbella, J.; Domingo, J. L. (1996) Placental effects of lead in mice. Placenta 17: 371-376.

Fujita, H.; Orii, Y.; Sano, S. (1981) Evidence of increased synthesis of "delta"-aminolevulinic acid dehydratase in experimental lead-poisoned rats. Biochim. Biophys. Acta 678: 39-50.

Fujita, H.; Sato, K,; Sano, S. (1982) Increase in the amount of Erythrocyte delta-aminolevulinic acid dehydratase in workers with moderate lead exposure. Int. Arch. Occup. Environ. Health 50: 287-297.

Fujiwara, Y.; Kaji, T. (1999) Possible mechanism for lead inhibition of vascular endothelial cell proliferation: a lower response to basic fibroblast growth factor through inhibition of heparan sulfate synthesis. Toxicology 133: 147-157.

Fujiwara, Y.; Kaji, T.; Yamamoto, C.; Sakamoto, M.; Kozuka, H. (1995) Stimulatory effect of lead on the proliferation of cultured vascular smooth-muscle cells. Toxicology 98: 105-110.

Fujiwara, Y.; Watanabe, S.; Sakamoto, M.; Kaji, T. (1998) Repair of wounded monolayers of cultured vascular endothelial cells after simultaneous exposure to lead and zinc. Toxicol. Lett. 94: 181-188.

Fukumoto, K.; Karai, I.; Horiguchi, S. (1983) Effect of lead on erythrocyte membranes. Br. J. Ind. Med. 40: 220-223.

Fullmer, C. S. (1991) Intestinal calcium and lead absorption: effects of dietary lead and calcium. Environ. Res. 54: 159-169.

Fullmer, C. S. (1992) Intestinal interactions of lead and calcium. Neurotoxicology 13: 799-807.

Fullmer, C. S. (1995) Dietary calcium levels and treatment interval determine the effects of lead ingestion on plasma 1,25-dihydroxyvitamin D concentration in chicks. J. Nutr. 125: 1328-1333.

Fullmer, C. S. (1997) Lead--calcium interactions: involvement of 1,25-dihydroxyvitamin D. Environ. Res. 72: 45-55.

Fullmer, C. S.; Rosen, J. F. (1990) Effect of dietary calcium and lead status on intestinal calcium absorption. Environ. Res. 51: 91-99.

Fullmer, C. S.; Edelstein, S.; Wasserman, R. H. (1985) Lead-binding properties of intestinal calcium-binding proteins. J. Biol. Chem. 260: 6816-6819.

Fullmer, C. S.; Chandra, S.; Smith, C. A.; Morrison, G. H.; Wasserman, R. H. (1996) Ion microscopic imaging of calcium during 1,25-dihydroxyvitamin D-mediated intestinal absorption. Histochem. Cell Biol. 106: 215-222.

Furono, K.; Suetsugu, T.; Sugihara, N. (1996) Effects of metal ions on lipid peroxidation in cultured rat hepatocytes loaded with alpha-linolenic acid. J. Toxicol. Environ. Health 48: 121-129.

Gainer, J. H. (1977) Effects of heavy metals and of deficiency of zinc on mortality rates in mice infected with encephalomyocarditis virus. Am. J. Vet. Res. 38: 869-872.

Gallicchio, L.; Scherer, R. W.; Sexton, M. (2002) Influence of nutrient intake on blood lead levels of young children at risk for lead poisoning. Environ. Health Perspect. 110: A767-A772.

Gandley, R.; Anderson, L.; Silbergeld, E. K. (1999) Lead: male-mediated effects on reproduction and development in the rat. Environ. Res. A 89: 355-363.

Garavan, H.; Morgan, R. E.; Levitsky, D. A.; Hermer-Vazquez, L.; Strupp, B. J. (2000) Enduring effects of early lead exposure: evidence for a specific deficit in associative ability. Neurotoxicol. Teratol. 22: 151-164.

Garcia, T. A.; Corredor, L. (2004) Biochemical changes in the kidneys after perinatal intoxication with lead and/or cadmium and their antagonistic effects when coadministered. Ecotoxicol. Environ. Saf. 57: 184-189.

Gautam, A. K.; Chowdhury, A. R. (1987) Effect of lead on erythropoietic system of intact and splenectomized rats. Indian J. Physiol. Pharmacol. 31: 117-124.

Gerhardsson, L.; Brune, D.; Nordberg, G. F.; Wester, P. O. (1986) Distribution of cadmium, lead and zinc in lung, liver and kidney in long-term exposed smelter workers. Sci. Total Environ. 50: 65-85.

Gerhardsson, L.; Hagmar, L.; Rylander, L.; Skerfving, S. (1995a Mortality and cancer incidence among secondary lead smelter workers. Occup. Environ. Med. 52: 667-672.

Gerlach, R. F.; Souza, A. P.; Cury, J. A.; Line, S. R. P. (2000a) Effect of lead, cadmium and zinc on the activity of enamel matrix proteinases in vitro. Eur. J. Oral Sci. 108: 327-334.

Gerlach, R. F.; Toledo, D. B.; Novaes, P. D.; Merzel, J.; Line, S. R. P. (2000b) The effect of lead on the eruption rates of incisor teeth in rats. Arch. Oral Biol. 45: 951-955.

Gerlach, R. F.; Cury, J. A.; Krug, F. J.; Line, S. R. P. (2002) Effect of lead on dental enamel formation. Toxicology 175: 27-34.

Gerr, F.; Letz, R.; Stokes, L.; Chettle, D.; McNeill, F.; Kaye, W. (2002) Association between bone lead concentration and blood pressure among young adults. Am. J. Ind. Med. 42: 98-106.

Gewirtz, A. T.; Liu, Y.; Sitaraman, S. V.; Madara, J. L. (2002) Intestinal epithelial pathobiology: past, present and future. Best Pract. Res. Clin. Gastroenterol. 16: 851-867.

Giavini, E.; Prati, M.; Vismara, C. (1980) Effects of cadmium, lead and copper on rat preimplantation embryos. Bull. Environ. Contam. Toxicol. 25: 702-705.

Gibson, S. L. M.; Goldberg, A. (1970) Defects in haem synthesis in mammalian tissues in experimental lead poisoning and experimental porphyria. Clin. Sci. 38: 63-72.

Gilbert, M. E.; Mack, C. M. (1998) Chronic lead exposure accelerates decay of long-term potentiation in rat dentate gyrus in vivo. Brain Res. 789: 139-149.

Gilbert, M. E.; Mack, C. M.; Lasley, S. M. (1996) Chronic developmental lead exposure increases the threshold for long-term potentiation in rat dentate gyrus in vivo. Brain Res. 736: 118-124.

Gilbert, M. E.; Mack, C. M.; Lasley, S. M. (1999a) The influence of developmental period of lead exposure on long-term potentiation in the adult rat dentate gyrus in vivo. Neurotoxicology 20: 57-69.

Gilbert, M. E.; Mack, C. M.; Lasley, S. M. (1999b) Chronic developmental lead exposure and hippocampal long-term potentiation: biphasic dose-response relationship. Neurotoxicology 20: 71-82.

Gilbert, M. E.; Kelly, M. E.; Samsam, T. E.; Goodman, J. H. (2005) Chronic developmental lead exposure reduces neurogenesis in adult rat hippocampus but does not impair spatial learning. Toxicol. Sci. 86:

Giridhar, J.; Isom, G. E. (1990) Interaction of lead acetate with atrial natriuretic factor in rats. Life Sci. 46: 569-576.

Gobel, T. W. F. (1996) The T-dependent immune system. In. Davidson, T. F.; Morris, T. R.; Payne, L. N., ed. Poultry immunology. Carfax Pub. Abingdon. 83-114.

Goebel, C.; Kirchhoff, K.; Wasmuth, H.; Flohe, S. B.; Elliott, R. B.; Kolb, H. (1999) The gut cytokine balance as a target of lead toxicity. Life Sci. 64: 2207-2214.

Goebel, C.; Flohe, S. B.; Kirchhoff, K.; Herder, C.; Kolb, H. (2000) Orally administered lead chloride induces bias of mucosal immunity. Cytokine 12: 1414-1418.

Goering, P. L.; Fowler, B. A. (1984) Regulation of lead inhibition of delta-aminolevulinic acid dehydratase by a low molecular weight, high affinity renal lead-binding protein. J. Pharmacol. Exp. Ther. 231: 66-71.

Goering, P. L.; Fowler, B. A. (1985) Mechanism of renal lead-binding protein reversal of "delta"-aminolevulinic acid dehydratase inhibition by lead. J. Pharmacol. Exp. Ther. 234: 365-371.

Goering, P. L.; Mistry, P.; Fowler, B. A. (1986) A low molecular weight lead-binding protein in brain attenuates lead inhibition of "delta"-aminolevulinic acid dehydratase: comparison with a renal lead-binding protein. J. Pharmacol. Exp. Ther. 237: 220-225.

Goering, P. L.; Fowler, B. A. (1987a) Regulatory roles of high-affinity metal-binding proteins in mediating lead effects on δ-aminolevulinic acid dehydratase. Ann. N. Y. Acad. Sci. 514: 235-247.

Goering, P. L.; Fowler, B. A. (1987b) Kidney zinc-thionein regulation of delta-aminolevulinic acid dehydratase inhibition by lead. Arch. Bichem. Biophys. 253: 48-55.

Goldstein, G. W. (1993) Evidence that lead acts as a calcium substitute in second messenger metabolism. Presented at: Ninth international neurotoxicology conference; October 1991; Little Rock, AR. Neurotoxicology 14(2-3): 97-101.

Golubovich, E. Ya.; Avkhimenko, M. M.; Chirkova, E. M. (1968) Biochemical and morphological changes in the testicles of rats induced by small doses of lead. Toksikol. Nov. Prom. Khim. Veschestv. 10: 63-73.

Gonick, H. C.; Khalil-Manesh, F.; Raghavan, S. R. V. (1985) Characterization of human erythrocyte lead-binding protein. In: Lekkas, T. D., ed. International conference: heavy metals in the environment; September; Athens, Greece, v. 1. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 313-316.

Gonick, H. C.; Ding, Y.; Bondy, S. C.; Ni, Z.; Vaziri, N. D. (1997) Lead-induced hypertension: interplay of nitric oxide and reactive oxygen species. Hypertension 30: 1487-1492.

Gonick, H. C.; Ding, Y.; Vaziri, N. D. (1998) Effect of low lead exposure on eicosanoid excretion in rats. Prostaglandins Other Lipid Mediators 55: 77-82.

Gonzalez-Cossio, T.; Peterson, K. E.; Sanin, L.-H.; Fishbein, E.; Palazuelos, E.; Aro, A.; Hernandez-Avila, M.; Hu, H. (1997) Decrease in birth weight in relation to maternal bone-lead burden. Pediatrics 100: 856-862.

Gonzalez-Riola, J.; Hernandez, E. R.; Escribano, A.; Revilla, M.; Villa, C.-S. L. F.; Rico, H. (1997) Effect of lead on bone and cartilage in sexually mature rats: a morphometric and histomorphometry study. Environ. Res. 74: 91-93.

Gorbel, F.; Boujelbene, M.; Makni-Ayadi, F.; Guermazi, F.; Croute, F.; Soleilhavoup, J. P.; El Feki, A. (2002) Exploration des effets cytotoxiques du plomb sur la fonction sexuelle endocrine et exocrine chez le rat pubere male et femelle. Mise en evidence d'une action apoptotique [Impact of lead given in drinking water on the endocrine and exocrine sexual activity in pubescent rats. Determination of an apoptotic process]. C. R. Biol. 325: 927-940.

Goyer, R. A. (1968) The renal tubule in lead poisoning. I. Mitochondrial swelling and aminoaciduria. Lab. Invest. 19: 71-77.

Goyer, R. A.; Rhyne, B. C. (1973) Pathological effects of lead. Int. Rev. Exp. Pathol. 12: 1-77.

Goyer, R. A.; Wilson, M. H. (1975) Lead-induced inclusion bodies: results of ethylenediaminetetraacetic acid treatment. Lab. Invest. 32: 149-156.

Goyer, R. A.; Krall, A.; Kimball, J. P. (1968) The renal tubule in lead poisoning. II. In vitro studies of mitochondrial structure and function. Lab. Invest. 19: 78-83.

Goyer, R. A.; Leonard, D. L.; Bream, P. R.; Irons, T. G. (1970a) Aminoaciduria in experimental lead poisoning. Proc. Soc. Exp. Biol. Med. 135: 767-771.

Goyer, R. A.; Leonard, D. L.; Moore, J. F.; Rhyne, B. Krigman, M. R. (1970b) Lead dosage and the role of the intranuclear inclusion body: an experimental study. Arch. Environ. Health 20: 705-711.

Goyer, R. A.; May, P.; Cates, M. M.; Krigman, M. R. (1970c) Lead and protein content of isolated intranuclear inclusion bodies from kidneys of lead-poisoned rats. Lab. Invest. 22: 245-251.

Goyer, R. A.; Cherian, M. G.; Delaquerriere-Richardson, L. (1978) Renal effects of repeated administration of calcium disodium ethylenediamnetetraacetate during excessive exposure to lead in rats. J. Environ. Pathol. Toxicol. 1: 403-410.

Goyer, R. A.; Epstein, S.; Bhattacharyya, M.; Korach, K. S.; Pounds, J. (1994) Environmental risk factors for osteoporosis. Environ. Health Perspect. 102: 390-394.

Grabowska, M.; Guminska, M. (1996) The effect of lead on lactate formation, ATP level and membrane ATPase activities in human erythrocytes in vitro. Int. J. Occup. Med. Environ. Health 9: 265-274.

Graca, A.; Ramalho-Santos, J.; De Lourdes Pereira, M. (2004) Effect of lead chloride on spermatogenesis and sperm parameters in mice. Asian J. Androl. 6: 237-241.

Granick, J. L.; Sassa, S.; Granick, S.; Levere, R. D.; Kappas, A. (1973) Studies in lead poisoning. II. correlation between the ratio of activated to inactivated "delta"-aminolevulinic acid dehydratase of whole blood and the blood lead level. Biochem. Med. 8: 149-159.

Grant, L. D.; Kimmel, C. A.; West, G. L.; Martinez-Vargas, C. M.; Howard, J. L. (1980) Chronic low-level lead toxicity in the rat. II. Effects on postnatal physical and behavioral development. Toxicol. Appl. Pharmacol. 56: 42-58.

Grobler, S. R.; Rossouw, R. J.; Kotze, D. (1985) Lead in teeth of weanling rats received via the maternal drinking water. Arch. Oral Biol. 30: 509-511.

Grobler, S. R.; Rossouw, R. J.; Kotze, T. J. V.; Stander, I. A. (1991) The effect of airborne lead on lead levels of blood, incisors and alveolar bone of rats. Arch. Oral Biol. 36: 357-360.

Grover, C. A.; Nation, J. R.; Brattom. G. R. (1993) Chronic exposure to lead attenuates cocaine-induced behavioral activation. Pharmacol. Biochem. Behav. 44: 221-225.

Gruber, H. E.; Gonick, H. C.; Khalil-Manesh, F.; Sanchez, T. V.; Motsinger, S.; Meyer, M.; Sharp, C. F. (1997) Osteopenia induced by long-term, low- and high-level exposure of the adult rat to lead. Miner. Electrolyte Metab. 23: 65-73.

Guilarte T. R.; McGlothan, J. L. (1998) Hippocampal NMDA receptor mRNA undergoes subunit specific changes during developmental lead exposure. Brain Res. 790: 98-107.

Guilarte T. R.; McGlothan, J. L. (2003) Selective decrease in NR1 subunit splice variant mRNA in the hippocampus of Pb2+-exposed rats: implications for synaptic targeting and cell surface expression of NMDAR complexes. Mol. Brain Res. 113: 37-43.

Guilarte, T. R.; Miceli, R. C. (1992) Age-dependent effects of lead on [3H]MK-801 binding to the NMDA receptor-gated ionophore: in vitro and in vivo studies. Neurosci. Lett. 148: 27-30.

Guilarte, T. R.; McGlothan, J. L.; Nihei, M. K. (2000) Hippocampal expression of N-methyl-D-aspartate receptor (NMDAR1) subunit splice variant mRNA is altered by developmental exposure to Pb2+. Mol. Brain Res. 76: 299-305.

Guity, P.; McCabe, M. J.; Pitts, D. K.; Santini, R. P.; Pounds, J. G. (2002) Protein kinase C does not mediate the inhibitory action of lead on vitamin D3-dependent production of osteocalcin in osteoblastic bone cells. Toxicol. Appl. Pharmacol. 178: 109-116.

Guo, T. L.; Mudzinski, S. P.; Lawrence, D. A. (1996) The heavy metal lead modulates the expression of both TNF-"alpha" and TNF-"alpha" receptors in lipopolysaccharide-activated human peripheral blood mononuclear cells. J. Leukoc. Biol. 59: 932-939.

Gupta, K.; Upreti, R. K.; Kidwai, A. M. (1994) Toxicokinetic study of rat intestinal brush border membrane enzymes following in vitro exposure to lead and vanadium. Bull. Environ. Contam. Toxicol. 52: 919-926.

Gupta, P.; Husain, M. M.; Shankar, R.; Seth, P. K.; Maheshwari, R. K. (2002) Lead exposure enhances virus multiplication and pathogenesis in mice. Vet. Hum. Toxicol. 44: 205-210.

Gurer, H.; Ercal, N. (2000) Can antioxidants be beneficial in the treatment of lead poisoning? Free Rad. Biol. Med. 29: 927-945.

Gurer, H.; Ozgunes, H.; Neal, R.; Spitz, D. R.; Ercal, N. (1998) Antioxidant effects of N-acetylcysteine and succimer in red blood cells from lead-exposed rats. Toxicology 128: 181-189.

Gurer, H.; Neal, R.; Yang, P.; Oztezcan, S.; Ercal, N. (1999a) Captopril as an antioxidant in lead-exposed Fischer 344 rats. Hum. Exp. Toxicol. 18: 27-32.

Gurer, H.; Ozgunes, H.; Oztezcan, S.; Ercal, N. (1999b) Antioxidant role of α-lipoic acid in lead toxicity. Free Radical Biol. Med. 27: 75-81.

Gürer, H.; Özgünes, H.; Saygin, E.; Ercal, N. (2001) Antioxidant effect of taurine against lead-induced oxidative stress. Arch. Environ. Contam. Toxicol. 41: 397-402.

Gutowski, M.; Altmann, L.; Sveinsson, K.; Wiegand, H. (1997) Postnatal development of synaptic plasticity in the CA3 hippocampal region of control and lead-exposed Wistar rats. Dev. Brain Res. 98: 82-90.

Gutowski, M.; Altmann, L.; Sveinsson, K.; Wiegand, H. (1998) Synaptic plasticity in the CA1 and CA3 hippocampal region of pre- and postnatally lead-exposed rats. Toxicol. Lett. 95: 195-203.

Habermann, E.; Crowell, K.; Janicki, P. (1983) Lead and other metals can substitute for Ca2+ in calmodulin. Arch. Toxicol. 54: 61-70.

Hac, E.; Krechniak, J. (1996) Lead levels in bone and hair of rats treated with lead acetate. Biol. Trace Elem. Res. 52: 293-301.

Hacker, H.-J.; Bannasch, P.; Columbano, A. (1990) Effect of lead nitrate on liver carbohydrate enzymes and glycogen content in the rat. Carcinogenesis 11: 2199-2204.

Hamilton, J. D.; O'Flaherty, E. J. (1994) Effects of lead exposure on skeletal development in rats. Fundam. Appl. Toxicol. 22: 594-604.

Hamilton, J. D.; O'Flaherty, E. J. (1995) Influence of lead on mineralization during bone growth. Fundam. Appl. Toxicol. 26: 265-271.

Hamilton, J. D.; O'Flaherty, E. J.; Ross, R.; Shukla, R.; Gartside, P. S. (1994) Structural equation modeling and nested ANOVA: effects of lead exposure on maternal and fetal growth in rats. Environ. Res. 64: 53-64.

Hammad, T. A.; Sexton, M.; Langenberg, P. (1996) Relationship between blood lead and dietary iron intake in preschool children: a cross-sectional study. Ann. Epidemiol. 6: 30-33.

Hammond, P. B.; Chernausek, S. D.; Succop, P. A.; Shukla, R.; Bornschein, R. L. (1989) Mechanisms by which lead depresses linear and ponderal growth in weanling rats. Toxicol. Appl. Pharmacol. 99: 474-486.

Hammond, P. B.; Minnema, D. J.; Shulka, R. (1990) Lead exposure lowers the set point for food consumption and growth in weanling rats. Toxicol. Appl. Pharmacol. 106: 80-87.

Hammond, P. B.; Minnema, D. J.; Succop, P. A. (1993) Reversibility of lead-induced depression of growth. Toxicol. Appl. Pharmacol. 123: 9-15.

Han, S.; Qiao, X.; Simpson, S.; Ameri, P.; Kemp, F. W.; Bogden, J. D. (1996) Weight loss alters organ concentrations and contents of lead and some essential divalent metals in rats previously exposed to lead. J. Nutr. 126: 317-323.

Han, S.; Qiao, X.; Kemp, F. W.; Bogden, J. D. (1997) Lead exposure at an early age substantially increases lead retention in the rat. Environ. Health Perspect. 105: 412-417.

Han, S.; Li, W.; Jamil, U.; Dargan, K.; Orefice, M.; Kemp, F. W.; Bogden, J. D. (1999) Effects of weight loss and exercise on the distribution of lead and essential trace elements in rats with prior lead exposure. Environ. Health Perspect. 107: 657-662.

Han, S.; Pfizenmaier, D. H.; Garcia, E.; Eguez, M. L.; Ling, M.; Kemp, F. W.; Bogden, J. D. (2000) Effects of lead exposure before pregnancy and dietary calcium during pregnancy on fetal development and lead accumulation. Environ. Health Perspect. 108: 527-531.

Hanna, L. A.; Peters, J. M.; Wiley, L. M.; Clegg, M. S.; Keen, C. L. (1997) Comparative effects of essential and non-essential metals on preimplantation mouse embryo development in vitro. Toxicology 116: 123-131.

Hanson, E. H.; Imperatore, G.; Burke, W. (2001) HFE gene and hereditary hemochromatosis: a HuGE review. Am. J. Epidemiol. 154: 193-206.

Hartman, D. E. (1995) Neuropsychological toxicology. 2nd ed. New York, NY: Plenum Press; pp. 95-125.

Hartwig, A.; Schlepegrell, R.; Beyersmann, D. (1990) Indirect mechanism of lead-induced genotoxicity in cultured mammalian cells. Mutat. Res. 241: 75-82.

Hashmi, N. S.; Kachru, D. N.; Khandelwal, S.; Tandon, S. K. (1989) Interrelationship between iron deficiency and lead intoxication (part 2). Biol. Trace Elem. Res. 22: 299-307.

Hayashi, M. (1983a) Lead toxicity in the pregnant rat. I. the effect of high - level lead on "delta"-aminolevulinic acid dehydratase activity in maternal and fetal blood or tissues. Environ. Res. 30: 152-160.Hayes, R. B. (1997) The carcinogenicity of metals in humans. Cancer Causes Control 8: 371-385.

Hayashi, M. (1983b) Lead toxicity in the pregnant rat. II. Effects of low-level lead on delta-aminolevulinic acid dehydratase activity in maternal and fetal blood or tissue. Ind. Health 21: 127-135.

He, L.; Poblenz, A. T.; Medrano, C. J.; Fox, D. A. (2000) Lead and calcium produce rod photoreceptor cell apoptosis by opening the mitrochondrial permeability transition pore. J. Biol. Chem. 275: 12175-12184.

He, L.; Perkins, G. A.; Poblenz, A. T.; Harris, J. B.; Hung, M.; Ellisman, M. H.; Fox, D. A.. (2003) Bcl-xL overexpression blocks bax-mediated mitochondrial contact site formation and apoptosis in rod photoreceptors of lead-exposed mice. Proc. Natl. Acad. Sci. U. S. A. 100: 1022-1027.

Heiman, A. S.; Tonner, L. E. (1995) The acute effect of lead acetate on glucocorticoid regulation of tyrosine aminotransferase in hepatoma cells. Toxicology 100: 57-68.

Helleday, T.; Nilsson, R.; Jenssen, D. (2000) Arsenic [III] and heavy metal ions induce intrachromosomal homologous recombination in the hprt gene of V79 Chinese hamster cells. Environ. Mol. Mutagen. 35: 114-122.

Hellstrom-Lindahl, E.; Oskarsson, A. (1990) Cellular response after mobilization of metals by diethyldithiocarbamate in rat hepatocyte cultures. Toxicology 65: 23-32.

Hemphill, F. E.; Kaeberle, M. L.; Buck, W. B. (1971) Lead suppression of mouse resistance to Salmonella typhimurium. Science (Washington, DC) 172: 1031-1032.

Hengstler, J. G.; Bolm-Audorff, U.; Faldum, A.; Janssen, K.; Reifenrath, M.; Gotte, W.; Jung, D.; Mayer-Popken, O.; Fuchs, J.; Gebhard, S.; Bienfait, H. G.; Schlink, K.; Dietrich, C.; Faust, D.; Epe, B.; Oesch, F. (2003) Occupational exposure to heavy metals: DNA damage induction and DNA repair inhibition prove co-exposures to cadmium, cobalt and lead as more dangerous than hitherto expected. Carcinogenesis 24: 63-73.

Henning, S. J.; Cooper, L. C. (1988) Intestinal accumulation of lead salts and milk lead by suckling rats (42645). Proc. Soc. Exp. Biol. Med. 187: 110-116.

Heo, Y.; Parsons, P. J.; Lawrence, D. A. (1996) Lead differentially modifies cytokine production in vitro and in vivo. Toxicol. Appl. Pharmacol. 138: 149-157.

Heo, Y.; Lee, W. T.; Lawrence, D. A. (1997) In vivo the environmental pollutants lead and mercury induce oligoclonal T cell responses skewed toward type-2 reactivities. Cell. Immunol. 179: 185-195.

Heo, Y.; Lee, W. T.; Lawrence, D. A. (1998) Differential effects of lead and cAMP on development and activities of Th1- and Th2-lymphocytes. Toxicol. Sci. 43: 172-185.

Heo, Y.; Lee, B.-K.; Ahn, K.-D.; Lawrence, D. A. (2004) Serum IgE elevation correlates with blood lead levels in battery manufacturing workers. Hum. Exp. Toxicol. 23: 209-213.

Hermes-Lima, M.; Pereira, B.; Bechara, E. J. H. (1991) Are free radicals involved in lead poisoning? Xenobiotica 21: 1085-1090.

Hernandez-Avila, M.; Gonzalez-Cossio, T.; Hernandez-Avila, J. E.; Romieu, I.; Peterson, K. E.; Aro, A.; Palazuelos, E.; Hu, H. (2003) Dietary calcium supplements to lower blood lead levels in lactating women: a randomized placebo-controlled trial. Epidemiology 14: 206-212.

Hicks, D. G.; O'Keefe, R. J.; Reynolds, K. J.; Cory-Slechta, D. A.; Puzas, J. E.; Judkins, A.; Rosier, R. N. (1996) Effects of lead on growth plate chondrocyte phenotype. Toxicol. Appl. Pharmacol. 140: 164-172.

Hilbertz, U.; Kramer, U.; De Ruiter, N.; Baginski, B. (1986) Effects of cadmium and lead on oxidative metabolism and phagocytosis by mouse peritoneal macrophages. Toxicology 39: 47-57.

Hilderbrand, D. C.; Der, R.; Griffin, W. T.; Fahim, M. S. (1973) Effect of lead acetate on reproduction. Am. J. Obstet. Gynecol. 115: 1058-1065.

Hill, A. B. (1965) The environment and disease: association or causation? Proc. R. Soc. Med. 58: 295-300.

Hilson, J. A.; Strupp, B. J. (1997) Analyses of response patterns clarify lead effects in olfactory reversal and extradimensional shift tasks: assessment of inhibitory control, associative ability, and memory. Behav. Neurosci. 111: 532-542.

Hinton, D. E.; Lipsky, M. M.; Heatfield, B. M.; Trump, B. F. (1979) Opposite effects of lead on chemical carcinogenesis in kidney and liver of rats. Bull. Environ. Contam. Toxicol. 23: 464-469.

Hogan, K.; Marcus, A.; Smith, R.; White, P. (1998) Integrated exposure uptake biokinetic model for lead in children: empirical comparisons with epidemiologic data. Environ. Health Perspect. 106(suppl. 6): 1557-1567.

Holgate, S.; Casale, T.; Webzek, S.; Bousquet, J.; Deniz, Y.; Reisner, C. (2005) The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J. Allergy Clin. Immunol. 115: 459-465.

Holian, A.; Uthman, M. O.; Goltsova, T.; Brown, S. D.; Hamilton, R. F. J. (1997) Asbestos and silica-induced changes in human alveolar macrophage phenotype. Environ. Health Perspect. 105: 1139-1142.

Holladay, S. D. (1999) Prenatal immunotoxicant exposure and postnatal autoimmune disease. Environ. Health Perspect. 107: 687-691.

Holladay, S. D. (2005) Developmental immunotoxicology. Boca Raton, FL: CRC Press, Inc.

Holsapple, M. P.; West, L. J.; Landreth, K. S. (2003) Species comparison of anatomocial and functional immune system development. Birth Defects Res. B. 68: 321-334.

Honchel, R.; Marsano, L.; Cohen, D.; Shedlofsky, S.; McClain, C. J. (1991) Lead enhances lipopolysaccharide and tumor necrosis factor liver injury. J. Lab. Clin. Med. 117: 202-208.

Hotter, G.; Fels, L. M.; Closa, D.; Rosello, J.; Stolte, H.; Gelpi, E. (1995) Altered levels of urinary prostanoids in lead-exposed workers. Toxicol. Lett. 77: 309-312.

Hu, H. (1991) A 50-year follow-up of childhood plumbism: hypertension, renal function, and hemoglobin levels among survivors. Am. J. Dis. Child. 145: 681-687.

Hu, H.; Wu, M.-T.; Cheng, Y.; Sparrow, D.; Weiss, S.; Kelsey, K. (2001) The "delta"-aminolevulinic acid dehydratase (ALAD) polymorphism and bone and blood lead levels in community-exposed men: the Normative Aging Study. Environ. Health Perspect. 109: 827-832.

Huang, F., Schneider, J. S. (2004) Effects of lead exposure on proliferation and differentiation of neural stem cells derived from different regions of embryonic rat brain. Neurotoxicology.25: 1001-1012.

Hubermont, G.; Buchet, J.-P.; Roels, H.; Lauwerys, R. (1976) Effect of short-term administration of lead to pregnant rats. Toxicology 5: 379-384.

Hudson, C. A.; Cao, L.; Kasten-Jolly, J.; Kirkwood, J. N.; Lawrence, D. A. (2003) Susceptibility of lupus-prone NZM mouse strains to lead exacerbation of systemic lupus erythematosus symptoms. J. Toxicol. Environ. Health A 66: 895-918.

Hussain, I.; Piepenbrink, M. S.; Dietert, R. R. (2005) Impact of in ovo-administered lead and testosterone on developing female thymocytes. J. Toxicol. Environ. Health A. 68: 1309-1319.

Hwang, K.-Y.; Lee, B.-K.; Bressler, J. P.; Bolla, K. I.; Stewart, W. F.; Schwartz, B. S. (2002) Protein kinase C activity and the relations between blood lead and neurobehavioral function in lead workers. Environ. Health Perspect. 110: 133-138.

Hwua, Y. S.; Yang J. L. (1998) Effect of 3-aminotriazole on anchorage independence and mutagenicity in cadmium- and lead-treated diploid human fibroblasts. Carcinogenesis 19: 881-888.

Iavicoli, I.; Carelli, G.; Stanek, E. J., III; Castellino, N.; Calabrese, E. J. (2003) Effects of low doses of dietary lead on red blood cell production in male and female mice. Toxicol. Lett. 137: 193-199.

Ichiba, M.; Tomokuni, K. (1987) Urinary excretion of 5-hydroxyindoleacetic acid, "delta"-aminolevulinic acid and coproporphyrin isomers in rats and men exposed to lead. Toxicol. Lett. 38: 91-96.

Ichiba, M.; Tomokuni, K.; Sugimoto, K. (1987) Erythrocyte pyrimidine 5'-nucleotidase test for occupational lead exposure. Ind. Health 25: 195-203.

Ikebuchi, H.; Teshima, R.; Suzuki, K.; Terao, T.; Yamane, Y. (1986) Simultaneous induction of Pb-metallothionein-like protein and Zn-thionein in the liver of rats given lead acetate. Biochem. J. 233: 541-546.

Inskip, M. J.; Franklin, C. A.; Baccanale, C. L.; Manton, W. I.; O'Flaherty, E. J.; Edwards, C. M. H.; Blenkinsop, J. B.; Edwards, E. B. (1996) Measurement of the flux of lead from bone to blood in a nonhuman primate (Macaca fascicularis) by sequential administration of stable lead isotopes. Fundam. Appl. Toxicol. 33: 235-245.

Ishihara, K.; Alkondon, M.; Montes, J. G.; Albuquerque, E. X. (1995) Nicotinic responses in acutely dissociated rat hippocampal neurons and the selective blockade of fast-desensitizing nicotinic currents by lead. J. Pharmacol. Exp. Ther. 273: 1471-1482.

Isolauri, E.; Huurre, A.; Salminen, S.; Impivaara, O. (2004) The allergy epidemic extends beyond the past few decades. Clin. Exp. Allergy. 34: 1007-1010.

Ito, Y.; Niiya, Y.; Kurita, H.; Shima, S.; Sarai, S. (1985) Serum lipid peroxide level and blood superoxide dismutase activity in workers with occupational exposure to lead. Int. Arch. Occup. Environ. Health 56: 119-127.

Jacobs, J. M.; Sinclair, P. R.; Sinclair, J. F.; Gorman, N.; Walton, H. S.; Wood, S. G.; Nichols, C. (1998) Formation of zinc protoporphyrin in cultured hepatocytes: effects of ferrochelatase inhibition, iron chelation or lead. Toxicology 125: 95-105.

Jacquet, P. (1976) Effets du plomb administre durant la gestation a des souris C57B1 [Effects of lead administered during the gestation period of mice C57B1]. C. R. Seances Soc. Biol. Ses Fil. 170: 1319-1322.

Jacquet, P. (1977) Early embryonic development in lead-intoxicated mice. Arch. Pathol. Lab. Med. 101: 641-643.

Jacquet, P.; Leonard, A.; Gerber, G. B. (1975) Embryonic death in mouse due to lead exposure. Experientia 31: 24-25.

Jacquet, P.; Leonard, A.; Gerber, G. B. (1976) Action of lead on early divisions of the mouse embryo. Toxicology 6: 129-132.

Jacquet, P.; Gerber, G. B.; Maes, J. (1977) Biochemical studies in embryos after exposure of pregnant mice to dietary lead. Bull. Environ. Contam. Toxicol. 18: 271-277.

Jagetia, G. C.; Aruna, R. (1998) Effect of various concentrations of lead nitrate on the induction of micronuclei in mouse bone marrow. Mutat. Res. 415: 131-137.

Jehan, Z. S.; Motlag, D. B. (1995) Metal induced changes in the erythrocyte membrane of rats. Toxicol. Lett. 78: 127-133.

Jemal, A.; Graubard, B. I.; Devesa, S. S.; Flegal, K. M. (2002) The association of blood lead level and cancer mortality among whites in the United States. Environ. Health Perspect. 110: 325-329.

Jett, D. A.; Beckles, R. A.; Navoa, R. V.; McLemore, G. L. (2002) Increased high-affinity nicotinic receptor-binding in rats exposed to lead during development. Neurotoxicol. Teratol. 24: 805-811.

Jian, Z.; Ying-han, X.; Hong-fu, C. (1985) The effects of lead ion on immune function of rabbit alveolar macrophages: Quantitation of immune phagocytosis and rosette formation by 51-Cr in vitro. Toxicol. Appl. Pharmacol. 78: 484-487.

Johansson, L. (1989) Premature acrosome reaction in spermatozoa from lead-exposed mice. Toxicology 54: 151-162.

Johansson, L.; Pellicciari, C. E. (1988) Lead-induced changes in the stabilization of the mouse sperm chromatin. Toxicology 51: 11-24.

Johansson, L.; Wide, M. (1986) Long-term exposure of the male mouse to lead: effects on fertility. Environ. Res. 41: 481-487.

Johansson, L.; Sjoblom, P.; Wide, M. (1987) Effects of lead on the male mouse as investigated by in vitro fertilization and blastocyst culture. Environ. Res. 42: 140-148.

Jones, M. M.; Basinger, M. A.; Gale, G. R.; Atkins, L. M.; Smith, A. B.; Stone, A. (1994) Effect of chelate treatments on kidney, bone and brain levels of lead-intoxicated mice. Toxicology 89: 91-100.

Joseph, C. L. M.; Havstad, S.; Ownby, D. R.; Peterson, E. L.; Maliark, M.; McCabe, J., M.J.; Barone, C.; Johnson, C. C. (2005) Blood lead levels and risk of asthma. Environ. Health Perspect. 113: 900-904.

Jover, R.; Lindberg, R. L. P.; Meyer, U. A. (1996) Role of heme in cytochrome P450 transcription and function in mice treated with lead acetate. Mol. Pharmacol. 50: 474-481.

Junaid, M.; Chowdhuri, D. K.; Narayan, R.; Shanker, R.; Saxena, D. K. (1997) Lead-induced changes in ovarian follicular development and maturation in mice. J. Toxicol. Environ. Health 50: 31-40.

Kaji, T.; Yamamoto, C.; Sakamoto, M. (1991) Effect of lead on the glycosaminoglycans metabolism of bovine aortic endothelial cells in culture. Toxicology 68: 249-257.

Kaji, T.; Yamamoto, C.; Sakamoto, M.; Kozuka, H. (1992) Inhibitory effect of lead on the release of tissue plasminogen activator from human vascular endothelial cells in culture. Toxicology 73: 219-227.

Kaji, T.; Suzuki, M.; Yamamoto, C.; Mishima, A.; Sakamoto, M.; Kozuka, H. (1995a) Severe damage of cultured vascular endothelial cell monolayer after simultaneous exposure to cadmium and lead. Arch. Environ. Contam. Toxicol. 28: 168-172.

Kaji, T.; Fujiwara, Y.; Hoshino, M.; Yamamoto, C.; Sakamoto, M.; Kozuka, H. (1995b) Inhibitory effect of lead on the proliferation of cultured vascular endothelial cells. Toxicology 95: 87-92.

Kaji, T.; Ohkawara, S.; Nakajima, M.; Yamamoto, C.; Fujiwara, Y.; Miyajima, S.; Koizumi, F. (1997) Lead-induced alteration of heparan sulfate proteoglycans in cultured vascular endothelial cells. Toxicology 118: 1-10.

Kamel, F.; Umbach, D. M.; Lehman, T. A.; Park, L. P.; Munsat, T. L.; Shefner, J. M.; Sandler, D. P.; Hu, H.; Taylor, J. A. (2003) Amyotrophic lateral sclerosis, lead, and genetic susceptibility: polymorphisms in the "delta"-aminolevulinic acid dehydratase and vitamin D receptor genes. Environ. Health Perspect. 111: 1335-1339.

Kanduc, D.; Prisco, M. (1992) Hepatic DNA methylation in young, middle-aged, and senescent rats: the effect of mitogen-induced cell proliferation. Biochem. Med. Metab. Biol. 48: 286-291.

Kanduc, D.; Rossiello, M. R.; Aresta, A.; Cavazza, C.; Quagliariello, E.; Farber, E. (1991) Transitory DNA hypomethylation during liver cell proliferation induced by a single dose of lead nitrate. Arch. Biochem. Biophys. 286: 212-216.

Kanitz, M. H.; Witzmann, F. A.; Zhu, H.; Fultz, C. D.; Skaggs, S.; Moorman, W. J.; Savage, R. E., Jr. (1999) Alterations in rabbit kidney protein expression following lead exposure as analyzed by two-dimensional gel electrophoresis. Electrophoresis 20: 2977-2985.

Karmakar, N.; Anand, S. (1989) Study of the inhibitory effect of lead acetate on duodenal contractility in rat. Clin. Exp. Pharmacol. Physiol. 16: 745-750.

Karmakar, N.; Saxena, R.; Anand, S. (1986) Histopathological changes induced in rat tissues by oral intake of lead acetate. Environ. Res. 41: 23-28.

Karmaus, W.; Brooks, K. R.; Nebe, T.; Witten, J.; Obi-Osius, N.; Kruse, H. (2005) Immune function biomarkers in children exposed to lead and organochlorine compounds: a cross-sectional study. Environ. Health Glob. Access Sci. 4: 1-10.

Kato, Y.; Takimoto, S.; Ogura, H. (1977) Mechanism of induction of hypercalcemia and hyperphosphatemia by lead acetate in the rat. Calcif. Tissue Res. 24: 41-46.

Kauppinen, T.; Riala, R.; Seitsamo, J.; Hernberg, S. (1992) Primary liver cancer and occupational exposure. Scand. J. Work Environ. Health. 18: 18-25.

Kelada, S. N.; Shelton, E.; Kaufmann, R. B.; Khoury, M. J. (2001) "Delta"-aminolevulinic acid dehydratase genotype and lead toxicity: a HuGE review. Am. J. Epidemiol. 154: 1-13.

Keller, C. A.; Doherty, R. A. (1980) Bone lead mobilization in lactating mice and lead transfer to suckling offspring. Toxicol. Appl. Pharmacol. 55: 220-228.

Kempinas, W. G.; Lamano-Carvalho, T. L.; Petenusci, S. O.; Lopes, R. A.; Azoubel, R. (1988) Morphometric and stereological analysis of rat testis and epididymis in an early phase of saturnism. Exp. Biol. 8: 51-56.

Kempinas, W. G.; Melo, V. R.; Oliveira-Filho, R. M.; Santos, A. C.; Favaretto, A. L.; Lamano-Carvalho, T. L. (1990) Saturnism in the male rat: endocrine effects. Braz. J. Med. Biol. Res. 23: 1171-1175.

Kempinas, W. G.; Favaretto, A. L. V.; Melo, V. R.; Lamano Carvalho, T. L.; Petenusci, S. O.; Oliveira-Filho, R. M. (1994) Time-dependent effects of lead on rat reproductive functions. J. Appl. Toxicol. 14: 427-433.

Kennedy, G. L.; Arnold, D. W.; Calandra, J. C. (1975) Teratogenic evaluation of lead compounds in mice and rats. Food Cosmet. Toxicol. 13: 629-632.

Keogh, J. P.; Steffen, B.; Siegers, C.-P. (1994) Cytotoxicity of heavy metals in the human small intestinal epithelial cell line I-407: the role of glutathione. J. Toxicol. Environ. Health 43: 351-359.

Kern, M.; Audesirk, G. (2000) Stimulatory and inhibitory effects of inorganic lead on calcineurin. Toxicology 150: 171-178.

Kerper, L. E.; Hinkle, P. M. (1997) Cellular uptake of lead is activated by depletion of intracellular calcium stores. J. Biol. Chem. 272: 8346-8352.

Khalil-Manesh, F.; Gonick, H. C. Cohen, A. H.; Alinovi, R.; Bergamaschi, E.; Mutti, A.; Rosen, V. J. (1992a) Expermiental model of lead nephropathy. I. Continuous high-dose lead administration. Kidney Int. 41: 1192-1203.

Khalil-Manesh, F.; Gonick, H. C.; Cohen, A.; Bergamaschi, E.; Mutti, A. (1992b) Experimental model of lead nephropathy. II. Effect of removal from lead exposure and chelation treatment with dimercaptosuccinic acid (DMSA). Environ. Res 58: 35-54.

Khalil-Manesh, F.; Gonick, H. C.; Cohen, A. H. (1993a) Experimental model of lead nephropathy. III. Continuous low-level lead administration. Arch. Environ. Health 48: 271-278.

Khalil-Manesh, F.; Gonick, H. C.; Weiler, E. W. J.; Prins, B.; Weber, M. A.; Purdy, R. E. (1993b) Lead-induced hypertension: possible role of endothelial factors. Am. J. Hypertens. 6: 723-729.

Khalil-Manesh, F.; Gonick, H. C.; Weiler, E. W. J.; Prins, B.; Weber, M. A.; Purdy, R.; Ren, Q. (1994) Effect of chelation treatment with dimercaptosuccinic acid (DMSA) on lead-related blood pressure changes. Environ. Res. 65: 86-99.

Khan, M. Z.; Szarek, J. (1994) Effects of concurrent oral administration of lead, selenium or monensin on hepatic porphyrin levels in broiler chickens during sub-acute toxicosis. J. Vet. Med. B. 41: 77-82.

Kim, D.; Lawrence, D. A. (2000) Immunotoxic effects of inorganic lead on host resistance of mice with different circling behavior preferences. Brain Behav. Immun. 14: 305-317.

Kim, J. S.; Hamilton, D. L.; Blakley, B. R.; Rousseaux, C. G. (1992) The effects of thiamin on lead metabolism: organ distribution of lead 203. Can. J. Vet. Res. 56: 256-259.

Kim, R.; Rotnitsky, A.; Sparrow, D.; Weiss, S. T.; Wager, C.; Hu, H. (1996) A longitudinal study of low-level lead exposure and impairment of renal function. The Normative Aging Study. JAMA J. Am. Med. Assoc. 275: 1177-1181.

Kim, H.-S.; Lee, S.-S.; Lee, G.-S.; Hwangbo, Y.; Ahn, K.-D.; Lee, B.-K. (2004) The protective effect of "delta"-aminolevulinic acid dehydratase 1-2 and 2-2 isozymes against blood lead with higher hematologic parameters. Environ. Health Perspect. 112: 538-541.

Kimber, I.; Stonard, M. D.; Gidlow, D. A.; Niewola, Z. (1986) Influence of chronic low-level exposure to lead on plasma immunoglobulin concentration and cellular immune function in man. Int. Arch. Occup. Environ. Health 57: 117-125.

Kiremidjian-Schumacher, L.; Stotzky, G.; Dickstein, R. A.; Schwartz, J. (1981) Influence of cadmium, lead, and zinc on the ability of guinea pig macrophages to interact with macrophage migration inhibitory factor. Environ. Res. 24: 106-116.

Kishikawa, H.; Lawrence, D. A. (1998) Differential production of interleukin-6 in the brain and spleen of mice treated with lipopolysaccharide in the presence and absence of lead. J. Toxicol. Environ. Health A 53: 357-373.

Kishikawa, H.; Song, R.; Lawrence, D. A. (1997) Interleukin-12 promotes enhanced resistance to Listeria monocytogenes infection of lead-exposed mice. Toxicol. Appl. Pharmacol. 147: 180-189.

Kishimoto, T.; Oguri, T.; Ueda, D.; Tada, M. (1995) Effect of lead on tube formation by cultured human vascular endothelial cells. Arch. Toxicol. 69: 718-721.

Klann, E.; Shelton, K. R. (1989) The effect of lead on the metabolism of a nuclear matrix protein which becomes prominent in lead-induced intranuclear inclusion bodies. J. Biol. Chem. 264: 16,969-16,972.

Klein, R. F.; Wiren, K. M. (1993) Regulation of osteoblastic gene expression by lead. Endocrinology 132: 2531-2537.

Knowles, S. O.; Donaldson, W. E. (1990) Dietary modification of lead toxicity: Effect on fatty acid and eicosanoid metabolism in chicks. Comp. Biochem. Physiol. C. 95: 99-104.

Knowles, S. O.; Donaldson, W. E. (1997) Lead disrupts eicosanoid metabolism, macrophage function, and disease resistance in birds. Biol. Trace Element Res. 60: 13-26.

Kobayashi, N.; Okamoto, T. (1974) Effects of lead oxide on the induction of lung tumors in Syrian hamsters. J. Natl. Cancer Inst. 52: 1605-1610.

Kohila, T.; Tahti, H. (2004) Effects of aluminium and lead on ATPase activity of knockout +/- mouse cerebral synaptosomes in vitro. Altern. Lab. Anim. 32: 361-367.

Kojima, M.; Nemoto, K.; Murai, U.; Yoshimura, N.; Ayabe, Y.; Degawa, M. (2002) Altered gene expression of hepatic lanosterol 14x-demethylase (CYP51) in lead nitrate-treated rats. Arch. Toxicol. 76: 398-403.

Kojima, M.; Masui, T.; Nemoto, K.; Degawa, M. (2004) Lead nitrate-induced development of hypercholesterolemia in rats: sterol-independent gene regulation of hepatic enzymes responsible for cholesterol homeostasis. Toxicol. Lett. 154: 35-44.

Koller, L. D. (1973) Immunosuppression produced by lead, cadmium, and mercury. Am. J. Vet. Res. 34: 1457-1458.

Koller, L. D.; Kovacic, S. (1974) Decreased antibody formation in mice exposed to lead. Nature 250: 148-150.

Konantakieti, C.; Beuthin, F. C.; Louis-Ferdinand, R. T. (1986) Erythrocyte pyrimidine 5'-nucleotidase inhibition by acute lead exposure in neonatal rats. J. Biochem. Toxicol. 1: 51-59.

Koo, P.; Nagai, M. K.; Farber, E. (1994) Multiple sites of control of glutathione S-transferase P1-1 in rat liver. J. Biol. Chem. 269: 14601-14606.

Korashy, H. M.; El-Kadi, A. O. S. (2004) Differential effects of mercury, lead and copper on the constitutive and inducible expression of aryl hydrocarbon receptor (AHR)-regulated genes in cultured hepatoma Hepa 1c1c7 cells. Toxicology 201: 153-172.

Korrick, S. A.; Hunter, D. J.; Rotnitzky, A.; Hu, H.; Speizer, F. E. (1999) Lead and hypertension in a sample of middle-aged women. Am. J. Public Health 89: 330-335.

Kostial, K.; Blanusa, M.; Piasek, M.; Restek-Samarzija, N.; Jones, M. M.; Singh, P. K. (1999) Combined chelation therapy in reducing tissue lead concentrations in suckling rats. J. Appl. Toxicol. 19: 143-147.

Kowolenko, M.; Tracy, L.; Mudzinski, S.; Lawrence, D. A. (1988) Effect of lead on macrophage function. J. Leukocyte Biol. 43: 357-364.

Kowolenko, M.; Tracy, L.; Lawrence, D. A. (1989) Lead-induced alterations of in vitro bone marrow cell responses to colony stimulating factor-1. J. Leukocyte Biol. 45: 198-206.

Kowolenko, M.; Tracy, L.; Lawrence, D. (1991) Early effects of lead on bone marrow cell responsiveness in mice challenged with Listeria monocytogenes. Fundam. Appl. Toxicol. 17: 75-82.

Kramer, H. J.; Gonick, H. C.; Lu, E. (1986) In vitro inhibition of Na-K-ATPase by trace metals: relation to renal and cardiovascular damage. Nephron 44: 329-336.

Kristensen, P.; Andersen, A. (1992) A cohort study on cancer incidence in offspring of male printing workers. Epidemiology 3: 6-10.

Kristensen, P.; Eilertsen, E.; Einarsdottir, E.; Ovrebo, S.; Haugen, A. (1993) Effect modification by inorganic lead in the dominant lethal assay. Mutat. Res. 302: 33-38.

Krocova, Z.; Macela, A.; Kroca, M.; Hernychova, L. (2000) The immunomodulatory effect(s) of lead and cadmium on the cells of immune system in vitro. Toxicol. In Vitro. 14: 33-40.

Kubo, Y.; Yasunaga, M.; Masuhara, M.; Terai, S.; Nakamura, T.; Okita, K. (1996) Hepatocyte proliferation induced in rats by lead nitrate is suppressed by several tumor necrosis factor "alpha" inhibitors. Hepatology 23: 104-114.

Kumar, K. V.; Das, U. N. (1993) Are free radicals involved in the pathobiology of human essential hypertension? Free Radical Res. Commun. 19: 59-66.

Lai, C.-C.; Lin, H. H.; Chen, C. W.; Chen, S.-H.; Chiu, T. H. (2002) Excitatory action of lead on rat sympathetic preganglionic neurons in vitro and in vivo. Life Sci. 71: 1035-1045.

Lake, L.; Gerschenson, L. E. (1978) Cellular and molecular toxicology of lead. III. Effect of lead on heme synthesis. J. Toxicol. Environ. Health 4: 527-540.

Lal, B.; Goldstein, G.; Bressler, J. P. (1996) Role of anion exchange and thiol groups in the regulation of potassium efflux by lead in human erythrocytes. J. Cell Physiol. 167: 222-228.

Langrish, C. L.; Buddle, J. C.; Thrasher, A. J.; Goldblatt, D. (2002) Neonatal dendritic cells are intrinsically biased against Th-1 immune responses. Clin. Exp. Immunol. 128: 118-123.

Lanphear, B. P.; Bearer, C. F. (2005) Biomarkers in paediatric research and practice. Arch. Dis. Child. 90: 594-600.

Lanphear, B. P.; Dietrich, K.; Auinger, P.; Cox, C. (2000) Cognitive deficits associated with blood lead concentrations < 10 µg/dL in U.S. children and adolescents. Public Health Rep. 115: 521-529.

Lanphear, B. P.; Hornung, R.; Khoury, J.; Yolton, K.; Baghurst, P.; Bellinger, D. C.; Canfield, R. L.; Dietrich, K. N.; Bornschein, R.; Greene, T.; Rothenberg, S. J.; Needleman, H. L.; Schnaas, L.; Wasserman, G.; Graziano, J.; Roberts, R. (2005) Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ. Health Perspect. 113: 894-899.

Lara-Tejero, M.; Pamer, E. G. (2004) T cell responses to Listeria monocytogenes. Curr. Opin. Microbiol. 7: 45-50.

Larsson, A. (1974) Studies on dentinogenesis in the rat. The interaction between lead-pyrophosphate solutions and dentinal globules. Calcif. Tiss. Res. 16: 93-107.

Larsson, A.; Helander, H. F. (1974) Studies on dentinogenesis in the rat. Light, electron microscopic and histochemical studies on the interaction between lead pyrophosphate solutions and dentin-producing tissues. Calcif. Tiss. Res. 14: 87-104.

Laschi-Loquerie, A.; Decotes, J.; Tachon, P.; Evreux, J. C. (1984) Influence of lead acetate on hypersensitivity experimental study. J. Immunopharmacol. 6: 87-93.

Lasley, S. M.; Gilbert, M. E. (1996) Presynaptic glutamatergic function in dentate gyrus in vivo is diminished by chronic exposure to inorganic lead. Brain Res. 736: 125-134.

Lasley, S. M.; Gilbert, M. E. (1999) Lead inhibits the rat N-methyl-d-aspartate receptor channel by binding to a site distinct from the zinc allosteric site. Toxicol. Appl. Pharmacol. 159: 224-233.

Lasley, S. M.; Gilbert, M. E. (2000) Glutamatergic components underlying lead-induced impairments in hippocampal synaptic plasticity. Neurotoxicology 21: 1057-1067.

Lasley, S. M.; Gilbert, M. E. (2002) Rat hippocampal glutamate and GABA release exhibit biphasic effects as a function of chronic lead exposure level. Toxicol. Sci. 66: 139-147.

Lasley, S. M.; Green, M. C.; Gilbert, M. E. (1999) Influence of exposure period on in vivo hippocampal glutamate and GABA release in rats chronically exposed to lead. Neurotoxicology 20: 619-629.

Lasley, S. M.; Green, M. C.; Gilbert, M. E. (2001) Rat hippocampal NMDA receptor binding as a function of chronic lead exposure level. Neurotoxicol. Teratol. 23: 185-189.

Laughlin, N. K.; Bowman, R. E.; Franks, P. A.; Dierschke, D. J. (1987) Altered menstural cycles in rhesus monkeys induced by lead. Fundam. Appl. Toxicol. 9: 722-729.

Lauwerys, R.; Bernard, A.; Cardenas, A. (1992) Monitoring of early nephrotoxic effects of industrial chemicals. Toxicol. Lett. 64-65: 33-42.

Lawler, E. M.; Duke, G. E.; Redig, P. T. (1991) Effect of sublethal lead exposure on gastric motility of red-tailed hawks. Arch. Environ. Contam. Toxicol. 21: 78-83.

Lawrence, D. A. (1981) In vivo and in vitro effects of lead on humoral and cell- mediated immunity. Infect. Immun. 31: 136-143.

Lawrence, D. A.; Kim, D. (2000) Central/peripheral nervous system and immune responses. Toxicology 142: 189-201.

Lawrence, D. A.; McCabe, M. J., Jr. (2002) Immunomodulation by metals. Int. Immunopharmacol. 2: 293-302.

Ledda-Columbano, G. M.; Columbano, A.; Cannas, A.; Simbula, G.; Okita, K.; Kayano, K.; Kubo, Y.; Katyal, S. L.; Shinozuka, H. (1994) Dexamethasone inhibits induction of liver tumor necrosis factor-"alpha" mRNA and liver growth induced by lead nitrate and ethylene dibromide. Am. J. Pathol. 145: 951-958.

Lee, J. J.; Battles, A. H. (1994) Lead toxicity via arachidonate signal transduction to growth responses in the splenic macrophages. Environ Res. 67: 209-219.

Lee, J.-E.; Dietert, R. R. (2003) Developmental immunotoxicity of lead: impact on thymic function. Birth Defects Res. A Clin. Mol. Teratol. 67: 861-867.

Lee, J.-E.; Dietert, R. R. (2005) Toxicity of lead to the developing immune system. In. Holladay, S. D., ed. Developmental immunotoxicology. CRC Press, Inc. Boca Raton, FL. 169-177.

Lee, J.-E.; Chen, S.; Golemboski, K. A.; Parsons, P. J.; Dietert, R. R. (2001) Developmental windows of differential lead-induced immunotoxicity in chickens. Toxicology 156: 161-170.

Lee, B.-K.; Lee, G.-S.; Stewart, W. F.; Ahn, K.-D.; Simon, D.; Kelsey, K. T.; Todd, A. C.; Schwartz, B. S. (2001) Associations of blood pressure and hypertension with lead dose measures and polymorphisms in the vitamin D receptor and "delta"-aminolevulinic acid dehydratase genes. Environ. Health Perspect. 109: 383-389.

Lee, J.-E.; Naqi, S. A.; Kao, E.; Dietert, R. R. Embryonic exposure to lead: Comparison of immune and cellular responses in unchallenged and virally stressed chickens. Arch Toxicol. 75: 717-724. (2002) Embryonic exposure to lead: Comparison of immune and cellular responses in unchallenged and virally stressed chickens. Arch. Toxicol. 75: 717-724.

Legare, M. E.; Barhoumi, R.; Herbert, E.; Bratton, G. R.; Burghardt, R. C.; Tiffany-Castiglioni E. (1998) Analysis of Pb2+ entry into cultured astroglia. Toxicol. Sci. 46: 90-100.

Leggett, R. W. (1993) An age-specific kinetic model of lead metabolism in humans. Environ. Health Perspect. 101: 598-616.

Lezak, M. (1995) Neuropsychological assessment. New York, NY: Oxford University Press.

Lidsky, T. I.; Schneider, J. S. (2003) Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain 126: 5-19.

Lidsky, T. I.; Schneider, J. S. (2005) Adverse effects of childhood lead poisoning: the clinical neuropsychological perspective. Environ. Res.: in press.

Lilienthal, H.; Winneke, G. (1996) Lead effects on the brain stem auditory evoked potential in monkeys during and after the treatment phase. Neurotoxicol. Teratol. 18:17-32.

Lin, R. H.; Lee, C. H.; Chen, W. K.; Lin-Shiau, S. Y. (1994) Studies on cytotoxic and genotoxic effects of cadmium nitrate and lead nitrate in Chinese hamster ovary cells. Environ. Mol. Mutagen. 23: 143-149.

Lin, C.; Kim, R.; Tsaih, S.-W.; Sparrow, D.; Hu, H. (2004) Determinants of bone and blood lead levels among minorities living in the Boston area. Environ. Health Perspect. 112: 1147-1151.

Lindahl, L. S.; Bird, L.; Legare, M. E.; Mikeska, G.; Bratton, G. R.; Tiffany-Castiglioni, E. (1999) Differential ability of astroglia and neuronal cells to accumulate lead: dependence on cell type and on degree of differentiation. Toxicol Sci. 50: 236-243.

Liu, J.; Kershaw, W. C.; Klaassen, C. D. (1991) The protective effect of metallothionein on the toxicity of various metals in rat primary hepatocyte culture. Toxicol. Appl. Pharmacol. 107: 27-34.

Liu, J.-Y.; Lin, J.-K.; Liu, C.-C.; Chen, W.-K.; Liu, C.-P.; Wang, C.-J.; Yen, C.-C.; Hsieh, Y.-S. (1997) Augmentation of protein kinase C activity and liver cell proliferation in lead nitrate-treated rats. Biochem. Mol. Biol. Int. 43: 355-364.

Logdberg, B.; Berlin, M.; Schutz, A. (1987) Effects of lead exposure on pregnancy outcome and the fetal brain of squirrel monkeys. Scand. J. Work Environ. Health 13: 135-145.

Logdberg, B.; Brun, A.; Berlin, M.; Schutz, A. (1988) Congenital lead encephalopathy in monkeys. Acta Neuropathol. 77: 120-127.

Loipfuhrer, A. M.; Reichlmayr-Lais, A. M.; Kirchgessner, M. (1993) Concentration of free calcium in erythrocytes of lead-depleted rats. J. Trace Elem. Electrolytes Health Dis. 7: 37-40.

Lolin, Y.; O'Gorman, P. (1988) An intra-erythrocyctic low molecular weight lead-binding protein in acute and chronic lead exposure and its possible protective role in lead toxicity. Ann. Clin. Biochem. 25: 688-97.

Long, G. J.; Rosen, J. F. (1992) Lead perturbs epidermal growth factor (EGF) modulation of intracellular calcium metabolism and collagen synthesis in clonal rat osteoblastic (ROS 17/2.8) cells. Toxicol. Appl. Pharmacol. 114: 63-70.

Long, G. J.; Rosen, J. F.; Pounds, J. G. (1990) Lead impairs the production of osteocalcin by rat osteosarcoma (ROS 17/2.8) cells. Toxicol. Appl. Pharmacol. 106: 270-277.

Long, G. J.; Pounds, J. G.; Rosen, J. F. (1992) Lead intoxication alters basal and parathyroid hormone-regulated cellular calcium homeostasis in rat osteosarcoma (ROS 17/2.8) cells. Calcif. Tissue Int. 50: 451-458.

Long, G. J.; Rosen, J. F.; Schanne, F. A. X. (1994) Lead activation of protein kinase C from rat brain. Determination of free calcium, lead, and zinc by 19F NMR. J. Biol. Chem. 269: 834-837.

Lucas, S. R.; Sexton, M.; Langenberg, P. (1996) Relationship between blood lead and nutritional factors in preschool children: a cross-sectional study. Pediatrics 97: 74-78.

Luebke, R.; Chen, D.; Dietert, R. R.; King, M.; Yang, Y.; Luster, M. I. (2005) Increased sensitivity of the developing immune system to xenobiotics: Experimental evidence supporting the concept of developmental immunotoxicity testing guidelines. J. Toxicol. Environ. Health B: in press.

Luster, M. I.; Portier, C.; Pait, D. G.; White, K. L. J.; Gennings, C.; Munson, A. E.; Rosenthal, G. J. (1992) Risk assessment in immunotoxicology. I. Sensitivity and predictability of immune tests. Fund. Appl. Toxicol. 18: 200-210.

Lutz, P. M.; Wilson, T. J.; Ireland, A. L.; Gorman, J. S.; Gale, N. L.; Johnson, J. C.; Hewett, J. E. (1999) Elevated immunoglobulin E (IgE) levels in children with exposure to environmental lead. Toxicology 134: 63-78.

Ma, T.; Chen, H. H.; Chang, H. L.; Hume, A. S.; Ho, I. K. (1997) Effects of chronic lead exposure on [3H]MK-801 binding in the brain of rat. Toxicol. Lett. 92: 59-66.

Maezawa, Y.; Nakajima, H.; Seto, Y.; Suto, A.; Kumana, K.; Kubo, S.; Karasuyama, H.; Saito, Y.; Iwamoto, I. (2004) IgE-dependent enhancement of Th2 cell-mediated allergic inflammation in the airways. Clin. Exp. Immunol. 135: 12-18.

Mahaffey, K. R.; Capar, S. G.; Gladen, B. C.; Fowler, B. A. (1981) Concurrent exposure to lead, cadmium, and arsenic. J. Lab. Clin. Med. 98: 463-481.

Mahaffey, K. R.; Rosen, J. F.; Chesney, R. W.; Peeler, J. T.; Smith, C. M.; De Luca, H. F. (1982) Association between age, blood lead concentration, and serum 1,25-dihydroxycholecalciferol levels in children. Am. J. Clin. Nutr. 35: 1327-1331.

Mahaffey, K. R.; Gartside, P. S.; Glueck, C. J. (1986) Blood lead levels and dietary calcium intake in 1-11 year-old children: the second national health and nutrition examination survey, 1976-1980. Pediatrics 78: 257-262.

Maisin, J. R.; Lambiet-Collier, M.; De Saint-Georges, L. (1978) Toxicite du plomb pour les embryons de la souris [Lead toxicity for mouse embryos]. C. R. Seances Soc. Biol. Ses. Fil. 172: 1041-1043.

Maitani, T.; Watahiki, A.; Suzuki, K. T. (1986) Induction of metallothionein after lead administration by three injection routes in mice. Toxicol. Appl. Pharmacol. 83: 211-217.

Maker, H. S.; Lehrer, G. M.; Silides, D. J. (1975) The effect of lead on mouse brain development. Environ. Res. 10: 76-91.

Malamitsi-Pichner, A.; Protonotariou, E.; Boutsikou, T.; Makrakis, E.; Sarandakou, A.; Creatas, G. (2005) The influence of the mode of delivery on circulating cytokine concentration in the perinatal period. Early Hum. Dev. 81: 387-392.

Malcoe, L. H.; Lynch, R. A.; Kegler, M. C.; Skaggs, V. J. (2002) Lead sources, behaviors, and socioeconomic factors in relation to blood lead of Native American and white children: a community-based assessment of a former mining area. Environ. Health Perspect. Suppl. 110(2): 221-231.

Maldonado-Vega, M.; Cerbon-Solorzano, J.; Albores-Medina, A.; Hernandez-Luna, C.; Calderon-Salinas, J. V. (1996) Lead: intestinal absorption and bone mobilization during lactation. Hum. Exp. Toxicol. 15: 872-877.

Maldonado-Vega, M.; Cerbon-Solorzano, J.; Calderon-Salinas, J. V. (2002) The effects of dietary calcium during lactation on lead in bone mobilization: implications for toxicology. Hum. Exp. Toxicol. 21: 409-414.

Malvezzi, C. K.; Moreira, E. G.; Vassilieff, I.; Vassilieff, V. S.; Cordellini, S. (2001) Effect of L-arginine, dimercaptosuccinic acid (DMSA) and the association of L-arginine and DMSA on tissue lead mobilization and blood pressure level in plumbism. Braz. J. Med. Biol. Res. 34: 1341-1346.

Manton, W. I.; Cook, J. D. (1984) High accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid. Br. J. Ind. Med. 41: 313-319.

Manton, W. I.; Angle, C. R.; Stanek, K. L.; Reese, Y. R.; Kuehnemann, T. J. (2000) Acquisition and retention of lead by young children. Environ. Res. 82: 60-80.

Manton, W. I.; Rothenberg, S. J.; Manalo, M. (2001) The lead content of blood serum. Environ. Res. 86: 263-273.

Marcus, A. H. (1985a) Multicompartment kinetic models for lead. I. Bone diffusion models for long-term retention. Environ. Res. 36: 441-458.

Marcus, A. H. (1985b) Multicompartment kinetic models for lead. II. Linear kinetics and variable absorption in humans without excessive lead exposures. Environ. Res. 36: 459-472.

Marcus, A. H. (1985c) Multicompartment kinetic model for lead. III. Lead in blood plasma and erythrocytes. Environ. Res. 36: 473-489.

Markovac, J.; Goldstein, G. W. (1988a) Lead activates protein kinase C in immature rat brain microvessels. Toxicol. Appl. Pharmacol. 95: 14-23.

Markovac, J.; Goldstein, G. W. (1988b) Picomolar concentrations of lead stimulate brain protein kinase C. Nature (London, U.K.) 334: 71-73.

Markowitz, M. E.; Sennett, M.; Rosen, J. F. (2004) A randomized trial of calcium supplementation for childhood lead poisoning. Pediatrics 113: e34-e39.

Marques, M.; Millas, I.; Jimenez, A.; Garcia-Colis, E.; Rodriguez-Feo, J. A.; Velasco, S.; Barrientos, A.; Casado, S.; Lopez-Farre, A. (2001) Alteration of the soluble guanylate cyclase system in the vascular wall of lead-induced hypertension in rats. J. Am. Soc. Nephrol. 12: 2594-2600.

Martín, L. M.; Martín, C. C.; Vidas, M. M.; Vaziri, N. D.; Mateos-Cáceres, P. J.; Pérez, S. C.; Macaya, C.; Barriento, A.; López-Farré, A. J. (2005) Involvement of endothelium and endothelin-1 in lead-induced smooth muscle cell dysfunction in rats. Kidney Int.: in press.

Martins, M. B.; Sabatier, L.; Ricoul, M.; Pinton, A.; Dutrillaux, B. (1993) Specific chromosome instability induced by heavy ions: a step towards transformation of human fibroblasts? Mutat. Res. 1285: 229-237.

Mas-Oliva, J. (1989) Effect of lead on the erythrocyte (Ca2+,Mg2+)-ATPase activity. Calmodulin involvement. Mol. Cell. Biochem. 89: 87-93.

Mason, H. J.; Somervaille, L. J.; Wright, A. L.; Chettle, D. R.; Scott, M. C. (1990) Effect of occupational lead exposure on serum 1,25-dihydroxyvitamin D levels. Hum. Exp. Toxicol. 9: 29-34.

Massie, H. R.; Aiello, V. R. (1992) Lead accumulation in the bones of aging male mice. Gerontology 38: 13-17.

Mauel, J.; Ransijn, A.; Buchmuller-Rouiller, Y. (1989) Lead inhibits intracellular killing of Leishmania parasites and extracellular cytolysis of target cells by macrophages exposed to macrophage activating factor. J. Leukoc. Biol. 45: 401-409.

Mazzolini, M.; Traverso, S.; Marchetti, C. (2001) Multiple pathways of Pb(2+) permeation in rat cerebellar granule neurones. J. Neurochem. 79: 407-416.

McCabe, M. J., Jr. (1994) Mechanisms and consequences of immunomodulation by lead. In: Dean, J. H.; Luster, M. I.; Munson, A. E.; Kimber, I., eds. Immunotoxicology and immunopharmacology. 2nd ed. New York, NY: Raven Press, Ltd.; pp. 143-162.

McCabe, M. J., Jr.; Lawrence, D. A. (1990) The heavy metal lead exhibits B cell-stimulatory factor activity by enhancing B cell Ia expression and differentiation. J. Immunol. 145: 671-677.

McCabe, M. J.; Lawrence, D. A. (1991) Lead, a major environmental pollutant, is immunomodulatory by its differential effects on CD4+ T cell subsets. Toxicol. Appl. Pharmacol. 111: 13-23.

McCabe, M. J., Jr.; Dias, J. A.; Lawrence, D. A. (1991) Lead influences translational or posttranslational regulation of Ia expression and increases invariant chain expression in mouse B cells. J. Biochem. Toxicol. 6: 269-276.

McCabe, M. J., Jr.; Singh, K. P.; Reiners, J. J., Jr. (1999) Lead intoxication impairs the generation of a delayed type hypersensitivity response. Toxicology 139: 255-264.

McCabe, M. J., Jr.; Singh, K. P.; Reiners, J. J., Jr. (2001) Low level lead exposure in vitro stimulates the proliferation and expansion of alloantigen-reactive CD4high T cells. Toxicol. Appl. Pharmacol. 177: 219-231.

McDonald, J. A.; Potter, N. U. (1996) Lead's legacy? Early and late mortality of 454 lead-poisoned children. Arch. Environ. Health 51: 116-121.

McGivern, R. F.; Sokol, R. Z.; Berman, N. G. (1991) Prenatal lead exposure in the rat during the third week of gestation: long-term behavioral, physiological and anatomical effects associated with reproduction. Toxicol. Appl. Pharmacol. 110: 206-215.

McGowan, C.; Donaldson, W. E. (1987) Effect of lead toxicity on the organ concentration of glutathione and glutathione-related free amino acids in the chick. Toxicol. Lett. 38: 265-270.

McLachlin, J. R.; Goyer, R. A.; Cherian, M. G. (1980) Formation of lead-induced inclusion bodies in primary rat kidney epithelial cell cultures: effect of actinomycin D and cycloheximide. Toxicol. Appl. Pharmacol. 56: 418-431.

McNeill, F. E.; Laughlin, N. K.; Todd, A. C.; Sonawane, B. R.; Van de Wal, K. M.; Fowler, B. A. (1997) Geriatric bone lead metabolism in a female nonhuman primate population. Environ. Res. 72: 131-139.

McNeill, D. R.; Narayana, A.; Wong, H. K.; Wilson, D. M. III. (2004) Inhibition of Ape1 nuclease activity by lead, iron, and cadmium. Environ. Health Perspect. 112: 799-804.

Menegazzi, M.; Carcereri De Prati, A.; Ledda-Columbano, G. M.; Columbano, A.; Uchida, K.; Miwa, M.; Suzuki, H. (1990) Regulation of poly(ADP-ribose) polymerase mRNA levels during compensatory and mitogen-induced growth of rat liver. Arch. Biochem. Biophys. 279: 232-236.

Menegazzi, M.; Carcereri de Prati, A.; Ogura, T.; Columbano, A.; Ledda-Columbano, G. M.; Libonati, M.; Esumi, H.; Suzuki, H. (1992) Involvement of DNA polymerase beta in proliferation of rat liver induced by lead nitrate or partial hepatectomy. Febs. Lett. 310: 135-138.

Menegazzi, M.; Carcereri-De Prati, A.; Suzuki, H.; Shinozuka, H.; Pibiri, M.; Piga, R.; Columbano, A.; Ledda-Columbano, G. M. (1997) Liver cell proliferation induced by nafenopin and cyproterone acetate is not associated with increases in activation of transcription factors NF-"kappa"B and AP-1 or with expression of tumor necrosis factor "alpha". Hepatology 25: 585-592.

Meng, X.-M.; Zhu, D.-M.; Ruan, D.-Y.; She, J.-Q.; Luo, L. (2005) Effects of chronic lead exposure on H MRS of hippocampus and frontal lobes in children. Neurology 64: 1644-1647.

Miller, L.; Qureshi, M. A. (1992) Heat-shock protein synthesis in chicken macrophages: Influence of in vivo and in vitro heat shock, lead acetate, and lipopolysaccharide. Poul. Sci. 71: 988-998.

Miller, T. E.; Golemboski, K. A.; Ha, R. S.; Bunn, T.; Sanders, F. S.; Dietert, R. R. (1998) Developmental exposure to lead causes persistent immunotoxicity in Fischer 344 rats. Toxicol. Sci. 42: 129-135.

Miller, D. K.; Nation, J. R.; Bratton, G. R. (2001) The effects of perinatal exposure to lead on the discriminative stimulus properties of cocaine and related drugs in rats. Psychopharmacology (Berl). 158: 165-174.

Milosevic, N.; Maier, P. (2000) Lead stimulates intercellular signalling between hepatocytes and Kupffer cells. Eur. J. Pharmacol. 401: 317-328.

Minnema, D. J.; Hammond, P. B. (1994) Effect of lead exposure on patterns of food intake in weanling rats. Neurotoxicol. Teratol. 16: 623-629.

Minozzo, R.; Deimling, L. I.; Gigante, L. P.; Santos-Mello, R. (2004) Micronuclei in peripheral blood lymphocytes of workers exposed to lead. Mutat. Res. 565: 53-60.

Misra, M.; Acharya, U. R. (2004) Protective action of vitamins on the spermatogenesis in lead-treated Swiss mice. J. Trace Elem. Med. Biol. 18: 173-178.

Mishra, K. P.; Singh, V. K.; Rani, R.; Yadav, V. S.; Chandran, V.; Srivastava, S. P.; Seth, P. K. (2003) Effect of lead exposure on the immune response of some occupationally exposed individuals. Toxicology 188: 251-259.

Mistry, P.; Lucier, G. W.; Fowler, B. A. (1985) High-affinity lead binding proteins in rat kidney cytosol mediate cell-free nuclear translocation of lead. J. Pharmacol. Exp. Ther. 232: 462-469.

Miyahara, T.; Komiyama, H.; Miyanishi, A.; Takata, M.; Nagai, M.; Kozuka, H.; Hayashi, T.; Yamamoto, M.; Ito, Y.; Odake, H.; Koizumi, F. (1995) Stimulative effects of lead on bone resorption in organ culture. Toxicology 97: 191-197.

Mobarak, N.; P'an, A. Y. (1984) Lead distribution in the saliva and blood fractions of rats after intraperitoneal injections. Toxicology 32: 67-74.

Mojzis, J.; Nistiar, F. (2001) Lead-induced changes of cation-osmotic hemolysis in rats. Gen. Physiol. Biophys. 20: 315-319.

Momcilovic, B.; Kostial, K. (1974) Kinetics of lead retention and distribution in suckling and adult rats. Environ. Res. 8: 214-220.

Moore, J. F.; Goyer, R. A. (1974) Lead-induced inclusion bodies: composition and probable role in lead metabolism. Environ. Health Perspect. 7: 121-127.

Moore, J. F.; Goyer, R. A.; Wilson, M. (1973) Lead-induced inclusion bodies: solubility, amino acid content, and relationship to residual acidic nuclear proteins. Lab. Invest. 29: 488-494.

Morgan, R. E.; Levitsky, D. A.; Strupp, B. J. (2000) Effects of chronic lead exposure on learning and reaction time in a visual discrimination task. Neurotoxicol Teratol. 22: 337-345.

Morgan, R. E.; Garavan, H.; Smith, E. G.; Driscoll, L. L.; Levitsky, D. A.; Strupp, B. J. (2001) Early lead exposure produces lasting changes in sustained attention, response initiation, and reactivity to errors. Neurotoxicol. Teratol. 23: 519-531.

Morita, Y.; Sakai, T.; Araki, S.; Araki, T.; Masuyama, Y. (1997) Nicotinamide adenine dinucleotide synthetase activity in erythrocytes as a tool for the biological monitoring of lead exposure. Int. Arch. Occup. Environ. Health 70: 195-198.

Moser, R.; Oberley, T. D.; Daggett, D. A.; Friedman, A. L.; Johnson, J. A.; Siegel, F. L. (1995) Effects of lead administration on developing rat kidney: I. Glutathione S-transferase isoenzymes. Toxicol. Appl. Pharmacol. 131: 85-93.

Mousa, H. M.; Al-Qarawi, A. A.; Ali, B. H.; Abdel Rahman, H. A.; ElMougy, S. A. (2002) Effect of lead exposure on the erythrocytic antioxidant levels in goats. J. Vet. Med. A Physiol. Pathol. Clin. Med. 49: 531-534.

Mouw, D. R.; Vander, A. J.; Cox, J.; Fleischer, N. (1978) Acute effects of lead on renal electrolyte excretion and plasma renin activity. Toxicol. Appl. Pharmacol. 46: 435-447.

Mudd, S. H.; Levy, H. L.; Skovby, F. (1995) Disorders of transsulfuration. In: Scriver, C. R.; Beaudet, A. L.; Sly, W. S.; Valle, D., eds. The metabolic and molecular bases of inherited disease. New York, NY: McGraw-Hill Publishing Co.; pp. 1279-1328.

Muller, S.; Gillert, K.-E.; Krause, C.; Gross, U.; L'Age-Stehr, J.; Diamantstein, T. (1977) Suppression of delayed type hypersensitivity of mice by lead. Experientia 33: 667-668.

Murphy, K.J.; Regan, C. M. (1999) Low-level lead exposure in the early postnatal period results in persisting neuroplastic deficits associated with memory consolidation. J. Neurochem. 72: 2099-2104.

Nakagawa, K. (1991) Decreased glutathione S-transferase activity in mice livers by acute treatment with lead, independent of alteration in glutathione content. Toxicol. Lett. 56: 13-17.

Nakajima, T.; Deguchi, T.; Kagawa, K.; Hikita, H.; Ueda, K.; Katagishi, T.; Ohkawara, T.; Kakusui, M.; Kimura, H.; Okanoue, T.; Kashima, K.; Ashihara, T. (1995) Identification of apoptotic hepatocytes in situ in rat liver after lead nitrate administration. J. Gastroenterol. 30: 725-730.

Nation, J. R.; Livermore, C. L.; Burkey, R. T. (1996) Chronic lead exposure attenuates sensitization to the locomotor-stimulating effects of cocaine. Drug Alcohol Depend. 41: 143-149.

Nation, J. R.; Cardon, A. L.; Heard, H. M.; Valles, R.; Bratton, G. R. (2003) Perinatal lead exposure and relapse to drug-seeking behavior in the rat: a cocaine reinstatement study. Psychopharmacology (Berl). 168:236-243.

Nation, J. R.; Smith, K. R.; Bratton, G. R. (2004) Early developmental lead exposure increases sensitivity to cocaine in a self-administration paradigm. Pharmacol. Biochem. Behav. 77: 127-135.

National Research Council, Committee on Measuring Lead in Critical Populations. (1993) Measuring lead exposure in infants, children, and other sensitive populations. Washington, DC: National Academy Press. Available: http://www.nap.edu/openbook/030904927X/html/ [21 July, 2005].

Nayak, B. N.; Ray, M.; Persaud, T. V. N. (1989) Maternal and fetal chromosomal aberrations in mice following prenatal exposure to subembryotoxic doses of lead nitrate. Acta Anat. 135: 185-188.

Nayak, B. N.; Ray, M.; Persaud, T. V. N.; Nigli, M. (1989) Relationship of embryotoxicity to genotoxicity of lead nitrate in mice. Exp. Pathol. 36: 65-73.

Needleman, H. L.; Gunnoe, C.; Leviton, A.; Reed, R.; Peresie, H.; Maher, C.; Barrett, P. (1979) Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N. Engl. J. Med. 300: 689-695.

Needleman, H. L.; Schell, A.; Bellinger, D.; Leviton, A.; Allred, E. N. (1990) The long-term effects of exposure to low doses of lead in childhood; an 11-year follow-up report. N. Engl. J. Med. 322: 83-88.

Needleman, H. L.; McFarland, C.; Ness, R. B.; Fienberg, S. E.; Tobin, M. J. (2002) Bone lead levels in adjudcated delinquents. A case control study. Neurotoxicol. Teratol. 24: 711-717.

Nehez, M.; Lorencz, R.; Desi, I. (2000) Simultaneous action of cypermethrin and two environmental pollutant metals, cadmium and lead, on bone marrow cell chromosomes of rats in subchronic administration. Ecotoxicol. Environ. Saf. 45: 55-60.

Nehru, B.; Kaushal, S. (1992) Effect of lead on hepatic microsomal enzyme activity. J. Appl. Toxicol. 12: 401-405.

Neilan, B. A.; O'Neill, K.; Handwerger, B. S. (1983) Effect of low-level lead exposure on antibody-dependent and natural killer cell-mediated cytotoxicity. Toxicol. Appl. Pharmacol. 69: 272-275.

Nemoto, K.; Miyata, S.; Nemoto, F.; Yasumoto, T.; Murai, U.; Kageyama, H.; Degawa, M. (2000) Gene expression of neutrophins and their receptors in lead nitrate-induced rat liver hyperplasia. Biochem. Biophys. Res. Commun. 275: 472-476.

Newland, M. C.; Yezhou, S.; Logdberg, B.; Berlin, M. (1994) Prolonged behavioral effects of in utero exposure to lead or methyl mercury: reduced sensitivity to changes in reinforcement contingencies during behavioral transitions and in steady state. Toxicol. Appl. Pharmacol. 126: 6-15.

Ni, Z.; Hou, S.; Barton, C. H.; Vaziri, N. D. (2004) Lead exposure raises superoxide and hydrogen peroxide in human endothelial and vascular smooth muscle cells. Kidney Int. 66: 2329-2336.

Nihei, M. K.; Guilarte, T. R. (1999) NMDAR-2A subunit protein expression is reduced in the hippocampus of rats exposed to Pb2+ during development. Mol. Brain Res. 66: 42-49.

Nihei, M. K.; Desmond, N. L.; McGlothan, J. L.; Kuhlmann, A. C.; Guilarte, T. R. (2000) N-methyl-D-aspartate receptor subunit changes are associated with lead-induced deficits of long-term potentiation and spatial learning. Neuroscience 99: 233-242.

Nikolova, P.; Kavaldzhieva, B. (1991) The effect of certain heavy metals (Mn and Pb) on parameters of erythrocyte energy metabolism. J. Hyg. Epidemiol. Microbiol. Immunol. 35: 361-365.

Nilsson, B. O.; Ljung, L.; Wide, M. (1991) Electron microscopy and X-ray microanalyses of uterine epithelium from lead-injected mice in an experimental delay of implantation. Arch. Toxicol. 65: 239-243.

Nolan, C. V.; Shaikh, Z. A. (1992) Lead nephrotoxicity and associated disorders: biochemical mechanisms. Toxicology 73: 127-146.

Novak, J.; Banks, R. O. (1995) Lead and nickel alter the cardiorenal actions of endothelin in the rat. Proc. Soc. Exp. Biol. Med. 208: 191-198.

O'Flaherty, E. J.; Inskip, M. J.; Franklin, C. A.; Durbin, P. W.; Manton, W. I.; Baccanale, C. L. (1998) Evaluation and modification of a physiologically based model of lead kinetics using data from a sequential isotope study in cynomolgus monkeys. Toxicol. Appl. Pharmacol. 149: 1-16.

Oberley, T. D.; Friedman, A. L.; Moser, R.; Siegel, F. L. (1995) Effects of lead administration on developing rat kidney. II. functional, morphologic, and immunohistochemical studies. Toxicol. Appl. Pharmacol. 131: 94-107.

Odenbro, A.; Arrhenius, E. (1984) Effects of triethyllead chloride on hepatic microsomal N- and C-oxygenation of N,N-dimethylaniline in rats. Toxicol. Appl. Pharmacol. 74: 357-363.

Odenbro, A.; Kihlstrom, J. E. (1977) Frequency of pregnancy and ova implantation in triethyl lead-treated mice. Toxicol. Appl. Pharmacol. 39: 359-363.

Odenbro, A.; Rafter, J. (1988) Effects of triethyl lead chloride on oestradiol metabolism in the female rat liver microsomal fraction. Pharmacol. Toxicol. (Copenhagen) 63: 248-52.

Odenbro, A.; Kihlstrom, I.; Kihlstrom, J. E. (1988) Perinatal growth retardation caused by triethyl lead chloride treatment of mice during late gestation. Pharmacol. Toxicol. (Copenhagen) 63: 253-256.

Oishi, H.; Nakashima, M.; Totoki, T.; Tomokuni, K. (1996) Chronic lead exposure may inhibit endothelium-dependent hyperpolarizing factor in rats. J. Cardiovasc. Pharmacol. 28: 558-563.

Olshan, A. F.; Breslow, N. E.; Daling, J. R.; Falletta, J. M.; Grufferman, S.; Robison, L. L.; Waskerwitz, M., Hammond, G. D. (1990) Wilms' tumor and paternal occupation. Cancer Res. 50: 3212-3217.

Ong, C. N.; Lee, W. R. (1980) Distribution of lead-203 in human peripheral blood in vitro. Br. J. Ind. Med. 37: 78-84.

Oomen, A. G.; Tolls, J.; Sips, A. J.; Groten, J. P. (2003) In vitro intestinal lead uptake and transport in relation to speciation. Arch. Environ. Contam. Toxicol. 44: 116-124.

Oskarsson, A.; Fowler, B. A. (1985) Effects of lead inclusion bodies on subcellular distribution of lead in rat kidney: the relationship to mitochondrial function. Exp. Mol. Pathol. 43: 397-408.

Oskarsson, A.; Squibb, K. S.; Fowler, B. A. (1982) Intracellular binding of lead in the kidney: the partial isolation and characterization of postmitochondrial lead binding components. Biochem. Biophys. Res. Commun. 104: 290-298.

Oskarsson, A.; Hellström-Lindahl, E. (1989) Lead-dithiocarbamate interaction. Effect on ALAD activity in isolated rat hepatocytes. Biol. Trace Elem. Res. 21: 325-330.

Osterode, W.; Ulberth, F. (2000) Increased concentration of arachidonic acid in erythrocyte membranes in chronically lead-exposed men. J. Toxicol. Environ. Health A 59: 87-95.

Othman, A. I.; El Missiry, M. A. (1998) Role of selenium against lead toxicity in male rats. J. Biochem. Mol. Toxicol. 12: 345-349.

Otto, D. A.; Fox, D. A. (1993) Auditory and visual dysfunction following lead exposure. Presented at: Ninth international neurotoxicology conference; October 1991; Little Rock, AR. Neurotoxicology 14(2-3): 191-207.

Pace, B. M.; Lawrence, D. A.; Behr, M. J.; Parsons, P. J.; Dias, J. A. (2005) Neonatal lead exposure changes quality of sperm and number of macrophages in testes of BALB/c mice. Toxicology 210: 247-256.

Pagliara, P.; Carla, E. C.; Caforio, S.; Chionna, A.; Massa, S.; Abbro, L.; Dini, L. (2003a) Kupffer cells promote lead nitrate-induced hepatocyte apoptosis via oxidative stress. Comp. Hepatol. 2: 8-21.

Pagliara, P.; Chionna, A.; Carla, E. C.; Caforio, S.; Dini, L. (2003b) Lead nitrate and gadolinium chloride administration modify hepatocyte cell surfaces. Cell Tissue Res. 312: 41-48.

Palminger Hallen, I.; Jonsson, S.; Karlsson, M. O.; Oskarsson, A. (1996) Kinetic observations in neonatal mice exposed to lead via milk. Toxicol. Appl. Pharmacol. 140: 13-18.

Palus, J.; Rydzynski, K.; Dziubaltowska, E.; Wyszynska, K.; Natarajan, A. T.; Nilsson, R. (2003) Genotoxic effects of occupational exposure to lead and cadmium. Mutat. Res. 540: 19-28.

Pande, M.; Flora, S. J. (2002) Lead induced oxidative damage and its response to combined administration of "alpha"-lipoic acid and succimers in rats. Toxicology 177: 187-196.

Panemangalore, M.; Bebe, F. N. (1996) Effects of low oral lead and cadmium exposure and zinc status on heme metabolites in weanling rats. Int. J. Occup. Med. Environ. Health 9: 141-151.

Pani, P.; Dessi, S.; Rao, K. N.; Batetta, B.; Laconi, E. (1984) Changes in serum and hepatic cholesterol in lead-induced liver hyperplasia. Toxicol. Pathol. 12: 162-167.

Pappas, J. B.; Ahlquist, J. T.; Allen, E. M.; Banner, W., Jr. (1995) Oral dimercaptosuccinic acid and ongoing exposure to lead: effects on heme synthesis and lead distribution in a rat model. Toxicol. Appl. Pharmacol. 133: 121-129.

Patierno, S. R.; Landolph, J. R. (1989) Soluble vs insoluble hexavalent chromate. Relationship of mutation to in vitro transformation and particle uptake. Biol. Trace Elem. Res. 21: 469-474.

Patierno, S. R.; Banh, D.; Landolph, J. R. (1988) Transformation of C3H/10T1/2 mouse embryo cells to focus formation and anchorage independence by insoluble lead chromate but not soluble calcium chromate: relationship to mutagenesis and internalization of lead chromate particles. Cancer Res. 48: 5280-5288.

Patra, R. C.; Swarup, D. (2000) Effect of lead on erythrocytic antioxidant defence, lipid peroxide level and thiol groups in calves. Res. Vet. Sci. 68: 71-74.

Patra, R. C.; Swarup, D.; Dwivedi, S. K. (2001) Antioxidant effects of "alpha" tocopherol, ascorbic acid and L-thenionine on lead induced oxidative stress to the liver, kidney and brain in rats. Toxicology 162: 81-88.

Payne, K. J.; Crooks, G. M. (2002) Human hematopoietic lineages. Immunol. Rev. 187: 46-64.

Peixoto, N. C.; Roza, T.; Pereira, M. E. (2004) Sensitivity of "delta"-ALA-D (E.C. 4.2.1.24) of rats to metals in vitro depends on the stage of postnatal growth and tissue. Toxicol. in Vitro 18: 805-809.

Pentschew, A.; Garro, F. (1966) Lead encephalo-myelopathy of the suckling rat and its implications on the porphyrinopathic nervous diseases, with special reference to the permeability disorders of the nervous system's capillaries. Acta Neuropathol. 6: 266-278.

Pereira, B.; Curi, R.; Kokubun, E.; Bechara, E. J. H. (1992) 5-aminolevulinic acid-induced alterations of oxidative metabolism in sedentary and exercise-trained rats. J. Appl. Physiol. 72: 226-230.

Perez-Bravo, F.; Ruz, M; Moran-Jimenez, M. J.; Olivares, M.; Rebolledo, A.; Codoceo, J.; Sepulveda, J.; Jenkin, A.; Santos, J. L.; Fontanellas, A. (2004) Association between aminolevulinate dehydrase genotypes and blood lead levels in children from a lead-contaminated area in Antofagasta, Chile. Arch. Environ. Contam. Toxicol. 47(2): 276-280.

Pergande, M.; Jung, K.; Precht, S.; Fels, L. M.; Herbort, C.; Stolte, H. (1994) Changed excretion of urinary proteins and enzymes by chronic exposure to lead. Nephrol. Dial. Transplant. 9: 613-618.

Piasek, M.; Kostial, K. (1991) Reversibility of the effects of lead on the reproductive performance of female rats. Reprod. Toxicol. 5: 45-51.

Piccinini, F.; Favalli, L.; Chiari, M. C. (1977) Experimental investigations on the conctraction induced by lead in arterial smooth muscle. Toxicology 8: 43-51.

Pillai, A.; Gupta, S. (2005) Effect of gestational and lactational exposure to lead and/or cadmium on reproductive performance and hepatic oestradiol metabolising enzymes. Toxicol. Lett. 155: 179-186.

Pineda-Zavaleta, A. P.; Gracia-Vargas, G.; Borja-Aburto, V. H.; Acosta-Saavedea, L. C.; Vera Aguilar, E.; Gomez-Munoz, A.; Cebrian, M. E. Calderon-Aranda, E. S. (2004) Nitric oxide and superoxide anion production in monocytes from children exposed to arsenic and lead in region Lagunera, Mexico. Toxicol. Appl. Pharmacol. 198: 283-290.

Pinkerton, L. E.; Biagini, R. E.; Ward, E. M.; Hull, R. D.; Deddens, J. A.; Boeniger, M. F.; Schnorr, T. M.; MacKenzie, B. A.; Luster, M. I. (1998) Immunologic findings among lead-exposed workers. Am. J. Ind. Med. 33: 400-408.

Pinon-Lataillade, G.; Thoreux-Manlay, A.; Coffigny, H.; Monchaux, G.; Masse, R.; Soufir, J.-C. (1993) Effect of ingestion and inhalation of lead on the reproductive system and fertility of adult male rats and their progeny. Hum. Exp. Toxicol. 12: 165-172.

Pinon-Lataillade, G.; Thoreux-Manlay, A.; Coffigny, H.; Masse, R.; Soufir, J. C. (1995) Reproductive toxicity of chronic lead exposure in male and female mice. Hum. Exp. Toxicol. 14: 872-878.

Pinto, D.; Ceballos, J. M.; Garcia, G.; Guzman, P.; Del Razo, L. M.; Vera, E.; Gomez, H.; Garcia, A.; Gonsebatt, M. E. (2000) Increased cytogenetic damage in outdoor painters. Mutat. Res. 467: 105-111.

Pires, J. B.; Bezerra, F. F.; Laboissiere, F. P.; Miekeley, N.; Donangelo, C. M. (2001) Lead levels in erythrocytes and biomarkers of bone turnover in pregnant and lactating women with marginal calcium intakes. Nutr. Res. 21: 831-841.

Pirkle, J. L.; Schwartz, J.; Landis, J. R.; Harlan, W. R. (1985) The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am. J. Epidemiol. 121: 246-258.

Pirkle, J. L.; Brody, D. J.; Gunter, E. W.; Kramer, R. A.; Paschal, D. C.; Flegal, K. M.; Matte, T. D. (1994) The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys (NHANES). JAMA J. Am. Med. Assoc. 272: 284-291.

Pirkle, J. L.; Kaufmann, R. B.; Brody, D. J.; Hickman, T.; Gunter, E. W.; Paschal, D. C. (1998) Exposure of the U.S. population to lead, 1991-1994. Environ. Health Perspect. 106: 745-750.

Planas-Bohne, F.; Elizalde, M. (1992) Activity of glutathione-S-transferase in rat liver and kidneys after administration of lead or cadmium. Arch. Toxicol. 66: 365-367.

Poblano, A.; Rothenberg, S. J.; Schnaas, L.; Elias, Y.; Cruz, M. L. (2001) Spatial distribution of EEG theta activity as a function of lifetime lead exposure in 9-year-old children. Neurotoxicology 22: 439-446.

Poretz, R. D.; Yang, A.; Deng, W.; Manowitz, P. (2000) The interaction of lead exposure and arylsulfatase A genotype affects sulfatide catabolism in human fibroblasts. Neurotoxicology 21: 379-387.

Pounds, J. G.; Rosen, J. F. (1986) Cellular metabolism of lead: a kinetic analysis in cultured osteoclastic bone cells. Toxicol. Appl. Pharmacol. 83: 531-545.

Pounds, J. G.; Long, G. J.; Rosen, J. F. (1991) Cellular and molecular toxicity of lead in bone. Environ. Health Perspect. 91: 17-32.

Prentice, R. C.; Kopp, S. J. (1985) Cardiotoxicity of lead at various perfusate calcium concentrations: functional and metabolic responses of the perfused rat heart. Toxicol. Appl. Pharmacol. 81: 491-501.

Price, R. G. (2000) Urinalysis to exclude and monitor nephrotoxicity. Clin. Chim. Acta 297: 173-182.

Price, R. G.; Taylor, S. A.; Chivers, I.; Arce-Tomas, M.; Crutcher, E.; Franchini, I.; Slinovi, R.; Cavazzini, S.; Bergamaschi, E.; Mutti, A.; Vettori, M. V.; Lauwerys, R.; Bernard, A.; kabanda, A.; Roels, H.; Thielemans, N.; Hotz, P.; De Broe, M. E.; Elseviers, M. M.; Nuyts, G. D.; Gelpi, E.; Hotter, G.; Rosello, J.; Ramis, I.; Stolte, H.; Fels, L. M.; Eisenberger, U. (1996) Development and validation of new screening tests for nephrotoxic effects. Hum. Exp. Toxicol. 15(suppl. 1): S10-S19.

Prigge, E.; Greve, J. (1977) Effekte einer Bleiinhalation allein und in Kombination mit Kohlenmonoxid bei nichttragenden und tragenden Ratten und deren Feten. II. Effekte auf die Aktivitat der δ-Aminolavulinsaure-Dehydratase, den Hematokrit und das Korpergewicht [Effects of lead inhaltion exposures alone and in combination with carbon monoxide in nonpregnant and pregnant rats and fetuses. II. Effects on δ-aminolevulinic acid dehydratase activity, hematocrit and body weight. Zentralbl. Bakteriol. Parasitenkd. Infektionskrankh. Hyg. 16: 294-304.

Purdy, R. E.; Smith, J. R.; Ding, Y.; Oveisi, F.; Varizi, N. D.; Gonick, H. C. (1997) Lead-induced hypertension is not associated with altered vascular reactivity in vitro. Am. J. Hypertens. 10: 997-1003.

Pyatt, D. W.; Zheng, J.-H.; Stillman, W. S.; Irons, R. D. (1996) Inorganic lead activates NF-kB in primary human CD4+ T lymphocytes. Biochem. Biophys. Res. Commun. 227: 380-385.

Qian, Z. M.; Morgan, E. H. (1990) Effect of lead on the transport of transferrin-free and transferrin-bound iron into rabbit reticulocytes. Biochem. Pharmacol. 40: 1049-1054.

Qian, Y.; Harris, E. D.; Zheng, Y.; Tiffany-Castiglioni, E. (2000) Lead targets GRP78, a molecular chaperone, in C6 rat glioma cells. Toxicol. Appl. Pharmacol.163: 260-266.

Qian, Y., Zheng, Y., Ramos, K. S.; Tiffany-Castiglioni, E. (2005) GRP78 compartmentalized redistribution in Pb-treated glia: role of GRP78 in lead-induced oxidative stress. Neurotoxicology. 26: 267-275.

Qu, W.; Diwan, B. A.; Liu, J.; Goyer, R. A.; Dawson, T.; Horton, J. L.; Cherian, M. G.; Waalkes, M. P. (2002) The metallothionein-null phenotype is associated with heightened sensitivity to lead toxicity and an inability to form inclusion bodies. Am. J. Pathol. 160: 1047-1056.

Queiroz, M. L. S.; Almeida, M.; Gallao, M. I.; Hoehr, N. F. (1993) Defective neutrophil function in workers occupationally exposed to lead. Pharmacol. Toxicol. 72: 73-77.

Quinlan, G. J.; Halliwell, B.; Moorhouse, C. P.; Gutteridge, J. M. (1988) Action of lead(II) and aluminium (III) ions on iron-stimulated lipid peroxidation in liposomes, erythrocytes and rat liver microsomal fractions. Biochim. Biophys. Acta. 962: 196-200.

Quintanilla-Vega, B.; Smith, D. R.; Kahng, M. W.; Hernandez, J. M.; Albores, A.; Fowler, B. A. (1995) Lead-binding proteins in brain tissue of environmentally lead-exposed humans. Chem. Biol. Interact. 98: 193-209.

Raghavan, S. R. V.; Culver, B. D.; Gonick, H. C. (1980) Erythrocyte lead-binding protein after occupational exposure. I. Relationship to lead toxicity. Environ. Res. 22: 264-270.

Raghavan, S. R. V.; Culver, B. D.; Gonick, H. C. (1981) Erythrocyte lead-binding protein after occupational exposure. II. influence on lead inhibition of membrane Na+, K+ - adenosinetriphosphatase. J. Toxicol. Environ. Health 7: 561-568.

Rajah, T. T.; Ahuja, Y. R. (1995) In vivo genotoxic effects of smoking and occupational lead exposure in printing press workers. Toxicol. Lett. 76: 71-75.

Rajah, T. T.; Ahuja, Y. R. (1996) In vivo genotoxicity of alcohol consumption and lead exposure in printing press workers. Alcohol 13: 65-68.

Ramesh, G. T.; Manna, S. M.; Aggrarwal, B. B.; Jadhav, A. L. (1999) Lead activates nuclear transcription factor NF-kB, activator protein-1 and amino-terminal c-Jun kinase in pheochromocytoma cells. Toxicol. Appl. Pharmacol. 155: 280-286.

Ramesh, G. T.; Manna, S. K.; Aggarwal, B. B.; Jadhav, A. L. (2001) Lead exposure activates nuclear factor kappa B, activator protein-1, c-Jun N-terminal kinase and caspases in the rat brain. Toxicol. Lett. 123: 195-207

Razani-Boroujerdi, S.; Edwards, B.; Sopori, M. L. (1999) Lead stimulates lymphocyte proliferation through enhanced T cell-B cell interaction. J. Pharmacol. Exp. Therap. 288: 714-719.

Redig, P. T.; Lawler, E. M.; Schwartz, S.; Dunnette, J. L.; Stephenson, B.; Duke, G. E. (1991) Effects of chronic exposure to sublethal concentrations of lead acetate on heme synthesis and immune function in red-tailed hawks. Arch. Environ. Contam. Toxicol. 21: 72-77.

Reigart, J. R.; Graber, C. D. (1976) Evaluation of the humoral immune response of children with low level lead exposure. Bull. Environ. Contam. Toxicol. 16: 112-117.

Restrepo, H. G.; Sicard, D.; Torres, M. M. (2000) DNA damage and repair in cells of lead exposed people. Am. J. Ind. Med. 38: 330-334.

Reuhl, K. R.; Rice, D. C.; Gilbert, S. G.; Mallett, J. (1989) Effects of chronic developmental lead exposure on monkey neuroanatomy: visual system. Toxicol. Appl. Pharmacol. 99: 501-509.

Revis, N. W.; Zinsmeister, A. R.; Bull, R. (1981) Atherosclerosis and hypertension induction by lead and cadmium ions: an effect prevented by calcium ion. Proc. Natl. Acad. Sci. U. S. A. 78: 6494-6498.

Reyes, A.; Mercado, E.; Goicoechea, B.; Rosado, A. (1976) Participation of membrane sulfhydryl groups in the epididymal maturation of human and rabbit spermatozoa. Fertil. Steril. 27: 1452-1458.

Rice, D. C. (1990) Lead-induced behavioral impairment on a spatial discrimination reversal task in monkeys exposed during different periods of development. Toxicol. Appl. Pharmacol. 106: 327-333.

Rice, D. C. (1992a) Lead exposure during different developmental periods produces different effects on FI performance in monkeys tested as juveniles and adults. Neurotoxicology 13: 757-770.

Rice, D. C. (1992b) Effect of lead during different developmental periods in the monkey on concurrent discrimination performance. Neurotoxicology 13: 583-592.

Rice, D. C. (1992c) Behavioral effects of lead in monkeys tested during infancy and adulthood. Neurotoxicol. Teratol. 14: 235-245.

Rice, D. C. (1997) Effects of lifetime lead exposure in monkeys on detection of pure tones. Fundam. Appl. Toxicol. 36: 112-118.

Rice, D.; Barone, S., Jr. (2000) Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ. Health Perspect. Suppl. 108(3): 511-533.

Rice, D. C.; Gilbert, S. G. (1990) Sensitive periods for lead-induced behavioral impairment (nonspatial discrimination reversal) in monkeys. Toxicol. Appl. Pharmacol. 102: 101-109.

Rice, D. C.; Gilbert, S. G. (1990) Lack of sensitive period for lead-induced behavioral impairment on a spatial delayed alternation task in monkeys. Toxicol. Appl. Pharmacol. 103: 364-373.

Richardt, G.; Federolf, G.; Habermann, E. (1986) Affinity of heavy metal ions to intracellular Ca2+-binding proteins. Biochem. Pharmacol. 35: 1331-1335.

Rico, J.; Kordas, K.; et al. (2005) The efficacy of iron and/or zinc supplementation on cognitive performance of lead-exposed mexican school children: a randomized, placebo-controlled trial. Pediatrics: in press.

Rijhsinghani, K.; Choi, H.-S. H.; Burton, L. A.; Paronetto, F.; Tavoloni, N. (1993) Immunoelectron microscopy identification of early proliferating cells in rat liver tissue during hyperplasia induced by lead nitrate. Hepatology (Baltimore) 17: 685-692.

Ris, M. D.; Dietrich, K. N.; Succop, P. A.; Berger, O. G.; Bornschein, R. L. (2004) Early exposure to lead and neuropsychological outcome in adolescence. J. Int. Neuropsychol. Soc. 10: 261-270.

Rizzi, C. A.; Manzo, L.; Tonini, M.; Minoia, C.; Crema, A. (1989) Propulsive motility of the guinea-pig colon after chronic lead treatment. Pharmacol. Res. 21: 127-128.

Roberts, J. R.; Reigart, J. R.; Ebeling, M.; Hulsey, T. C. (2001) Time required for blood lead levels to decline in nonchelated children. Clin. Toxicol. 39: 153-160.

Rocha, A.; Valles, R.; Cardon, A. L.; Bratton, G. R.; Nation, J. R. (2005) Enhanced acquisition of cocaine self-administration in rats developmentally exposed to lead. Neuropsychopharmacology 30: 2058-2064.

Rodamilans, M.; Mtz.-Osaba, M. J.; To-Figueras, J.; Rivera-Fillat, F.; Torra, M.; Perez, P.; Corbella, J. (1988) Inhibition of intratesticular testosterone synthesis by inorganic lead. Toxicol. Lett. 42: 285-290.

Rodrigues, A. L.; Rocha, J. B.; Pereira, M. E.; Souza, D. O. (1996) Delta-aminolevulinic acid dehydratase activity in weanling and adult rats exposed to lead acetate. Bull. Environ. Contam. Toxicol. 57: 47-53.

Rodriguez-Iturbe, B.; Vaziri, N. D.; Herrera-Acosta, J.; Johnson, R. J. (2004) Oxidative stress, renal infiltration of immune cells, and salt-sensitive hypertension: all for one and one for all. Am. J. Physiol. 286: F606-F616.

Rodriguez-Iturbe, B.; Sindhu, R. K.; Quiroz, Y.; Vaziri, N. D. (2005) Chronic exposure to low doses of lead results in renal infiltration of immune cells, NF-"kappa"B activation, and overexpression of tubulointerstitial angiotensin II. Antioxid. Redox Signaling 7: 1269-1274.

Roels, H.; Lauwerys, R.; Konings, J.; Buchet, J.-P.; Bernard, A.; Green, S.; Bradley, D.; Morgan, W.; Chettle, D. (1994) Renal function and hyperfiltration capacity in lead smelter workers with high bone lead. Occup. Environ. Med. 51: 505-512

Rogan, W. J.; Dietrich, K. N.; Ware, J. H.; Dockery, D. W.; Salganik, M.; Radcliffe, J.; Jones, R. L.; Ragan, N. B.; Chisolm, J. J., Jr.; Rhoads, G. G. (2001) The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. New Engl. J. Med. 344: 1421-1426.

Ronis, M. J. J.; Badger, T. M.; Shema, S. J.; Roberson, P. K.; Shaikh, F. (1996) Reproductive toxicity and growth effects in rats exposed to lead at different periods during development. Toxicol. Appl. Pharmacol. 136: 361-371.

Ronis, M. J.; Badger, T. M.; Shema, S. J.; Roberson, P. K.; Shaikh, F. (1998a) Effects on pubertal growth and reproduction in rats exposed to lead perinatally or continuously throughout development. J. Toxicol. Environ. Health A 53: 327-341.

Ronis, M. J. J.; Gandy, J.; Badger, T. (1998b) Endocrine mechanisms underlying reproductive toxicity in the developing rat chronically exposed to dietary lead. J. Toxicol. Environ. Health Part A 54: 77-99.

Ronis, M. J. J.; Badger, T. M.; Shema, S. J.; Roberson, P. K.; Templer, L.; Ringer, D.; Thomas, P. E. (1998c) Endocrine mechanisms underlying the growth effects of developmental lead exposure in the rat. J. Toxicol. Environ. Health Part A 54: 101-120.

Ronis, M. J. J.; Aronson, J.; Gao, G. G.; Hogue, W.; Skinner, R. A.; Badger, T. M.; Lumpkin, C. K., Jr. (2001) Skeletal effects of developmental lead exposure in rats. Toxicol. Sci. 62: 321-329.

Roomi, M. W.; Columbano, A.; Ledda-Columbano, G. M.; Sarma, D. S. R. (1986) Lead nitrate induces certain biochemical properties characteristic of hepatocyte nodules. Carcinogenesis 7: 1643-1646.

Roomi, M. W.; Columbano, A.; Ledda-Columbano, G. M.; Sarma, D. S. R. (1987) Induction of the placental form of glutathione S-transferase by lead nitrate administration in rat liver. Toxicol. Pathol. 15: 202-205.

Rosen, J. F. (1983) The metabolism of lead in isolated bone cell populations: interactions between lead and calcium. Toxicol. Appl. Pharmacol. 71: 101-112.

Rosen, J. F.; Markowitz, M. E. (1980) D-Penicillamine: its actions on lead transport in bone organ culture. Pediatr. Res. 14: 330-335.

Rosen, J. F.; Mushak, P. (2001) Primary prevention of childhood lead poisoning -- the only solution [comment]. N. Engl. J. Med. 344: 1470-1471.

Rosen, J. F.; Pounds, J. G. (1988) The cellular metabolism of lead and calcium: a kinetic analysis in cultured osteoclastic bone cells. In: De Broe, M. E.; Van de Vyver, F. L., eds. Bone and renal failure: international symposium; November 1986; Antwerp, Belgium. Basel, Switzerland: S. Karger; pp. 74-82. (Contributions to nephrology: v. 64.)

Rosen, J. F.; Pounds, J. G. (1989) Quantitative interactions between Pb2+ and Ca2+ homeostasis in cultured osteoclastic bone cells. Toxicol. Appl. Pharmacol. 98: 530-543.

Rosen, J. F.; Wexler, E. E. (1977) Studies of lead transport in bone organ culture. Biochem. Pharmacol. 26: 650-652.

Rosen, J. F.; Chesney, R. W.; Hamstra, A.; DeLuca, H. F.; Mahaffey, K. R. (1980) Reduction in 1,25-dihydroxyvitamin D in children with increased lead absorption. N. Engl. J. Med. 302: 1128-1131.

Rosen, J. F.; Kraner, H. W.; Jones, K. W. (1982) Effects of CaNa2EDTA on lead and trace metal metabolism in bone organ culture. Toxicol. Appl. Pharmacol. 64: 230-235.

Rossi, E.; Attwood, P. V.; Garcia-Webb, P. (1992) Inhibition of human lymphocyte coproporphyrinogen oxidase activity by metals, bilirubin and haemin. Biochim. Biophys. Acta 1135: 262-268.

Rothenberg, S. J.; Cansino, S.; Sepkoski, C.; Torres, L. M.; Medina, S.; Schnaas, L.; Poblano, A.; Karchmer, S. (1995) Prenatal and perinatal lead exposures alter acoustic cry parameters of neonate. Neurotoxicol. Teratol. 17: 151-160.

Rothenberg, S. J.; Poblano, A.; Schnaas, L. (2000) Brainstem auditory evoked response at five years and prenatal and postnatal blood lead. Neurotoxicol. Teratol. 22: 503-510.

Roy, A. K.; Dhir, H.; Sharma, A. (1992) Modification of metal-induced micronuclei formation in mouse bone marrow erythrocytes by Phyllanthus fruit extract and ascorbic acid. Toxicol. Lett. 62: 9-17.

Ruan, D.-Y.; Chen, J.-T.; Zhao, C.; Xu, Y.-Z.; Wang, M.; Zhao, W.-F. (1998) Impairment of long-term potentiation and paired-pulse facilitation in rat hippocampal dentate gyrus following developmental lead exposure in vivo. Brain Res. 806: 196-201.

Ruzittu, M.; Carla, E. C.; Montinari, M. R.; Maietta, G.; Dini, L. (1999) Modulation of cell surface expression of liver carbohydrate receptors during in vivo induction of apoptosis with lead nitrate. Cell Tissue Res. 298: 105-112.

Sabbioni, E.; Marafante, E. (1976) Identification of lead-binding components in rat liver: in vivo study. Chem. Biol. Interact. 15: 1-20.

Sanchez-Fructuoso, A. I.; Blanco, J.; Cano, M.; Ortega, L.; Arroyo, M.; Fernandez, C.; Prats, D.; Barrientos, A. (2002a) Experimental lead nephropathy: treatment with calcium disodium ethylenediaminetetraacetate. Am. J. Kidney Dis. 40: 59-67.

Sanchez-Fructuoso, A. I.; Cano, M.; Arroyo, M.; Fernandez, C.; Prats, D.; Barrientos, A. (2002b) Lead mobilization during calcium disodium ethylenediaminetetraacetate chelation therapy in treatment of chronic lead poisoning. Am. J. Kidney Dis. 40: 51-58.

Sandhir, R.; Gill, K. D. (1995) Effect of lead on lipid peroxidation in liver of rats. Biol. Trace Elem. Res. 48: 91-97.

Sanin, L. H.; Gonzalez-Cossio, T.; Romieu, I.; Peterson, K. E.; Ruiz, S.; Palazuelos, E.; Hernandez-Avila, M.; Hu, H. (2001) Effect of maternal lead burden on infant weight and weight gain at one month of age among breastfed infants. Pediatrics 107: 1016-1023.

Sant'Ana, M. G.; Spinosa, H. S.; Florio, J. C.; Bernardi, M. M.; Oliveira, C. A.; Sarkis, J. E.; Kakazu, M. H. (2001) Role of early GnRH administration in sexual behavior disorders of rat pups perinatally exposed to lead. Neurotoxicol. Teratol. 23: 203-212.

Santos, J. L.; Fontanellas, A.; Moran, M. J.; Enriquez de Salamanca, R. (1999) Nonsynergic effect of ethanol and lead on heme metabolism in rats. Ecotoxicol. Environ. Saf. 43: 98-102.

Sarasua, S. M.; Vogt, R. F.; Henderson, L. O.; Jones, P. A.; Lybarger, J. A. (2000) Serum immunoglobulins and lymphocyte subset distributions in children and adults living in communities assessed for lead and cadmium exposure. J. Toxicol. Environ. Health A. 60: 1-15.

Sargent, J. D.; Dalton, M. A.; O'Connor, G. T.; Olmstead, E. M.; Klein, R. Z. (1999) Randomized trial of calcium glycerophosphate-supplemented infant formula to prevent lead absorption. Am. J. Clin. Nutr. 69: 1224-1230.

Satija, N. K.; Vij, A. G. (1995) Preventive action of zinc against lead toxicity. Indian J. Physiol. Pharmacol. 39: 377-382.

Sauk, J. J.; Smith, T.; Silbergeld, E. K.; Fowler, B. A.; Somerman, M. J. (1992) Lead inhibits secretion of osteonectin/SPARC without significantly altering collagen or Hsp47 production in osteoblast-like ROS 17/2.8 cells. Toxicol. Appl. Pharmacol. 116: 240-247.

Saxena, D. K.; Lal, B.; Srivastava, R. S.; Chandra, S. V. (1990) Lead induced testicular hypersensitivity in stressed rats. Exp. Pathol. 39: 103-109.

Schafer, J. H.; Glass, T. A.; Bressler, J.; Todd, A. C.; Schwartz, B. S. (2005) Blood lead in a predictor of homocysteine levels in a population-based study of older adults. Environ. Health Perspect. 113: 31-35.

Schanne, F. A. X.; Dowd, T. L.; Gupta, R. K.; Rosen, J. F. (1989) Lead increases free Ca2+ concentration in cultured osteoblastic bone cells: simultaneous detection of intracellular free Pb2+ by 19F NMR. Proc. Natl. Acad. Sci. U. S. A. 86: 5133-5135.

Schanne, F. A. X.; Gupta, R. K.; Rosen, J. F. (1992) Lead inhibits 1,25-dihydroxyvitamin D-3 regulation of calcium metabolism in osteoblastic osteosarcoma cells (ROS 17/2.8). Biochim. Biophys. Acta 1180: 187-194.

Schanne, F. A. X.; Long, G. J.; Rosen, J. F. (1997) Lead induced rise in intracellular free calcium is mediated through activation of protein kinase C in osteoblastic bone cells. Biochim. Biophys. Acta 1360: 247-254.

Schechtman, L. M.; Hatch, G. G.; Anderson, T. M.; Putman, D. L.; Kouri, R. E.; Cameron, J. W.; Nims, R. W.; Spalding, J. W.; Tennant, R. W.; Lubet, R. A. (1986) Analysis of the interlaboratory and intralaboratory reproducibility of the enhancement of simian adenovirus SA7 transformation of Syrian hamster embryo cells by model carcinogenic and noncarcinogenic compounds. Environ. Mutagen. 8: 495-514.Shelkovnikov,

S. A.; Gonick, H. C. (2001) Influence of lead on rat thoracic aorta contraction and relaxation. Am. J. Hypertens. 14: 873-878.
Scheuhammer, A. M. (1987) Erythrocyte "delta"-aminolevulinic acid dehydratase in birds. II. The effects of lead exposure in vivo. Toxicology 45: 165-175.
Schirrmacher, K.; Wiemann, M.; Bingmann, D.; Busselberg, D. (1998) Effects of lead, mercury, and methyl mercury on gap junctions and [CA2+]i in bone cells. Calcified Tiss. Int. 63: 134-139.
Schlick, E.; Friedberg, K. D. (1981) The influence of low lead doses on the reticulo-endothelial system and leucocytes of mice. Arch. Toxicol. 47: 197-207.
Schlipkoter, H.-W.; Frieler, L. (1979) Der Einfluss kurzzeitiger Bleiexposition auf die Bakterienclearance der Lunge [The influence of short-term lead exposure on the bacterial clearance of the lung]. Zentralbl. Bakteriol. Parasitenkd. Infektionskr. Hyg. Abt. 1: Orig. Reihe B 168: 256-265.
Schneider, J. S.; Anderson, D. W.; Wade, T. V.; Smith, M. G.; Leibrandt, P.; Zuck, L.; Lidsky, T. I. (2005) Inhibition of progenitor cell proliferation in the dentate gyrus of rats following post-weaning lead exposure. Neurotoxicology 26: 141-145.
Schneyer, C. A.; Hall, H. D. (1970) Influence of physiological activity on mitosis in immature rat parotid gland. Proc. Soc. Exp. Biol. Med. 133: 349-352.
Schrauzer, G. N. (1987) Effects of selenium antagonists on cancer susceptibility: new aspects of chronic heavy metal toxicity. J. UOEH 9 Suppl: 208-215.
Schroeder, H. A.; Mitchener, M. (1971) Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health 23: 102-106.
Schwartz, J. (1994) Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ. Res. 65: 42-55.
Schwartz, J.; Angle, C.; Pitcher, H. (1986) Relationship between childhood blood lead and stature. Pediatrics 77: 281-288.
Schwartz, B. S.; Lee, B.-K.; Stewart, W.; Ahn, K.-D.; Kelsey, K.; Bresssler, J. (1997) Associations of subtypes of hemoglobin with delta-aminolevulinic acid dehydratase genotype and dimercaptosuccinic acid-chelatable lead levels. Arch. Environ. Health 52: 97-103.
Schwartz, B. S.; Stewart, W. F.; Bolla, K. I.; Simon, M. S.; Bandeen-Roche, K.; Gordon, B.; Links, J. M.; Todd, A. C. (2000) Past adult lead exposure is associated with longitudinal decline in cognitive function. Neurology 55: 1144-1150.
Selevan, S. G.; Kimmel, C. A.; Mendola, P. (2000) Identifying critical windows of exposure for children's health. Environ. Health Perspect. Suppl. 108(3): 451-455.
Selevan, S. G.; Rice, D. C.; Hogan, K. A.; Euling, S. Y.; Pfahles-Hutchens, A.; Bethel, J. (2003) Blood lead concentration and delayed puberty in girls. N. Engl. J. Med. 348: 1527-1536.
Selye, H.; Tuchweber, B.; Bertok, L. (1966) Effect of lead acetate on the susceptibility of rats to bacterial endotoxins. J. Bacteriol. 91: 884-890.
Sengupta, M.; Bishayi, B. (2002) Effect of lead and arsenic on murine macrophage response. Drug Chem. Toxicol. 25: 459-472.
Serrani, R. E.; Gioia, I. A.; Corchs, J. L. (1997) Lead effects on structural and functional cellular parameters in human red cells from a prenatal hematopoiesis stage. Biometals 10: 331-335.
Shabani, A.; Rabbani, A. (2000) Lead nitrate induced apoptosis in alveolar macrophages from rat lung. Toxicology 149: 109-114.
Shakoor, A.; Gupta, P. K.; Singh, Y. P.; Kataria, M. (2000) Beneficial effects of aluminum on the progression of lead-induced nephropathy in rats. Pharmacol. Toxicol. 87: 258-260.
Shalan, M. G.; Mostafa, M. S.; Hassouna, M. M.; El-Nabi, S. E.; El-Refaie, A. (2005) Amelioration of lead toxicity on rat liver with vitamin C and silymarin supplements. Toxicology 206: 1-15.
Shao, Z.; Suszkiw, J. B. (1991) Ca2+-surrogate action of Pb2+ on acetylcholine release from rat brain synaptosomes. J. Neurochem. 56: 568-574.
Sharifi, A. M.; Darabi, R.; Akbarloo, N.; Larijani, B.; Khoshbaten, A. (2004) Investigation of circulatory and tissue ACE activity during development of lead-induced hypertension. Toxicol. Lett. 153: 233-238.
Shelkovnikov, S. A.; Gonick, H. C. (2001) Influence of lead on rat thoracic aorta contraction and relaxation. Am. J. Hypertens. 14: 873-878.
Shelton, K. R.; Egle, P. M. (1982) The proteins of lead-induced intranuclear inclusion bodies. J. Biol. Chem. 257: 11802-11807.

Shelton, K. R.; Cunningham, J. G.; Klann, E.; Merchant, R. E.; Egle, P. M.; Bigbee, J. W. (1990) Low-abundance 32-kilodalton nuclear protein specifically enriched in the central nervous system. J. Neurosci. Res. 25: 287-294.

Shelton, K. R.; Egle, P. M.; Bigbee, J. W.; Klann, E. (1993) A nuclear matrix protein stabilized by lead exposure: current knowledge and future prospects. Presented at: Ninth international neurotoxicology conference; October 1991; Little Rock, AR. Neurotoxicology 14(2-3): 61-67.

Shinozuka, H.; Kubo, Y.; Katyal, S. L.; Coni, P.; Ledda-Columbano, G. M.; Columbano, A.; Nakamura, T. (1994) Roles of growth factors and of tumor necrosis factor-"alpha" on liver cell proliferation induced in rats by lead nitrate. Lab. Invest. 71: 35-41.

Shinozuka, H.; Ohmura, T.; Katyal, S. L.; Zedda, A. I.; Ledda-Columbano, G. M.; Columbano, A. (1996) Possible roles of nonparenchymal cells in hepatocyte proliferation induced by lead nitrate and by tumor necrosis factor "alpha". Hepatology 23: 1572-1577.

Shraideh, Z. (1999) Effect of triethyl lead on peristaltic contractile activity of the ileum of mice. Cytobios 99: 97-104.

Shukla, V. K.; Prakash, A.; Tripathi, B. D.; Reddy, D. C.; Singh, S. (1998) Biliary heavy metal concentrations in carcinoma of the gall bladder: case-control study. BMJ 317: 1288-1289.

Sidhu, M. K.; Fernandez, C.; Khan, M. Y.; Kumar, S. (1991) Induction of morphological transformation, anchorage-independent growth and plasminogen activators in non-tumorigenic human osteosarcoma cells by lead chromate. Anticancer Res. 11: 1045-1053.

Sieg, D. J.; Billings, R. E. (1997) Lead/cytokine-mediated oxidative DNA damage in cultured mouse hepatocytes. Toxicol. Appl. Pharmacol. 142: 106-115.

Sierra, E. M.; Tiffany-Castiglioni, E. (1992) Effects of low-level lead exposure on hypothalamic hormones and serum progesterone levels in pregnant guinea pigs. Toxicology 72: 89-97.

Silbergeld, E. K.; Hruska, R. E.; Bradley, D. (1982) Neurotoxic aspects of porphyrinopathies: lead and succinylacetone. Environ. Res. 29: 459-471.

Silkin, Y. A.; Silkina, E. N.; Sherstobitov, A. O.; Gusev, G. P. (2001) Activation of potassium channels in erythrocytes of marine teleost Scorpaena porcus. Membr. Cell Biol. 14: 773-782.

Simons, T. J. (1986a) Passive transport and binding of lead by human red blood cells. J. Physiol. 378: 267-286.

Simons, T. J. (1986b) The role of anion transport in the passive movement of lead across the human red cell membrane. J. Physiol. 378: 287-312.

Simons, T. J. B. (1988) Active transport of lead by the calcium pump in human red cell ghosts. J. Physiol. (London) 405: 105-13.

Simons, T. J. B. (1993a) Lead transport and binding by human erythrocytes in vitro. Pflugers Arch. 423: 307-313.

Simons, T. J. B. (1993b) Lead-calcium interactions in cellular lead toxicity. Presented at: Ninth international neurotoxicology conference; October 1991; Little Rock, AR. Neurotoxicology 14(2-3): 77-86.

Simons, T. J. B. (1995) The affinity of human erythrocyte porphobilinogen synthase for Zn2+ and Pb2+. Eur. J. Biochem. 234: 178-183.

Singh, U. S.; Saxena, D.K.; Singh, C.; Murthy, R. C.; Chandra, S. V. (1991) Lead-induced fetal nephrotoxicity in iron-deficient rats. Reprod. Toxicol. 5: 211-217.

Singh, A.; Cullen, C.; Dykeman, A.; Rice, D.; Foster, W. (1993) Chronic lead exposure induces ultrastructural alterations in the monkey testis. J. Submicrosc. Cytol. Pathol. 25: 479-486.

Singh, C.; Saxena, D. K.; Murthy, R. C.; Chandra, S. V. (1993) Embryo-fetal development influenced by lead exposure in iron-deficient rats. Hum. Exp. Toxicol. 12: 25-28.

Singh, J.; Parkash, P.; Gupta, G. S. (1999) State of pregnancy modifies lead toxicity in mice. Biol. Trace Elem. Res. 67: 205-213.

Singh, J.; Pritchard, D. E.; Carlisle, D. L.; Mclean, J. A.; Montaser, A.; Orenstein, J. M.; Patierno, S. R. (1999) Internalization of carcinogenic lead chromate particles by cultured normal human lung epithelial cells: formation of intracellular lead-inclusion bodies and induction of apoptosis. Toxicol. Appl. Pharmacol. 161: 240-248.

Singh, V. K.; Mishra, K. P.; Rani, R.; Yadav, V. S.; Awasthi, S. K.; Garg, S. K. (2003) Immunomodulation by lead. Immunol. Res. 28: 151-165.

Silvaprasad, R.; Nagaraj, M.; Varalakshmi, P. (2003) Combined efficacies of lipoic acid and meso-2,3-dimercaptosuccinic acid on lead-induced erythrocyte membrane lipid peroxidation and antioxidant status in rats. Hum. Exp. Toxicol. 22: 183-192.

Sivaprasad, R.; Nagaraj, M.; Varalakshmi, P. (2004) Combined efficacies of lipoic acid and 2,3-dimercaptosuccinic acid against lead-induced lipid peroxidation in rat liver. J. Nutr. Biochem. 15: 18-23

Skoczynska, A.; Smolik, R. (1994) The effect of combined exposure to lead and cadmium on serum lipids and lipid peroxides level in rats. Int. J. Occup. Med. Environ. Health 7: 263-271.

Skoczynska, A.; Smolik, R.; Jelen, M. (1993) Lipid abnormalities in rats given small doses of lead. Arch. Toxicol. 67: 200-204.

Skoczynska, A.; Smolik, R.; Milian, A. (1994) The effect of combined exposure to lead and cadmium on the concentration of zinc and copper in rat tissues. Int. J. Occup. Med. Environ. Health 7: 41-49.

Slobozhanina, E. I.; Kozlova, N. M.; Lukyanenko, L. M.; Oleksiuk, O. B.; Gabbianelli, R.; Fedeli, D.; Caulini, G. C.; Falcioni, G. (2005) Lead-induced changes in human erythrocytes and lymphocytes. J. Appl. Toxicol. 25: 109-114.

Smejkalova, J. (1990) The chromosomal aberrations investigation in children permanently living in the lead polluted area. Sb. Ved. Pr. Lek. Fak. Karlovy Univerzity Hradci Kralove 33: 539-564.

Smith, D. R.; Flegal, A. R. (1992) Stable isotopic tracers of lead mobilized by DMSA chelation in low lead-exposed rats. Toxicol. Appl. Pharmacol. 116: 85-91.

Smith, K. L.; Lawrence, D. A. (1988) Immunomodulation of in vitro antigen presentation by cations. Toxicol. Appl. Pharmacol. 96: 476-484.

Smith, C. M.; DeLuca, H. F.; Tanaka, Y.; Mahaffey, K. R. (1981) Effect of lead ingestion on functions of vitamin D and its metabolites. J. Nutr. 111: 1321-1329.

Smith, C. M.; Hu, H.; Wang, X.; Kelsey, K. T. (1995a) ALA-D genotype is not associated with HT or HB levels among workers exposed to low levels of lead. Med. Lav. 86: 229-235.

Smith, C. M.; Wang, X.; Hu, H.; Kelsey, K. T. (1995b) A polymorphism in the "delta"-aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead. Environ. Health Perspect. 103: 248-253.

Smith, D. R.; Kahng, M. W.; Quintanilla-Vega, B.; Fowler, B. A. (1998) High-affinity renal lead-binding proteins ini environmentally-exposed humans. Chem. Biol. Interact. 115: 39-52.

Smith, D. R.; Woolard, D.; Luck, M. L.; Laughlin, N. K. (2000) Succimer and the reduction of tissue lead in juvenile monkeys. Toxicol. Appl. Pharmacol. 166: 230-240.

Smith, D.; Hernandez-Avila, M.; Tellez-Rojo, M.M.; Mercado, A.; Hu, H. (2002) The relationship between lead in plasma and whole blood in women. Environ. Health Perspect. 110: 263-268.

Snyder, R. D.; Lachmann, P. J. (1989) Thiol involvement in the inhibition of DNA repair by metals in mammalian cells. J. Mol. Toxicol. 2: 117-128.

Snyder, J. E.; Filipov, N. M.; Parsons, P. J.; Lawrence, D. A. (2000) The efficiency of maternal transfer of lead and its influence on plasma IgE and splenic cellularity of mice. Toxicol. Sci. 57: 87-94.

Sokol, R. Z. (1987) Hormonal effects of lead acetate in the male rat: mechanism of action. Biol. Reprod. 37: 1135-1138.

Sokol, R. Z.; Berman, N. (1991) The effect of age of exposure on lead-induced testicular toxicity. Toxicology 69: 269-278.

Sokol, R. Z.; Berman, N.; Okuda, H.; Raum, W. (1998) Effects of lead exposure on GnRH and LH secretion in male rats: response to castration and "alpha"-methyl-p-tyrosine (AMPT) challenge. Reprod. Toxicol. 12: 347-355.

Sokol, R. Z.; Madding, C. E.; Swerdloff, R. S. (1985) Lead toxicity and the hypothalamic-pituitary-testicular axis. Biol. Reprod. 33: 722-728.

Sokol, R. Z.; Okuda, H.; Nagler, H. M.; Berman, N. (1994) Lead exposure in vivo alters the fertility potential of sperm in vitro. Toxicol. Appl. Pharmacol. 124: 310-316.

Sokol, R. Z.; Wang, S.; Wan, Y.-J. Y.; Stanczyk, F. Z.; Gentzschein, E.; Chapin, R. E. (2002) Long-term, low-dose lead exposure alters the gonadotropin-releasing hormone system int he male rat. Environ. Health Perspect. 110: 871-874.

Spit, B. J.; Wibowo, A. A. E.; Feron, V. J.; Zielhuis, R. L. (1981) Ultrastructural changes in the kidneys of rabbits treated with lead acetate. Arch. Toxicol. 49: 85-91.

Srivastava, D.; Hurwitz, R. L.; Fox, D. A. (1995) Lead- and calcium-mediated inhibition of bovine rod cGMP phosphodiesterase: interactions with magnesium. Toxicol. Appl. Pharmacol. 134: 43-52.

Srivastava, V.; Dearth, R. K.; Hiney, J. K.; Ramirez, L. M.; Bratton, G. R.; Dees, W. (2004) The effects of low-level Pb on steroidogenic acute regulatory protein (StAR) in the prepubertal rat ovary. Toxicol. Sci. 77: 35-40.

Steenland, K.; Selevan, S.; Landrigan, P. (1992) The mortality of lead smelter workers: an update. Am. J. Public Health 82: 1641-1644.

Stiles, K. M.; Bellinger, D. C. (1993) Neuropsychological correlates of low-level lead exposure in school-age children: a prospective study. Neurotoxicol. Teratol. 15: 27-35.

Stokes, J.; Casale, T. B. (2004) Rationale for new treatments aimed at IgE immunomodulation. Ann. Allergy Asthma Immunol. 93: 217-217.

Stokes, L.; Letz, R.; Gerr, F.; Kolczak, M.; McNeill, F. E.; Chettle, D. R.; Kaye, W. E. (1998) Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience. Occup. Environ. Med. 55: 507-516.

Stowe, H. D.; Goyer, R. A. (1971) Reproductive ability and progeny of F 1 lead-toxic rats. Fertil. Steril. 22: 755-760.

Studnitz, W. von; Haeger-Aronsen, B. (1962) Urinary excretion of amino acids in lead-poisoned rabbits. Acta Pharmacol. Toxicol. 19: 36-42.

Sugawara, E.; Nakamura, K.; Fukumura, A.; Seki, Y. (1990) Uptake of lead by human red blood cells and intracellular distribution. Kitasato Arch. Exp. Med. 63: 15-23.

Sugiura, S.; Dhar, S. K.; Arizono, K.; Ariyoshi, T. (1993) Induction of DT-diaphorase in the liver of rats treated with various metals. Jpn. J. Toxicol. Environ. Health 39: P-7.

Suketa, Y.; Hasegawa, S.; Yamamoto, T. (1979) Changes in sodium and potassium in urine and serum of lead-intoxicated rats. Toxicol. Appl. Pharmacol. 47: 203-207.

Sun, X.; Tian, X.; Tomsig, J. L.; Suszkiw, J. B. (1999) Analysis of differential effects of Pb2+ on protein kinase C isozymes. Toxicol. Appl. Pharmacol. 156: 40-45.

Sun, L.; Hu, J.; Zhao, Z.; Li, L.; Cheng, H. (2003) Influence of exposure to environmental lead on serum immunoglobulin in preschool children. Environ. Res. 92: 124-128.

Suszkiw, J.; Toth, G.; Murawsky, M.; Cooper, G. P. (1984) Effects of Pb2+ and Cd2+ on acetylcholine release and Ca2+ movements in synaptosomes and subcellular fractions from rat brain and Torpedo electric organ. Brain Res. 323: 31-46.

Suwalsky, M.; Villena, F.; Norris, B.; Cuevas, F.; Sotomayor, C. P.; Zatta, P. (2003) Effects of lead on the human erythrocyte membrane and molecular models. J. Inorg. Biochem. 97: 308-313.

Suzuki, T.; Morimura, S.; Diccianni, M. B.; Yamada, R.; Hochi, S.-I.; Hirabayashi, M.; Yuki, A.; Nomura. K.; Kitagawa, T.; Imagawa, M.; Muramatsu, M. (1996) Activation of glutathione transferase P gene by lead requires glutathione transferase P enhancer I. J. Biol. Chem. 271: 1626-1632.

Szabo, A.; Merke, J.; Hugel, U.; Mall, G.; Stoeppler, M.; Ritz, E. (1991) Hyperparathyroidism and abnormal 1,25(OH)2vitamin D3 metabolism in experimental lead intoxication. Eur. J. Clin. Invest. 21: 512-520.

Tabchoury, C. M.; Pearson, S. K.; Bowen, W. H. (1999) Influence of lead on the cariostatic effect of fluoride co-crystallized with sucrose in desalivated rats. Oral Dis. 5: 100-103.

Takeno, M.; Yoshikawa, H.; Kurokawa, M.; Takeba, Y.; Kashoiwakura, J. I.; Sakaguchi, M.; Yasueda, H.; Suzuki, N. (2004) Th1-dominant shift of T cell cytokine production and subsequent reduction of serum immunoglobulin E response by administration in vivo of plasmid expressing Txk/Rlk, a member of Tec family tyrosine kinases, in a mouse model. Clin. Exp. Immunol. 34: 965-970.

Taketani, S.; Tanaka, A.; Tokunaga, R. (1985) Reconstitution of heme-synthesizing activity from ferric ion and porphyrins, and the effect of lead on the activity. Arch. Biochem. Biophys. 242: 291-296.

Tandon, S. K.; Singh, S.; Jain, V. K. (1994a) Efficacy of combined chelation in lead intoxication. Chem. Res. Toxicol. 7: 585-589.

Tandon, S. K.; Khandelwal, S.; Jain, V. K.; Mathur, N. (1994b) Influence of dietary iron deficiency on nickel, lead and cadmium intoxication. Sci. Total Environ. 148: 167-173.

Tandon, S. K.; Singh, S.; Prasad, S.; Mathur, N. (1997) Influence of L-lysine and zinc administration during exposure to lead or lead and ethanol in rats. Biol. Trace Elem. Res. 57: 51-58.

Tang, H.-W.; Huel, G.; Campagna, D.; Hellier, G.; Boissinot, C.; Blot, P. (1999) Neurodevelopmental evaluation of 9-month-old infants exposed to low levels of lead in utero: involvement of monoamine neurotransmitters. J. Appl. Toxicol. 19: 167-172.

Taupeau, C.; Poupon, J.; Nome, F.; Lefevre, B. (2001) Lead accumulation in the mouse ovary after treatment-induced follicular atresia. Reprod. Toxicol. 15: 385-391.

Tavakoli-Nezhad, M.; Pitts, D. K. (2005) Postnatal inorganic lead exposure reduces midbrain dopaminergic impulse flow and decreases dopamine D1 receptor sensitivity in nucleus accumbens neurons. J. Pharmacol. Exp. Ther. 312: 1280-1288.

Tavakoli-Nezhad, M.; Barron, A. J.; Pitts, D. K. (2001) Postnatal inorganic lead exposure decreases the number of spontaneously active midbrain dopamine neurons in the rat. Neurotoxicology 22: 259-269.

Taylor, S. A.; Chivers, I. D.; Price, R. G.; Arce-Thomas, M.; Milligan, P.; Francini, I.; Alinovi, R.; Cavazzini, S.; Bergamaschi, E.; Vittori, M.; Mutti, A.; Lauwerys, R. R.; Bernard, A. M.; Roels, H. A.; De Broe, M. E.; Nuyts, G. D.; Elseviers, M. M.; Hotter, G.; Ramis, I.; Rosello, J.; Gelpi, E.; Stolte, H.; Eisenberger, U.; Fels,

L. M. (1997) The assessment of biomarkers to detect nephrotoxicity using an integrated database. Environ. Res. 75: 23-33.

Tchernitchin, N. N.; Tchernitchin, A. N.; Mena, M. A.; Villarroel, L.; Guzman, C.; Poloni, P. (1998a) Effect of subacute exposure to lead on responses to estrogen in the immature rat uterus. Bull. Environ. Contam. Toxicol. 60: 759-765.

Tchernitchin, N. N.; Villagra, A.; Tchernitchin, A. N. (1998b) Antiestrogenic activity of lead. Environ. Toxicol. Water Qual. 13: 43-53.

Tepper, R. I.; Levinson, D. A.; Stanger, B. Z.; Campos-Torres, J.; Abbas, A. K.; Leder, P. (1990) IL-4 induces allergic-like inflammatory disease and alters T cell development in transgenic mice. Cell 62: 457-467.

Teraki, Y.; Uchiumi, A. (1990) Inorganic elements in the tooth and bone tissues of rats bearing nickel acetate- and lead acetate-induced tumors. Shigaku. 78: 269-273.

Terayama, K.; Muratsugu, M. (1988) Effects of lead on sialic acid content and survival of rat erythrocytes. Toxicology 53: 269-276.

Terayama, K.; Maehara, N.; Muratsugu, M.; Makino, M.; Yamamura, K. (1986) Effect of lead on electrophoretic mobility of rat erythrocytes. Toxicology 40: 259-265.

Tessitore, L.; Perletti, G. P.; Sesca, E.; Pani, P.; Dianzani, M. U.; Piccinini, F. (1994) Protein kinase C isozyme pattern in liver hyperplasia. Biochem. Biophys. Res. Commun. 205: 208-214.

Tessitore, L.; Sesca, E.; Pani, P.; Dianzani, M. U. (1995) Sexual dimorphism in the regulation of cell turnover during liver hyperplasia. Chem. Biol. Interact. 97: 1-10.

Thaweboon, S.; Chunhabundit, P.; Surarit, R.; Swasdison, S.; Suppukpatana, P. (2002) Effects of lead on the proliferation, protein production, and osteocalcin secretion of human dental pulp cells in vitro. Southeast Asian J. Trop. Med. Public Health 33: 654-661.

Thind, I. S.; Khan, M. Y. (1978) Potentiation of the neurovirulence of Langat virus infection by lead intoxication in mice. Exp. Mol. Pathol. 29: 342-347.

Tian, L.; Lawrence, D. A. (1995) Lead inhibits nitric oxide production in vitro by murine splenic macrophages. Toxicol. Appl. Pharmacol. 132: 156-163.

Tian, L.; Lawrence, D. A. (1996) Metal-induced modulation of nitric oxide production in vitro by murine macrophages: Lead, nickel, and cobalt utilize different mechanisms. Toxicol. Appl. Pharmacol. 141: 540-547.

Tian, X.; Sun, X.; Suszkiw, J. B. (2000) Upregulation of tyrosine hydroxylase and downregulation of choline acetyltransferase in lead-exposed PC12 cells: the role of PKC activation. Toxicol. Appl. Pharmacol. 167: 246-252.

Tomczok, J.; Grzybek, H.; Sliwa, W.; Panz, B. (1988) Ultrastructural aspects of the small intestinal lead toxicology. Part II. The small intestine goblet cells of rats during lead poisoning. Exp. Pathol. 35: 93-100.

Tomokuni, K.; Ichiba, M. (1988) Comparison of inhibition of erythrocyte pyrimidine 5'-nucleotidase and delta-aminolevulinic acid dehydratase by lead. Toxicol. Lett. 40: 159-163.

Tomokuni, K.; Ichiba, M.; Hirai, Y. (1989) Effect of lead exposure on some biological indices related to porphyrin metabolism and the activity of erythrocyte pyrimidine 5'-nucleotidase in the mice. Arch. Toxicol. 63: 23-28.

Tomokuni, K.; Ichiba, M. (1990) Effect of lead on the activity of erythrocyte porphobilinogen deaminase in-vivo and in-vitro. Toxicol. Lett. 50: 137-142.

Tomokuni, K.; Ichiba, M.; Hirai, Y. (1991) Elevated urinary excretion of "beta"-aminoisobutyric acid and "delta"-aminolevulinic acid (ALA) and the inhibition of ALA-synthase and ALA-dehydratase activities in both liver and kidney in mice exposed to lead. Toxicol. Lett. 59: 169-173.

Tomsig, J. L.; Suszkiw, J. B. (1993) Intracellular mechanism of Pb2+-induced norepinephrine release from bovine chromaffin cells. Am. J. Physiol. 265: C1630-C1636.

Tomsig, J. L.; Suszkiw, J. B. (1995) Multisite interactions between Pb2+ and protein kinase C and its role in norepinephrine release from bovine adrenal chromaffin cells. J. Neurochem. 64: 2667-2673.

Tong, S.; Baghurst, P.; McMichael, A.; Sawyer, M.; Mudge, J. (1996) Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study. Br. Med. J. 312: 1569-1575.

Tong, S.; McMichael, A. J.; Baghurst, P. A. (2000) Interactions between environmental lead exposure and sociodemographic factors on cognitive development. Arch. Environ. Health 55: 330-335.

Tonner, L. E.; Heiman, A. S. (1997) Lead may affect glucocorticoid signal transduction in cultured hepatoma cells through inhibition of protein kinase C. Toxicology 119: 155-166.

Toplan, S.; Ozcelik, D.; Gulyasar, T.; Akyoleu, M. C. (2004) Changes in hemorheological parameters due to lead exposure in female rats. J. Trace Elem. Med. Biol. 18: 179-182.

Torres, D.; Barrier, M.; Bikl, F.; Quesniaux, V. J.; Maillet, I.; Akira, S.; Ryffel, B.; Erard, F. (2004) Toll-like receptor 2 is required for optimal control of Listeria monocytogenes infection. Infect. Immun. 72: 2131-2139.

Toscano, C. D.; Hashemzadeh-Gargari, H.; McGlothan, J. L.; Guilarte, T. R. (2002) Developmental Pb2+ exposure alters NMDAR subtypes and reduces CREB phosphorylation in the rat brain. Dev. Brain Res. 139: 217-226.

Trasande, L.; Thurston, G. D. (2005) The role of air pollution in asthma and other pediatric morbidities. J. Allergy Clin. Immunol. 115: 689-699.

Trejo, R. A.; Di Luzio, N. R.; Loose, L. D.; Hoffman, E. (1972) Reticuloendothelial and hepatic functional alterations following lead acetate administration. Exp. Mol. Pathol. 17: 145-158.

Trope, I.; Lopez-Villegas, D.; Cecil, K. M.; Lenkinski, R. E. (2001) Exposure to lead appears to selectively alter metabolism of cortical gray matter. Pediatrics 107: 1437-1443.

Tryphonas, H. (2001) Approaches to detecting immunotoxic effects of environmental contaminants in humans. Environ. Health Perspect. Suppl. 109(6): 877-884.

Tsaih, S.-W.; Korrick, S.; Schwartz, J.; Lee, M.-L. T.; Amarasiriwardena, C.; Aro, A.; Sparrow, D.; Hu, H. (2001) Influence of bone resorption on the mobilization of lead from bone among middle-aged and elderly men: the Normative Aging Study. Environ. Health Perspect. 109: 995-999.

Tsao, D.-A.; Yu, H.-S.; Cheng, J.-T.; Ho, C.-K.; Chang, H.-R. (2000) The change of "beta"-adrenergic system in lead-induced hypertension. Toxicol. Appl. Pharmacol. 164: 127-133.

Tulasi, S. J.; Reddy, P. U. M.; Ramana Rao, J. V. (1992) Accumulation of lead and effects on total lipids and lipid derivatives in the freshwater fish Anabas testudineus (Bloch). Ecotoxicol. Environ. Saf. 23: 33-38.

U.S. Environmental Protection Agency. (1986) Air quality criteria for lead. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-83/028aF-dF. 4v. Available from: NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency. (1990) Air quality criteria for lead: supplement to the 1986 addendum. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-89/049F. Available from: NTIS, Springfield, VA; PB91-138420.

Ueda, D.; Kishimoto, T.; Dekio, S.; Tada, M. (1997) Inhibitory effect of lead on tube formation by cultured human vascular endothelial cells. Hum. Cell 10: 283-291.

Undeger, U.; Basaran, N.; Canpinar, H.; Kansu, E. (1996) Immune alterations in lead-exposed workers. Toxicology 109: 167-172.

Vaglenov, A.; Carbonell, E.; Marcos, R. (1998) Biomonitoring of workers exposed to lead. Genotoxic effects, its modulation by polyvitamin treatment and evaluation of the induced radioresistance. Mutat. Res. 418: 79-92.

Vakharia, D. D.; Liu, N.; Pause, R.; Fasco, M.; Bessette, E.; Zhang, Q.-Y.; Kaminsky, L. S. (2001) Effect of metals on polycyclic aromatic hydrocarbon induction of CYP1A1 and CYP1A2 in human hepatocyte cultures. Toxicol. Appl. Pharmacol. 170: 93-103.

Valencia, I.; Castillo, E. E.; Chamorro, G.; Bobadilla, R. A.; Castillo, C. (2001) Lead induces endothelium- and Ca2+-independent contraction in rat aortic rings. Pharmacol. Toxicol. (Oxford, UK) 89: 177-182.

Valentino, M.; Governa, M.; Marchiseppe, I.; Visona, I. (1991) Effects of lead on polymorphonuclear leukocyte (PMN) functions in occupationally exposed workers. Arch. Toxicol. 65: 685-688.

Valverde, M.; Fortoul, T. I.; Diaz-Barriga, F.; Majia, J.; Del Castillo, E. R. (2002) Genotoxicity induced in CD-1 mice by inhaled lead: differential organ response. Mutagenesis 17: 55-61.

Van Larebeke, N.; Koppen, G.; Nelen, V.; Schoeters, G.; Van Loon H, Albering H, Riga L, Vlietinck, R.; Kleinjans, J.; Flemish Environment and Health Study Group. (2004) Differences in HPRT mutant frequency among middle-aged Flemish women in association with area of residence and blood lead levels. Biomarkers 9: 71-84.

Vander, A. J. (1988) Chronic effects of lead on the renin-angiotensin system. In: Victery, W., ed. Symposium on lead-blood pressure relationships; April 1987; Chapel Hill, NC. Environ. Health Perspect. 78: 77-83.

Vander, A. J.; Taylor, D. L.; Kalitis, K.; Mouw, D. R.; Victery, W. (1977) Renal handling of lead in dogs: clearance studies. Am. J. Physiol. 2: F532-F538.

Varnai, V. M.; Piasek, M.; Blanusa, M.; Juresa, D.; Saric, M.; Kostial, K. (2003) Ascorbic acid supplementation does not improve efficacy of meso-dimercaptosuccinic acid treatment in lead-exposed suckling rats. Pharmacol. Toxicol. (Oxford, UK) 93: 180-185.

Varnai, V. M.; Piasek, M.; Blanusa, M.; Saric, M. M.; Kostial, K. (2001) Succimer treatment during ongoing lead exposure reduces tissue lead in suckling rats. J. Appl. Toxicol. 21: 415-416.

Vaziri, N.; Ding, Y. (2001) Effect of lead on nitric oxide synthase expression in coronary endothelial cells: role of superoxide. Hypertension 37: 223-226.

Vaziri, N. D.; Wang, X. Q. (1999) cGMP-mediated negative-feedback regulation of endothelial nitric oxide synthase expression by nitric oxide. Hypertension 34: 1237-1241.

Vaziri, N. D.; Ding, Y.; Ni, Z.; Gonick, H. C. (1997) Altered nitric oxide metabolism and increased oxygen free radical activity in lead-induced hypertension: effect of lazaroid therapy. Kidney Int. 52: 1042-1046.

Vaziri, N. D.; Ding, Y.; Ni, Z. (1999a) Nitric oxide synthase expression in the course of lead-induced hypertension. Hypertension 34: 558-562.

Vaziri, N. D.; Liang, K.; Ding, Y. (1999b) Increased nitric oxide inactivation by reactive oxygen species in lead-induced hypertension. Kidney Int. 56: 1492-1498.

Vaziri, N. D.; Wang, X. Q.; Oveisi, F.; Rad, B. (2000) Induction of oxidative stress by glutathione depletion causes severe hypertension in normal rats. Hypertension 36: 142-146.

Vaziri, N. D.; Ding, Y.; Ni, Z. (2001) Compensatory up-regulation of nitric-oxide synthase isoforms in lead-induced hypertension; reversal by a superoxide dismutase-mimetic drug. J. Pharmacol. Exp. Ther. 298: 679-685.

Vaziri, N. D.; Lin, C.-Y.; Farmand, F.; Sindhu, R. K. (2003) Superoxide dismutase, catalase, glutathione peroxidase and NADPH oxidase in lead-induced hypertension. Kidney Int. 63: 186-194.

Vaziri, N. D.; Ding, Y.; Ni, Z.; Barton, C. H. (2005) Bradykinin down-regulates, whereas arginine analogs up-regulates, endothelial nitric-oxide synthase expression in coronary endothelial cells. J. Pharmacol. Exp. Ther. 313: 121-126.

Vermande-van Eck, G. J.; Meigs, J. W. (1960) Changes in the ovary of the rhesus monkey after chronic lead intoxication. Fertil. Steril. 11: 223-234.

Vicente, A.; Varas, A.; Acedon, R. S.; Jimenez, E.; Munoz, J. J.; Zapata, A. G. (1998) Appearance and maturation of T-cell subsets during rat thymus development. Dev. Comp. Immunol. 5: 319-331.

Victery, W.; Vander, A. J.; Mouw, D. R. (1979a) Effect of acid-base status on renal excretion and accumulation of lead in dogs and rats. Am. J. Physiol. 237: F398-F407.

Victery, W.; Vander, A. J.; Mouw, D. R. (1979b) Renal handling of lead in dogs: stop-flow analysis. Am. J. Physiol. 237: F408-F414.

Victery, W.; Soifer, N. E.; Weiss, J. S.; Vander, A. J. (1981) Acute effects of lead on the renal handling of zinc in dogs. Toxicol. Appl. Pharmacol. 61: 358-367.

Victery, W.; Vander, A. J.; Markel, H.; Katzman, L.; Shulak, J. M.; Germain, C. (1982a) Lead exposure, begun in utero, decreases renin and angiotensin II in adult rats. Proc. Soc. Exp. Biol. Med. 170: 63-67.

Victery, W.; Vander, A. J.; Shulak, J. M.; Schoeps, P.; Julius, S. (1982b) Lead, hypertension, and the renin-angiotensin system in rats. J. Lab. Clin. Med. 99: 354-362.

Victery, W.; Vander, A. J.; Schoeps, P.; Germain, C. (1983) Plasma renin is increased in young rats exposed to lead in utero and during nursing. Proc. Soc. Exp. Biol. Med. 172: 1-7.

Vij, A. G.; Satija, N. K.; Flora, S. J. (1998) Lead induced disorders in hematopoietic and drug metabolizing enzyme system and their protection by ascorbic acid supplementation. Biomed. Environ. Sci. 11: 7-14.

Villagra, R.; Tchernitchin, N. N.; Tchernitchin, A. N. (1997) Effect of subacute exposure to lead and estrogen on immature pre-weaning rat leukocytes. Bull. Environ. Contam. Toxicol. 58: 190-197.

Vyskocil, A.; Fiala, Z.; Salandova, J.; Popler, A.; Ettlerova, E.; Emminger, S. (1991) The urinary excretion of specific proteins in workers exposed to lead. Arch. Toxicol. Suppl. 14: 218-221.

Waalkes, M. P.; Liu, J.; Goyer, R. A.; Diwan, B. A. (2004) Metallothionein-I/II double knockout mice are hypersensitive to lead-induced kidney carcinogenesis: role of inclusion body formation. Cancer Res. 64: 7766-7772.

Wagerova, M.; Wagner, V.; Madlo, Z.; Zavazal, V.; Wokounva, D.; Kriz, J.; Mohyla, O. (1986) Seasonal variation in the levels of immunoglobulins and serum proteins of children differing by exposure to air-borne lead. J. Hyg. Epidem. Microbiol. 30: 127-139.

Walkowiak, J.; Altmann, L.; Kramer, U.; Sveinsson, K.; Turfeld, M.; Weishoff-Houben, M.; Winneke, G. (1998) Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. Neurotoxicol. Teratol. 20: 511-521.

Wang, J.; Huff, A. M.; Spence, J. D.; Hegele, R. A. (2004) Single nucleotide polymorphism in CTH associated with variation in plasma homocysteine concentration. Clin. Genet. 65: 483-486.

Wapnir, R. A.; Moak, S. A.; Lifshitz, F.; Teichberg, S. (1979) Alterations of intestinal and renal functions in rats after intraperitoneal injections of lead acetate. J. Lab. Clin. Med. 94: 144-151.

Wasserman, G. A.; Musabegovic, A.; Liu, X.; Kline, J.; Factor-Litvak, P.; Graziano, J. H. (2000) Lead exposure and motor functioning in 4 1/2-year-old children: the Yugoslavia prospective study. J. Pediatr. 137: 555-561.

Waterman, S. J.; El-Fawal, H. A. N.; Snyder, C. A. (1994) Lead alters the immunogenicity of two neural proteins: A potential mechanism for the progression of lead-induced neurotoxicity. Environ. Health Perspect. 102: 1052-1056.

Watson, G. E.; Davis, B. A.; Raubertas, R. F.; Pearson, S. K.; Bowen, W. H. (1997) Influence of maternal lead ingestion on caries in rat pups. Nature Med. 3: 1024-1025.

Watts, S. W.; Chai, S.; Webb, R. C. (1995) Lead acetate-induced contraction in rabbit mesenteric artery: interaction with calcium and protein kinase C. Toxicology 99: 55-65.

Webb, R. C.; Winquist, R. J.; Victery, W.; Vander, A. J. (1981) In vivo and in vitro effects of lead on vascular reactivity in rats. Am. J. Physiol. 241: H211-H216.

Weiler, E.; Khalil-Manesh, F.; Gonick, H. C. (1990) Effects of lead and a low-molecular-weight endogenous plasma inhibitor on the kinetics of sodium - potassium-activated adenosine triphosphatase and potassium-activated para-nitrophenylphosphatase. Clin. Sci. 79: 185-192.

Weisberg, I. S.; Park, E.; Ballman, K. V.; Berger, P.; Nunn, M.; Suh, D. S.; Breksa, A. P., III; Garrow, T. A.; Rozen, R. (2003) Investigation of a common genetic variant in betaine-homocysteine methyltransferase (BHMT) in coronary artery disease. Atherosclerosis 167: 205-214.

Weiss, B.; Landrigan, P. J. (2000) The developing brain and the environment: an introduction. Environ. Health Perspect. 108(Suppl. 3): 373-374.

Weisskopf, M. G.; Wright, R. O.; Schwartz, J.; Spiro, A., III; Sparrow, D.; Aro, A.; Hu, H. (2004) Cumulative lead exposure and prospective change in cognition among elderly men. The VA Normative Aging Study. Am. J. Epidemiol. 160: 1184-1193.

Weller, C. V. (1915) The blastophthoric effect of chronic lead poisoning. J. Med. Res. 33: 271-293.

Westerink, R. H.; Vijverberg, H. P. (2002) Ca2+-independent vesicular catecholamine release in PC12 cells by nanomolar concentrations of Pb2+. J. Neurochem. 80: 861-867.

Wetmur, J. G. (1994) Influence of the common human delta-aminolevulinate dehydratase polymorphism on lead body burden. Environ. Health Perspect. 102(suppl. 3): 215-219.

Wetmur, J. G.; Lehnert, G.; Desnick, R. J. (1991) The δ-aminolevulinate dehydratase polymorphism: higher blood lead levels in lead workers and environmentally exposed children with the 1-2 and 2-2 isozymes. Environ. Res. 56: 109-119.

White, R. F.; Diamond, R.; Proctor, S.; Morey, C.; Hu, H. (1993) Residual cognitive deficits 50 years after lead poisoning during childhood. Br. J. Ind. Med. 50: 613-622.

Wicklund, K. G.; Daling, J. R.; Allard, J.; Weiss, N. S. (1988) Respiratory cancer among orchardists in Washington State, 1968-1980. J. Occup. Med. 30: 561-564.

Wide, M. (1985) Lead exposure on critical days of fetal life affects fertility in the female mouse. Teratology 32: 375-380.

Wide, M.; D'Argy, R. (1986) Effect of inorganic lead on the primordial germ cells in the mouse embryo. Teratology 34: 207-212.

Wide, M.; Nilsson, O. (1977) Differential susceptibility of the embryo to inorganic lead during periimplantation in the mouse. Teratology 16: 273-276.

Wide, M.; Nilsson, B. O. (1979) Interference of lead with implantation in the mouse: a study of the surface ultrastructure of blastocysts and endometrium. Teratology 20: 101-113.

Wiebe, J. P.; Barr, K. J. (1988) Effect of prenatal and neonatal exposure to lead on the affinity and number of estradiol receptors in the uterus. J. Toxicol. Environ. Health 24: 451-460.

Wiebe, J. P.; Barr, K. J.; Buckingham, K. D. (1988) Effect of prenatal and neonatal exposure to lead on gonadotropin receptors and steroidogenesis in rat ovaries. J. Toxicol. Environ. Health 24: 461-476.

Wiemann, M.; Schirrmacher, K.; Busselberg, D. (1999) Interference of lead with the calcium release activated calcium flux of osteoblast-like cells. Calcif. Tissue Int. 65: 479-485.

Winneke, G.; Kramer, U. (1997) Neurobehavioral aspects of lead neurotoxicity in children. Cent. Eur. J. Public Health 5: 65-69.

Wise, J. P.; Leonard, J. C.; Patierno, S. R. (1992) Clastogenicity of lead chromate particles in hamster and human cells. Mutat. Res. 278: 69-79.

Wise, J. P.; Orenstein, J. M.; Patierno, S. R. (1993) Inhibition of lead chromate clastogenesis by ascorbate: relationship to particle dissolution and uptake. Carcinogenesis (London) 14: 429-434.

Wise, J. P., Sr.; Stearns, D. M.; Wetterhahn, K. E.; Patierno, S. R. (1994) Cell-enhanced dissolution of carcinogenic lead chromate particles: the role of individual dissolution products in clastogenesis. Carcinogenesis 15: 2249-2254.

Wise, S. S.; Schuler, J. H.; Holmes, A. L.; Katsifis, S. P.; Ketterer, M. E.; Hartsock, W. J.; Zheng, T.; Wise, J. P., Sr. (2004a) Comparison of two particulate hexavalent chromium compounds: Barium chromate is more genotoxic than lead chromate in human lung cells. Environ. Mol. Mutagen. 44: 156-162.

Wise S. S.; Holmes A. L.; Ketterer, M. E.; Hartsock, W. J.; Fomchenko, E.; Katsifis, S.; Thompson, W. D.; Wise, J. P. Sr. (2004b) Chromium is the proximate clastogenic species for lead chromate-induced clastogenicity in human bronchial cells. Mutat. Res. 560: 79-89.

Wise, S. S.; Holmes, A. L.; Moreland, J. A.; Xie, H .; Sandwick, S. J.; Stackpole, M. M.; Fomchenko, E.; Teufack, S.; May, A. J., Jr.; Katsfis, S. P.; Wise, J. P., Sr. (2005) Human lung cell growth is not stimulated by lead ions after lead chromate-induced genotoxicity. Mol. Cell. Biochem. 279: 75-84.

Wisotzky, J.; Hein, J. W. (1958) Effects of drinking solutions containing metallic ions above and below hydrogen in the electromotive series on dental caries in the Syrian hamster. J. Am. Dent. Assoc. 57: 796-800.

Witzmann, F. A.; Daggett, D. A.; Fultz, C. D.; Nelson, S. A.; Wright, L. S.; Kornguth, S. E.; Siegel, F. L. (1998) Glutathione S-transferases: two-dimensional electrophoretic protein markers of lead exposure. Electrophoresis 19: 1332-1335.

Wolf, A. W.; Jimenez, E.; Lozoff, B. (2003) Effects of iron therapy on infant blood lead levels. J. Pediatr. 143: 789-795.

Wolin, M. S. (2000) Interactions of oxidants with vascular signaling systems. Arterioscler. Thromb. Vasc. Biol. 20: 1430-1442.

Wood, N.; Bourque, K.; Donaldson, D. D.; Collins, M.; Vercelli, D.; Goldman, S. J.; Kasaian, M. T. (2004) IL-21 effects on human IgE production in response to IL-4 or IL-13. Cell. Immunol. 231: 133-145.

Wozniak, K.; Blasiak, J. (2003) In vitro genotoxicity of lead acetate: induction of single and double DNA strand breaks and DNA-protein cross-links. Mutat. Res. 535: 127-139.

Wright, R. O.; Shannon, M. W.; Wright, R. J.; Hu, H. (1999) Association between iron deficiency and low-level lead poisoning in an urban primary care clinic. Am. J. Public Health 89: 1049-1053.

Wright, R. O.; Silverman, E. K.; Schwartz, J.; Tsaih, S.-W.; Senter, J.; Sparrow, D.; Weiss, S. T.; Aro, A.; Hu, H. (2004) Association between hemochromatosis genotype and lead exposure among elderly men: the Normative Aging Study. Environ. Health Perspect. 112: 746-750.

Wu, T.; Buck, G. M.; Mendola, P. (2003) Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988-1994. Environ. Health Perspect. 111: 737-741.

Wu, W.; Rinaldi, L.; Fortner, K. A.; Russell, J. Q.; Tschoop, J.; Irvin, C.; Budd, R. C. (2004) Cellular FLIP long-transgenic mice manifest a Th2 cytokine bias and enhanced allergic airway inflammation. J. Immunol. 172: 4724-4732.

Xie, Y.; Chiba, M.; Shinohara, A.; Watanabe, H.; Inaba, Y. (1998) Studies on lead-binding protein and interaction between lead and selenium in the human erythrocytes. Ind. Health 36: 234-239.

Xie, L.; Gao, Q.; Xu, H. (2003) Ameliorative effect of L-methionine on Pb-exposed mice. Biol. Trace Elem. Res. 93: 227-236.

Xie, H.; Wise, S. S.; Holmes, A. L.; Xu, B, Wakeman, T. P.; Pelsue, S. C.; Singh, N. P.; Wise, J. P., Sr. (2005) Carcinogenic lead chromate induces DNA double-strand breaks in human lung cells. Mutat. Res. 586: 160-172.

Xu, D. X.; Shen, H. M.; Zhu, Q. X.; Chua, L.;, Wang, Q. N.; Chia, S. E.; Ong, C. N. (2003) The associations among semen quality, oxidative DNA damage in human spermatozoa and concentrations of cadmium, lead and selenium in seminal plasma. Mutat. Res. 534: 155-163.

Xupei et al., 1988.

Yamamoto, C.; Miyamoto, A.; Sakamoto, M.; Kaji, T.; Kozuka, H. (1997) Lead perturbs the regulation of spontaneous release of tissue plasminogen activator and plasminogen activator inhibitor-1 from vascular smooth muscle cells and fibroblasts in culture. Toxicology 117: 153-161.

Yanez, L.; Garcia-Nieto, E.; Rojas, E.; Carrizales, L.; Mejia, J.; Calderon, J.; Razo, I.; Diaz-Barriga, F. (2003) DNA damage in blood cells from children exposed to arsenic and lead in a mining area. Environ. Res. 93: 231-240.

Ye, S.-H. (1993) Hypoxanthine phosphoribosyl transferase assay of lead mutagenicity on keratinocytes. Zhongguo Yaoli Xuebao 14: 145-147.

Youssef, S. A. H. (1996) Effect of subclinical lead toxicity on the immune response of chickens to Newcastle's disease virus vaccine. Res. Vet. Sci. 60: 13-16.

Yu, S. Y.; Mizinga, K. M.; Nonavinakere, V. K.; Soliman, K. F. (1996) Decreased endurance to cold water swimming and delayed sexual maturity in the rat following neonatal lead exposure. Toxicol. Lett. 85: 135-141.

Yucesoy, B.; Turhan, A.; Ure, M.; Imir, T.; Karakaya, A. (1997) Simultaneous effects of lead and cadmium on NK cell activity and some phenotypic parameters. Immunopharmacol. Immunotoxicol. 19: 339-348.

Zareba, G.; Chmielnicka, J. (1992) Disturbances in heme biosynthesis in rabbits after administration per os of low doses of tin or lead. Biol. Trace Elem. Res. 34: 115-122.

Zelikoff, J. T.; Li, J. H.; Hartwig, A.; Wang, X. W.; Costa, M.; Rossman, T. G. (1988) Genetic toxicology of lead compounds. Carcinogenesis 9: 1727-1732.

Zelikoff, J. T.; Parsons, E.; Schlesinger, R. B. (1993) Inhalation of particulate lead oxide disrupts pulmonary macrophage-mediated functions important for host defense and tumor surveillance in the lung. Environ. Res. 62: 207-222.

Zhao, W.-F.; Ruan, D.-Y.; Xy, Y.-Z.; Chen, J.-T.; Wang, M.; Ge, S.-Y. (1999) The effects of chronic lead exposure on long-term depression in area CA1 and dentate gyrus of rat hippocampus in vitro. Brain Res. 818: 153-159.

Zhou, X. J.; Vaziri, N. D.; Wang, X. Q.; Silva, F. G.; Laszik, Z. (2002) Nitric oxide synthase expression in hypertension induced by inhibition of glutathione synthase. J. Pharmacol. Exp. Ther. 300: 762-767.

Zierold, K. M.; Anderson, H. (2004) Trends in blood lead levels among children enrolled in the Special Supplemental Nutrition Program for Women, Infants and Children from 1996 to 2000. Am. J. Public Health 94: 1513-1515.

Zimmermann, L.; Pages, N.; Antebi, H.; Hafi, A.; Boudene, C.; Alcindor, L. G. (1993) Lead effect on the oxidation resistance of erythrocyte membrane in rat triton-induced hyperlipidemia. Biol. Trace Elem. Res. 38: 311-318.

Zmuda, J. M.; Cauley, J. A.; Ferrell, R. E. (2000) Molecular epidemiology of vitamin D receptor gene variants. Epidemiol. Rev. 22: 203-217.

Zuscik, M. J.; Pateder, D. B.; Puzas, J. E.; Schwarz, E. M.; Rosier, R. N.; O'Keefe, R. J. (2002) Lead alters parathyroid hormone-related peptide and transforming growth factor-"beta"1 effects and AP-1 and NF-"kappa"B signaling in chondrocytes. J. Orthop. Res. 20: 811-818.

6. EPIDEMIOLOGIC STUDIES OF HUMAN HEALTH EFFECTS ASSOCIATED WITH LEAD EXPOSURE

6.1 INTRODUCTION

This chapter assesses information regarding the biological effects of lead exposure, with emphasis on (1) qualitative characterization of lead-induced effects and (2) delineation of concentration-response relationships for key health effects of most concern. Epidemiologic studies linking lead exposure to health effects were assessed in the 1986 Air Quality Criteria for Lead (U.S. Environmental Protection Agency, 1986a), an associated addendum (U.S. Environmental Protection Agency, 1986b), and a 1990 Supplement (U.S. Environmental Protection Agency, 1990). Many earlier studies reported lead effects on child development (psychometric intelligence), blood pressure and related cardiovascular endpoints, heme biosynthesis, kidney, and reproduction and development. Numerous more recent epidemiologic studies discussed in this chapter have further evaluated these relationships to lead exposure, thereby providing an expanded basis for assessment of health effects associated with exposure to lead at concentrations currently encountered by the general U.S. population.

Special emphasis is placed here on discussion of the effects of lead exposure in children. Children are particularly at risk due to sources of exposure, mode of entry, rate of absorption and retention, and partitioning of lead in soft and hard tissues. The greater sensitivity of children to lead toxicity, their inability to recognize symptoms, and their dependence on parents and healthcare professionals make them an especially vulnerable population requiring special consideration in developing criteria and standards for lead.

As discussed elsewhere in this document (Chapter 5), extensive experimental evidence links lead exposure with health effects in laboratory animals. Thus, many of the reported epidemiologic associations of lead health effects have considerable biological credibility. Accordingly, the new epidemiologic studies of lead assessed here are best considered in combination with information from the other chapters on lead exposure and on toxicological effects of lead in animals. The epidemiologic studies constitute important information on associations between health effects and exposures of human populations to “real world” lead concentrations and also help to identify susceptible subgroups and associated risk factors.

6.1.1 Approach to Identifying Lead Epidemiologic Studies

Numerous lead epidemiologic papers have been published since completion of the 1986 Lead AQCD/Addendum, and 1990 Supplement. A systematic approach has been employed to identify relevant new epidemiologic studies for consideration in this chapter. In general, an ongoing literature search has been used in conjunction with other strategies to identify lead epidemiologic literature pertinent to developing criteria for the National Ambient Air Quality Standards (NAAQS) for lead. A publication base was established using Medline, Pascal, BIOSIS, and Embase, and a set of search terms aimed at identifying pertinent literature.

While the above search regime accessed much of the pertinent literature, additional approaches augmented such traditional search methods. For example, a Federal Register Notice was issued requesting information and published papers from the public at large. Also, non-EPA chapter authors, expert in this field, identified literature on their own, and EPA staff also identified publications as part of their assessment and interpretation of the literature. Lastly, additional potentially relevant publications are expected to be identified and included as a result of external review of this draft document by the public and CASAC. The principal criteria used for selecting literature for the present assessment is to focus mainly on those identified studies that evaluate relationships between health outcome and lead exposure at concentrations in the range of those currently encountered in the United States. New studies published or accepted for publication through June 2005, as identified using the approaches above, have been included in this draft lead air quality criteria document (Lead AQCD), and additional efforts are being made to identify and assess more recent studies.

6.1.2 Approach to Assessing Epidemiologic Evidence

Epidemiologic studies have evaluated lead effects on a wide range of health endpoints that include, but are not limited to: neurotoxic effects (e.g., psychometric intelligence, behavioral disturbances, and neurodevelopmental deficits), renal effects, cardiovascular effects, reproductive and developmental effects, genotoxic and carcinogenic effects, and immune effects. The epidemiologic strategies most commonly used in lead health studies are: (1) cross-sectional studies that examine the exposure and health outcome at a single point in time; and (2) prospective longitudinal cohort studies that follow a group of individuals over time. Both of these are types of observational rather than experimental studies.

An overall approach useful for assessing epidemiologic evidence was stated in the 2004 PM AQCD (U.S. Environmental Protection Agency, 2004), as summarized here. That is, the critical assessment of epidemiologic evidence presented in this chapter is conceptually based upon consideration of salient aspects of the evidence of associations so as to reach fundamental judgments as to the likely causal significance of the observed associations (see Hill, 1965). The general evaluation of the strength of the epidemiologic evidence reflects consideration not only of the magnitude and precision of reported lead effect estimates and their statistical significance, but also of the robustness of the effects associations. Statistical significance corresponds to the allowable rate of error (Type I error) in the decision framework constructed from assuming that a simple null hypothesis of no association is true. It is a conditional probability; for statistical significance, typically there is a less than 0.05 chance of rejecting the null hypothesis given that it is true. Robustness of the associations is defined as stability in the effect estimates after considering a number of factors, including alternative models and model specifications, potential confounding by copollutants, as well as issues related to the consequences of measurement error.

Consideration of the consistency of the effects associations, as discussed in the following sections, involves looking across the results obtained by various investigators in different locations and times. Relevant factors are known to exhibit much variation across studies, e.g., (1) presence and levels of other toxicants or pollutants of concern and (2) relevant demographic factors related to sensitive subpopulations. Thus, consideration of consistency is appropriately understood as an evaluation of the similarity or general concordance of results, rather than an expectation of finding quantitative results within a very narrow range.

Looking beyond the epidemiologic evidence, evaluation of the biological plausibility of the lead-health effects associations observed in epidemiologic studies reflects consideration of both exposure-related factors and dosimetric/toxicologic evidence relevant to identification of potential biological mechanisms underlying the various health outcomes. These broader aspects of the assessment are only touched upon in this chapter but will be more fully integrated in discussions presented in Chapter 7 (Integrative Synthesis).

In assessing the relative scientific quality of epidemiologic studies reviewed here and to assist in interpreting their findings, the following considerations were taken into account:

(1) To what extent are the biological markers used of adequate quality and sufficiently representative to serve as credible exposure indicators, well-reflecting geographic or temporal differences in study population exposures?

(2) Were the study populations well defined and adequately selected so as to allow for meaningful comparisons between study groups or meaningful temporal analyses of health effects results?

(3) Were the health endpoint measurements meaningful and reliable, including clear definition of diagnostic criteria utilized and consistency in obtaining dependent variable measurements?

(4) Were the statistical analyses used appropriate, as well as being properly performed and interpreted?

(5) Were likely important covariates (e.g., potential confounders or effect modifiers) adequately controlled for or taken into account in the study design and statistical analyses?

(6) Were the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

These guidelines provide benchmarks for judging the relative quality of various studies and in assessing the body of epidemiologic evidence. Detailed critical analysis of all epidemiologic studies on lead health effects, especially in relation to all of the above questions, is beyond the scope of this document.

6.1.3 Considerations in the Interpretation of Epidemiologic Studies of Lead Health Effects

Prior to assessing results from recent lead epidemiologic studies, issues and questions arising from study designs and analysis methods used in the evaluation of lead health effects are briefly discussed. Study design can restrict the health effect parameters that can be estimated. Separate considerations need to be made for acute versus chronic effect studies, as well as individual versus aggregate-level analyses. Issues include measurement error, the functional form of relationships (especially at low exposure levels) and the potential for confounding. Aspects of these issues are briefly noted below, then are considered as various studies are reviewed in the following sections on specific health effect endpoints. Finally, they are further examined as part of the interpretive assessment(Section 6.9) at the end of this chapter.

Measurement error is an important factor to consider, both for measurement of the health effect outcome and the representativeness of the biomarkers of exposure (principally blood and bone lead) used in most key epidemiologic studies. For health outcome measures, the reliability and validity of the measurement need to be assessed. In addition, the appropriateness of the outcome measure for studying the hypothesis of interest needs to be determined. The critical issues of outcome measurement and classification are, to some extent, endpoint-specific, and will thusly be discussed further in the individual sections.

Exposure misclassification can result in a notable reduction of statistical power in studies, especially in those that focus on the lower end of the exposure range. Limitations of blood lead as an exposure index include the use of a single blood lead concentration to represent lead body burden. Also of concern is the most relevant blood sample collection time point for to use in evaluating possible associations with health outcomes (e.g., at 2 years of age when peak lead exposure is expected versus concurrent blood lead samples). Another consideration is that similar blood lead concentrations in two individuals do not necessarily reflect similar body burdens. An added complication is that the relationship between lead intake and blood lead concentration appears to be curvilinear. Bone lead determinations are typically considered a measure of longer-term lead exposure; but, the X-ray fluorescence (XRF) method typically used to assess lead levels in bone also has limitations, including the relatively high minimum detection limit. The type of bone measured to determine lead exposure is another important aspect.

The relationship between a measurement of a health outcome endpoint and an estimate of lead exposure based on a biomarker is an important concept. Modeling this relationship provides a numerical slope that quantifies the relationship between lead exposure and health outcome. These models must address differences in the relationship at different concentration ranges of exposure and present the functional form that best describes such data. Various models, both linear and nonlinear, have been considered to examine lead exposure-health effect relationships. This is especially important at low lead exposures. For example, a curvilinear relationship has been reported for neurodevelopmental and cardiovascular outcomes at low lead exposure levels.

Depending on the subjects being examined for lead exposure effects, various other factors can lead to confounding of the relationship being considered. Potential confounding factors largely depend on the health outcome of interest and the study population. Some potential

confounding factors in children, for whom the major health concerns include neurological and developmental deficiencies, include: socioeconomic status (SES); nutritional status; quality of home environment (e.g., HOME score); parental education; parental IQ; and birth weight, as a few examples. For adults, factors that may confound the association between lead and cardiovascular health outcomes include: age; diet; alcohol use; smoking; and potential for copollutant exposures, such as cadmium. Control for potential confounding factors can be attempted at the study design phase and/or during statistical analysis.

6.1.4 Approach to Presenting Lead Epidemiologic Evidence

In the main body of this chapter, each section starts by concisely highlighting important points derived from the 1986 Lead AQCD/Addendum, and the 1990 Supplement. Particular emphasis is focused on studies and analyses that provide pertinent information for the critical assessment of health risks from lead exposure. Not all studies are accorded equal weight in the overall interpretive assessment of evidence regarding lead-associated health effects. Among well-conducted studies with adequate control for confounding, increasing scientific weight is accorded in proportion to the precision of their effect estimates. To ensure a thorough appraisal of the evidence, more detailed information on key features (including study design, analysis, lead biomarkers of exposure, and health outcome results) of important new studies are summarized in tables in the Annex for this Chapter 6 (Annex AX6).

Emphasis is placed on main body text discussion below of (1) new studies employing standardized methodological analyses for evaluating lead effects across several cities and providing overall effect estimates based on combined analyses of information pooled across multiple cities; (2) studies conducted in the U.S. or Canada; and (3) meta-analyses of individual studies conducted in various cities. Multicity studies are of particular interest and value due to their evaluation of a wider range of lead exposures and large numbers of observations, thus generally providing more precise effect estimates than most smaller scale studies of single cities. Furthermore, multicity studies have the potential to provide especially valuable evidence regarding relative homogeneity and/or heterogeneity of lead health effects relationships across geographic locations. The potential impacts of the underlying health status of populations and cultural differences in the case of intelligence testing (one of the major health outcomes in children) also need to be accounted for in the assessment; thus, U.S. studies are emphasized over

non-U.S. studies. In accordance with the emphasis placed on the lead epidemiologic studies in this chapter, Chapter 6 Annex tables are organized by region, with multicity studies in each region presented first.

In the ensuing sections, epidemiological studies of biological markers of lead exposure are discussed first, in Section 6.2. The neurotoxic effects of lead are next discussed in Section 6.3 for children and adults, followed by discussion of the renal and cardiovascular effects of lead in Sections 6.4 and 6.5. Section 6.6 then discusses reproductive and developmental effects of lead, and Section 6.7 discusses genotoxic and carcinogenic effects of lead. Section 6.8 discusses the effects of lead on the immune system. The effects of lead on other organ systems (including the hematopoietic, endocrine, hepatic, gastrointestinal, and respiratory systems) are assessed in Section 6.9. Effects of lead on bone and teeth, as well as on ocular health are also discussed in Section 6.9. Finally, Section 6.10 provides an interpretative assessment of the overall epidemiologic evidence for lead health effects.

6.2 BIOLOGICAL MARKERS OF LEAD BODY BURDEN AND EXPOSURE

6.2.1 Lead in Blood

6.2.1.1 Summary of Key Findings from the 1986 Lead AQCD

The extensive use of blood lead concentration as a dose metric reflects mainly the greater feasibility of incorporating blood lead measurements into clinical or epidemiologic studies, compared to other potential dose indicators, such as lead in kidney, plasma, urine, or bone (Flegal and Smith, 1995; Graziano, 1994; Skerfving, 1988). However, blood lead measurements have several limitations as measures of lead body burden and exposure that relate to the kinetics of blood lead in relation to exposure and body burden. These limitations were noted in Section 13.3.2 of the 1986 Lead AQCD, which discusses attributes and limitations of blood lead concentration as an indicator of internal exposure. Relevant developments since the 1986 Lead AQCD was completed include numerous studies of determinants of lead levels in bone (see Section 6.2.2), which provide further support for the importance of this relatively slow kinetic compartment in assessing the blood lead concentration as an index of lead exposure. The enhanced understanding of lead biokinetics has also been consolidated into exposure-biokinetics

models (see Chapter 4), which not only serve to illustrate exposure-blood-body burden relationships, but also provide a means for making predictions about these relationships that can be tested experimentally or in epidemiologic studies. The basic concepts laid out in the 1986 Lead AQCD, that the concentration of lead in blood is largely determined by the relatively recent exposure history of the individual and that it reflects the level of lead in a relatively mobile and small compartment, remain valid. Especially in children, who experience a more rapid turnover of bone mineral, an endogenous source of lead, blood lead concentrations closely parallel changes in total body burden.

6.2.1.2 Analytical Methods for Measuring Lead in Blood

Analytical methods for measuring lead in blood include flame atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS), anode stripping voltammetry (ASV), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and inductively coupled plasma-mass spectrometry (ICP-MS). GFAAS and ASV are generally considered to be the methods of choice (Flegal and Smith, 1995). Background correction, such as Zeeman background correction that minimizes the impact of the absorbance of molecular species, must be applied. Limits of detection for lead using AAS are on the order of 5-10 μg/dL for flame AAS measurements, approximately 0.1 μg/dL for flameless AAS measurements, and 0.005 μg/dL for GFAAS (Flegal and Smith, 1995; National Institute for Occupational Safety and Health, 1994). A summary of standard methods that have been reported for blood lead analysis are provided in Annex Table AX6-2.1. Sample preparation usually consists of wet ashing in heated strong acid (National Institute for Occupational Safety and Health, 1977a,b,c,d,e); however, preparation methods not requiring wet ashing have also been reported (Aguilera de Benzo et al., 1989; Delves and Campbell, 1988; Manton and Cook, 1984; National Institute for Occupational Safety and Health, 1977f; Que Hee et al., 1985; Zhang et al., 1997). The presence of phosphate, ethylenediaminetetraacetic acid (EDTA), or oxalate can sequester lead and cause low readings in flame AAS (National Institute for Occupational Safety and Health, 1984). A comparison of IDMS, ASV, and GFAAS showed that all three of these methods can be used to quantify lead levels in blood (Que Hee et al., 1985).

6.2.1.3 Levels of Lead in Blood

Blood lead concentrations in the U.S. general population have been monitored in the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention. Data from the most recent survey (NHANES IV, Centers for Disease Control, 2005) are shown in Tables 6-2.1 and 6-2.2. For survey years 2001-2002, the geometric mean blood lead concentration for ages >1 year (n = 8,945) was 1.45 μg/dL (95% CI: 1.39, 1.52); with the geometric mean in males (n = 4,339) being 1.78 μg/dL (95% CI: 1.71, 1.86) and in females (n = 4,606) being 1.19 μg/dL (95% CI: 1.14, 1.25). Blood lead concentrations in the U.S. general population have decreased over the past three decades as regulations regarding lead paint, leaded fuels, and lead-containing plumbing materials have decreased exposure. Changes over time in children are shown in Figure 6-2.1.

Yassin et al. (2004) analyzed occupational category strata from NHANES III (1988–1994; Table 6-2.3). The geometric mean for all adults (n = 11,126) included in the analysis was 2.42 μg/dL (GSD 6.93), with the highest means estimated for vehicle mechanics (n = 169; GM 4.80 μg/dL [GSD 3.88]) and construction workers (n = 122; GM 4.44 μg/dL [GSD 7.84]). See Annex Table AX6-2.2 for a summary of selected measurements of blood lead levels in humans.

6.2.1.4 Blood Lead as a Biomarker of Lead Body Burden

A simple conceptual representation of the lead body burden is that it is comprised of a fast turnover pool, comprised mainly of soft tissue, and a slow pool, comprised mainly of skeletal tissues (Rabinowitz et al., 1976; see Chapter 4 for detailed discussion of this and other more complex models of lead biokinetics). The rapid pool has an elimination half-life of ~28 days and comprises <1% of the lead body burden. The slow pool has an elimination half-life of several decades and comprises >90% of the total lead body burden. Blood, which comprises ~1% of body burden, exchanges with both the slow and fast pools, and exhibits multiphasic elimination kinetics. The dominant phase, exhibited shortly after a change in exposure occurs, has a half-life of ~20–30 days. A slower phase becomes evident with longer observation periods following a

Table 6-2.1. Blood Lead Concentrations in U.S. by Age, NHANES IV (1999–2002)

Age	1–5 years		6–11 years		12–19 years		≥20 years	
Survey Period	*1999–2000*	*2001–2002*	*1999–2000*	*2001–2002*	*1999–2000*	*2001–2002*	*1999–2000*	*2001–2002*
N	723	898	909	1,044	2,135	2,231	4,207	4,772
Blood Lead (µg/dL)[a]	2.23 (1.96, 2.53)	1.70 (1.55, 1.87)	1.51 (1.36, 1.66)	1.25 (1.14, 1.36)	1.10 (1.04, 1.17)	0.94 (0.90, 0.99)	1.75 (1.68, 1.81)	1.56 (1.49, 1.62)

[a]Blood lead concentrations presented are geometric means (95% CI).

Table 6-2.2. Blood Lead Concentrations in U.S. by Gender, NHANES IV (1999–2002)

Gender	Males		Females	
Survey Period	1999–2000	2001–2002	1999–2000	2001–2002
n	3,913	4,339	4,057	4,606
Blood Lead (µg/dL)[a]	2.01 (1.93, 2.09)	1.78 (1.71, 1.86)	1.37 (1.32, 1.43)	1.19 (1.14, 1.25)

[a]Blood lead concentrations presented are geometric means (95% CI).

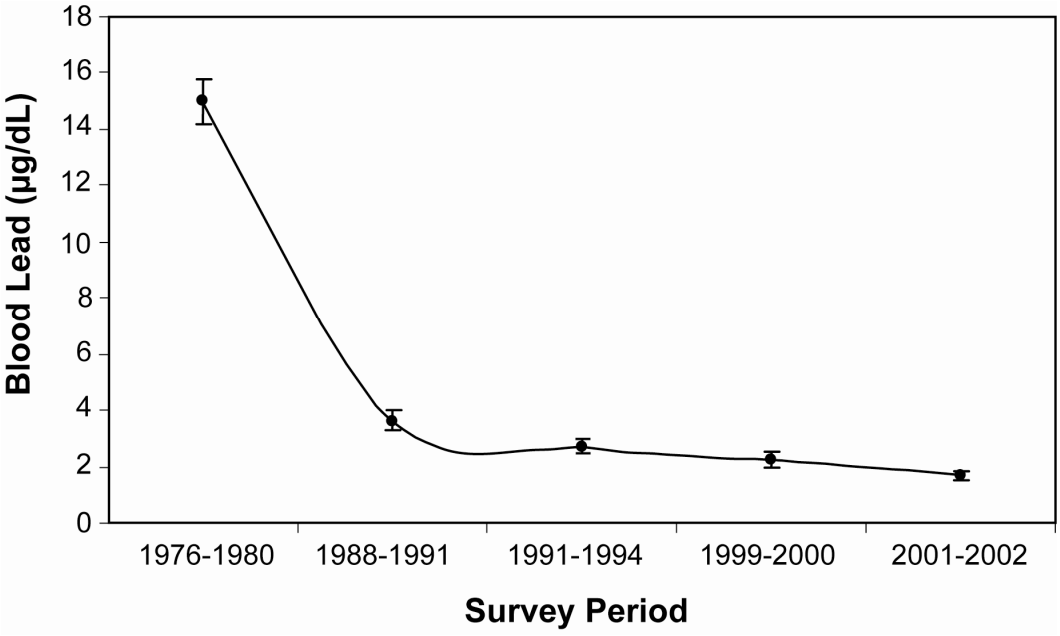


Figure 6-2.1. Blood lead concentrations in U.S. children, 1-5 years of age. Shown are geometric means and 95% confidence intervals as reported from the NHANES II (1976–1980) and NHANES III Phase 1 (1988–1991; Pirkle et al., 1994); NHANES III Phase 2 (1991–1994; Pirkle et al., 1998); and NHANES IV (1999-2000, 2001-2002; Centers for Disease Control, 2005).

decrease in exposure. The half-life of this slow phase has been estimated to be ~3 to 30 years and appears to correlate with finger bone lead levels. This characterization is supported by measurements of lead contents of cadaver tissues (Barry, 1975; Schroeder and Tipton, 1968), lead isotope kinetics in adults (Chamberlain et al., 1978; Rabinowitz et al., 1976; Griffin et al., 1975), and measurements of blood and bone lead levels in retired lead workers (Schütz et al., 1987; Christoffersson et al., 1986).

As a consequence of a relatively large fraction of the body burden having a relatively slow turnover compared to blood, a constant lead uptake (or constant intake and fractional absorption) gives rise to a quasi-steady state blood lead concentration, while the body burden continues to increase, largely as a consequence of retention of lead in bone (Figure 6-2.2). As a result, the contribution of blood lead to body burden decreases over time. An abrupt change in lead uptake gives rise to a relatively rapid change in blood lead, to a new quasi-steady state, achieved in ~75-100 days (i.e., 3-4 times the blood elimination half-life). In the hypothetical simulation shown in Figure 6-2.2, body burden has approximately doubled (from 5 to 10 mg) as a result of a

Table 6-2.3. Blood Lead Concentrations by Occupation, NHANES III (1988-1994)

Occupation	n	Blood Lead (µg/dL)		
		GM	GSD	Maximum
Vehicle mechanics	169	4.80	3.88	28.1
Food service workers	700	2.00	2.69	27.0
Management, professional, technical, and sales workers	4,768	2.13	4.05	39.4
Personal service workers	1,130	2.48	4.52	25.9
Agricultural workers	498	2.76	4.02	23.4
Production workers: machine operators, material movers, etc.	1,876	2.88	4.24	52.9
Laborers other than in construction	137	3.47	3.36	21.8
Transportation workers	530	3.49	5.19	22.3
Mechanics other than vehicle mechanics	227	3.50	4.91	16.6
Construction trades people	470	3.66	4.64	16.9
Construction laborers	122	4.44	7.84	36.0
Health service workers	499	1.76	2.24	22.4
All workers	**11,126**	**2.42**	**6.93**	**52.9**

Data from Yassin et al. (2004).

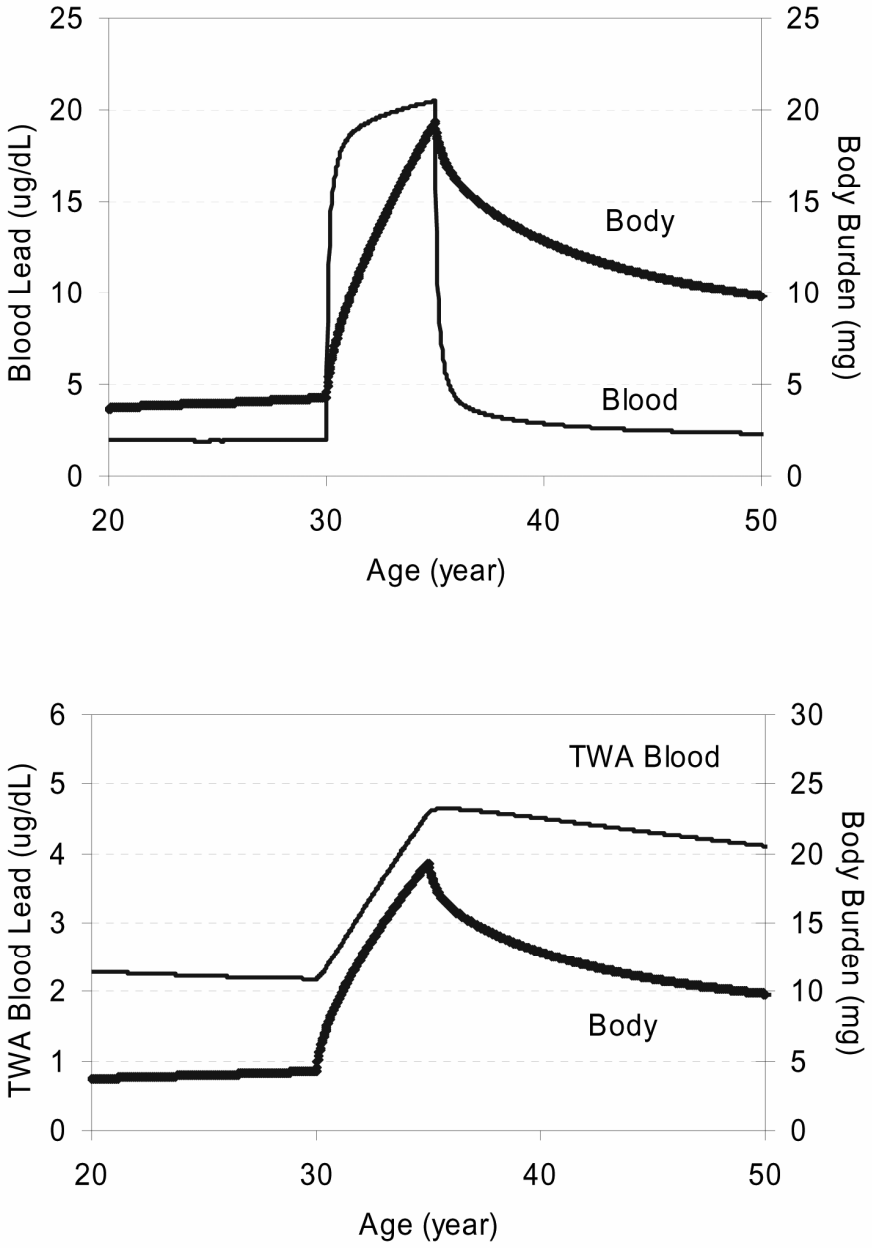


Figure 6-2.2. Simulation of relationship between blood lead concentration and body burden in adults. A constant baseline intake gives rise to a quasi-steady state blood lead concentration, while the body burden continues to increase, largely as a consequence of retention of lead in bone (upper panel). An abrupt change in lead uptake gives rise to a relatively rapid change in blood lead, to a new quasi-steady state, and a relatively small change in body burden. The long-term average blood lead concentration more closely tracks the pattern of change in body burden (lower panel). Simulation based on lead biokinetics model of Leggett (1993) .

5-year period of increased lead uptake; however, the blood lead concentration prior to and 1 year following cessation of the increased uptake has not changed (~2 μg/dL). Therefore, a single blood lead concentration measurement, or a series of measurements taken over a short-time span, can be expected to be a relatively poor index of lead body burden. On the other hand, an average of individual blood lead concentrations measured over a longer period of time (long-term average blood lead concentrations) can be expected to be a better index of body burden. In the hypothetical simulation shown in Figure 6-2.2, both the long-term average blood lead concentration and the body burden have approximately doubled.

The disparity in the kinetics of blood lead and body burden has important implications for the interpretation of blood lead concentration measurements in epidemiology studies. Cross-sectional studies, by design, sample blood lead concentration at one time or over relatively narrow windows of time. In these samples, the blood lead concentration may or may not reflect well the body burden; it is more likely to do so if the measured value is a reflection of the long-term average blood lead concentration. However, in cross-sectional samples, this cannot be ascertained. Longitudinal sampling provides a means for estimating average blood lead concentrations over time, and such estimates are more likely to be more strongly influenced by differences in body burden, than by differences in short-term variability in exposure. The degree to which repeated sampling will reflect the actual long-term time-weighted average blood lead concentration will depend on the sampling frequency in relation to variability in exposure. High frequency variability in exposures can produce episodic (or periodic) oscillations in blood lead concentration and body burden that may not be captured with low sampling frequencies.

The same basic concepts described above regarding lead biokinetics of adults also apply to children. The empirical basis for the understanding of the biokinetics of lead in children is much weaker than that for adults. However, based on the understanding of bone mineral kinetics and its importance as a mechanism for uptake and loss of lead from bone (Leggett, 1993; O'Flaherty, 1991, 1993, 1995), the slow pool, described above for adults, is thought to be much more labile in children, reflecting a more rapid turnover of bone mineral in children. As a result, changes in blood lead concentration in children are thought to more closely parallel changes in total body burden (Figure 6-2.3). Nevertheless, in children, as in adults, the long-term time-weighted average blood lead concentration is more likely to provide a better reflection of lead body burden than a single sample.

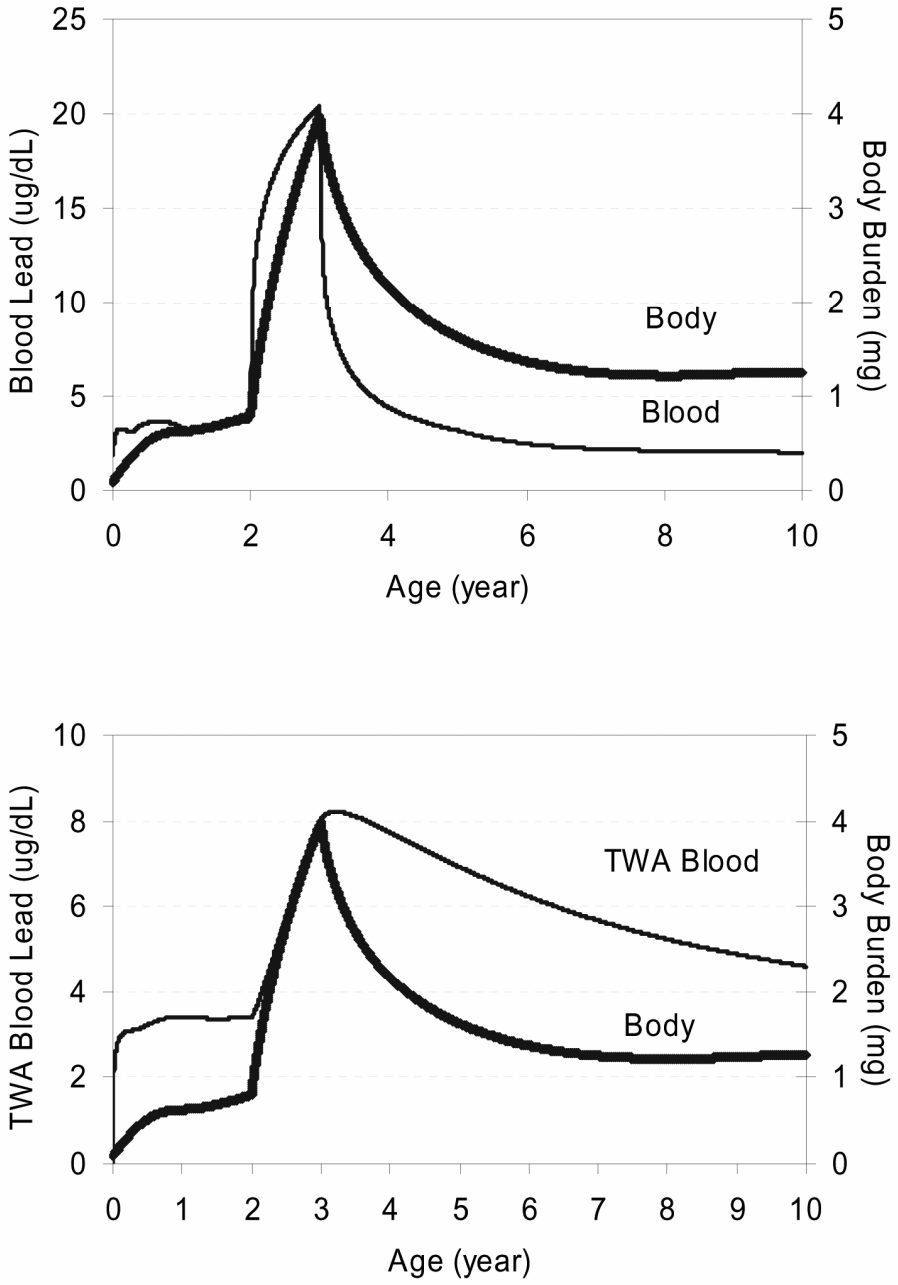


Figure 6-2.3. Simulation of relationship between blood lead concentration and body burden in children. Blood lead concentration is thought to parallel body burden more closely in children than in adults, due to more rapid turnover of bone and bone-lead stores in children (upper panel). Nevertheless, the long-term average blood lead concentration more closely tracks the pattern of change in body burden (lower panel). Simulation based on Leggett (1993) lead biokinetics model.

6.2.1.5 Blood Lead as a Biomarker of Lead Exposure

Characterizing quantitative relationships between external lead exposures and blood lead concentrations has become central to concentration-response analyses for human populations exposed to lead. The 1986 Lead AQCD summarized the empirical basis for this as it stood at the time. A summary of empirically-derived regression slope factors relating lead exposures and blood lead is provided in Abadin and Wheeler (1993). More recent meta-analyses, based on structure equation modeling, provide further support for quantitative relationships between lead exposures and blood lead concentrations in children (e.g., U.S. Environmental Protection Agency, 2001; Lanphear et al., 1998; Succop et al., 1998).

As noted above, the elimination half-life of lead in blood is ~25 to 30 days (Chamberlain et al., 1978; Rabinowitz et al., 1976; Griffin et al., 1975); therefore, the blood lead concentration mainly reflects the exposure history for the previous few months. However, a single blood lead measurement cannot distinguish between a history of long-term low level lead exposure or a history that includes higher acute exposures. This is illustrated in Figure 6-2.4. Two hypothetical children are simulated. Child A has a relatively constant lead intake from birth; whereas Child B has the same long-term lead intake as Child A, with a 1-year elevated intake which begins at age 24 months (Figure 6-2.4, upper panel). The absorption fraction is assumed to be the same for both children. Blood lead samples 1 and 5, or 2 and 4, will yield similar blood lead concentrations (~3 or 10 μg/dL, respectively), yet the exposure contexts for these samples are very different. Two samples (e.g., 1 and 2, or 4 and 5), at a minimum, are needed to ascertain if the blood lead concentration is changing over time. The rate of change can provide information about the magnitude of change in exposure, but not necessarily about the time history of the change (Figure 6-2.4, lower panel). Here again, time-integrated measurements of lead concentration may provide a means for accounting for some of these factors and, thereby, provide a better measure of long-term exposure. The same concepts apply to estimation of long-term exposure based on blood lead measurements in adults (Gerhardsson et al., 1992, 1995a; Roels et al., 1995).

An additional complication is that the relationship between lead intake and blood lead concentration is curvilinear; that is, the increment in blood lead concentration per unit of lead intake decreases with increasing blood lead concentration, both in children (Lacey et al., 1985; Ryu et al., 1983; Sherlock and Quinn, 1986) and in adults (Kehoe, 1987; Laxen et al., 1987;

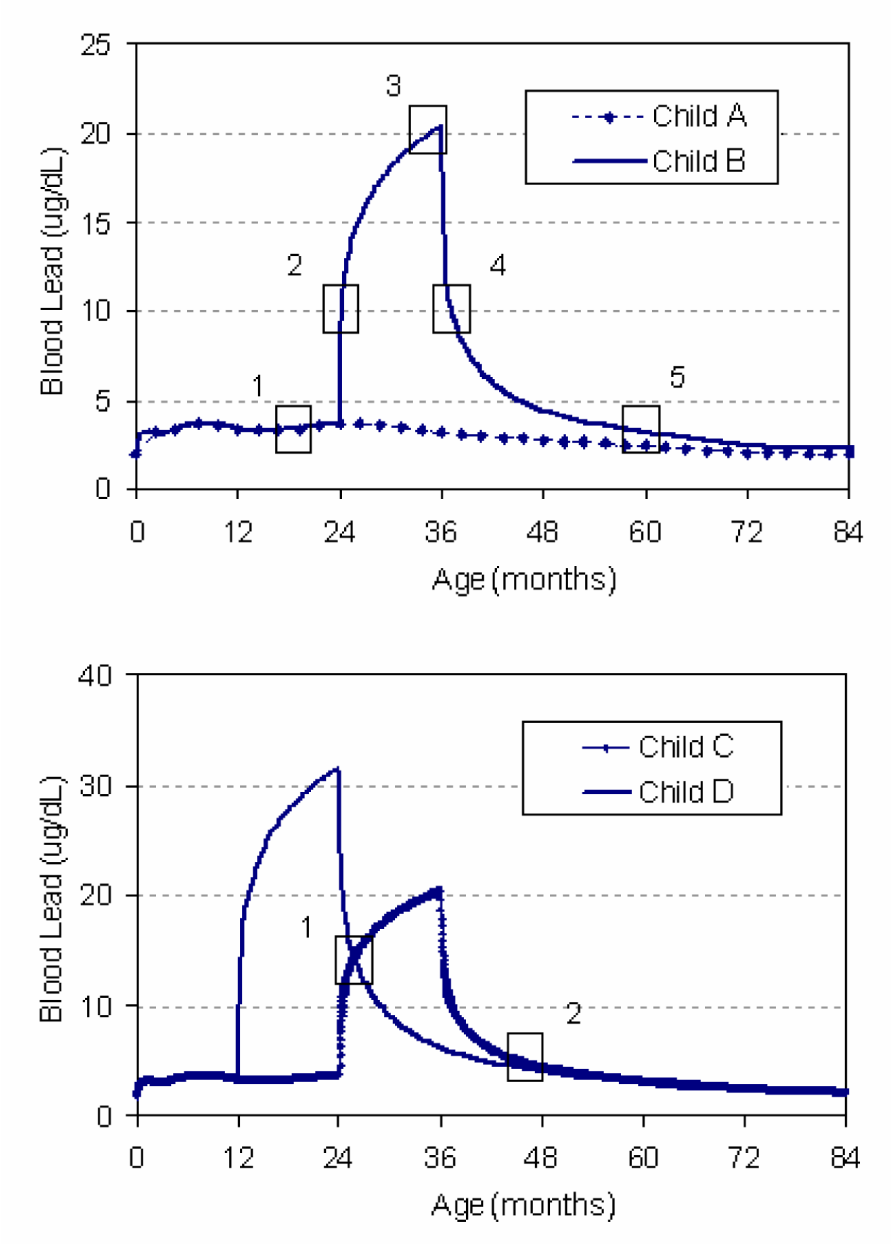


Figure 6-2.4. Simulation of temporal relationships between lead exposure and blood lead concentration in children. Child A and Child B have a relatively constant basal lead intake (µg/day/kg body weight) from birth; Child B experiences 1-year elevated intake which begins at age 24 months (upper panel). Blood lead samples 1 and 5, or 2 and 4, will yield similar blood lead concentrations (~3 or 10 µg/dL, respectively), yet the exposure scenarios for these samples are very different. As shown in the example of Child C and Child D, two samples can provide information about the magnitude of change in exposure, but not necessarily the temporal history of the change (lower panel).

Pocock et al., 1983; Sherlock et al., 1982, 1984). The nonlinearity is evident even at blood lead concentrations below 25 µg/dL (Figure 6-2.5). The nonlinearity in the lead intake-blood lead concentration relationship is derived, at least in part, from a capacity limitation in the accumulation of lead in erythrocytes (Bergdahl et al., 1997, 1998, 1999; Manton et al., 2001; Smith et al., 2002). A capacity-limited process may also reside at the level of intestinal absorption; however, the dose at which absorption becomes appreciably limited in humans is not known. Lead intake-blood lead relationships also vary (a) with age, as a result of age-dependency of gastrointestinal absorption of lead, and (b) with diet and nutritional status (Mushak, 1991).

The blood lead concentration is also influenced by lead in bone. Evidence for the exchange of bone lead and soft tissue lead stores comes from analyses of stable lead isotope signatures of lead in bone and blood. As noted earlier, bone lead likely contributes to the slow phase of elimination of lead from blood that has been observed in retired lead workers (Christoffersson et al., 1986; Schütz et al., 1987). Bone lead stores may contribute 40-70% of the lead in blood (Smith et al., 1996). This contribution increases during pregnancy, when mobilization of bone lead increases, apparently as the bone is resorbed to produce the fetal skeleton (Gulson et al., 2003). The mobilization of bone lead during pregnancy may contribute, along with other mechanisms (e.g., increased absorption), to the increase in lead concentration that has been observed during the later stages of pregnancy (Gulson et al., 1997; Lagerkvist et al., 1996; Schuhmacher et al., 1996). In addition to pregnancy, other states of increased bone resorption appear to result in release of bone lead to blood; these include lactation, osteoporosis, and menopause (Gulson et al., 2003). These observations are consistent with epidemiologic studies that have shown increases in blood lead concentration after menopause and in association with decreasing bone density in postmenopausal women (Hernandez-Avila et al., 2000; Nash et al., 2004; Symanski and Hertz-Picciotto, 1995). The relationship between blood and bone lead is discussed further in Section 6.2.2 on bone lead as a biomarker of lead exposure.

6.2.1.6 Summary of Blood Lead as a Biomarker of Lead Body Burden and Exposure

The blood lead concentration measured in an individual will be determined by the recent exposure history of the individual, as well as the long-term exposure history that gives rise to accumulated bone lead stores. The contribution of the latter to blood lead may change with the

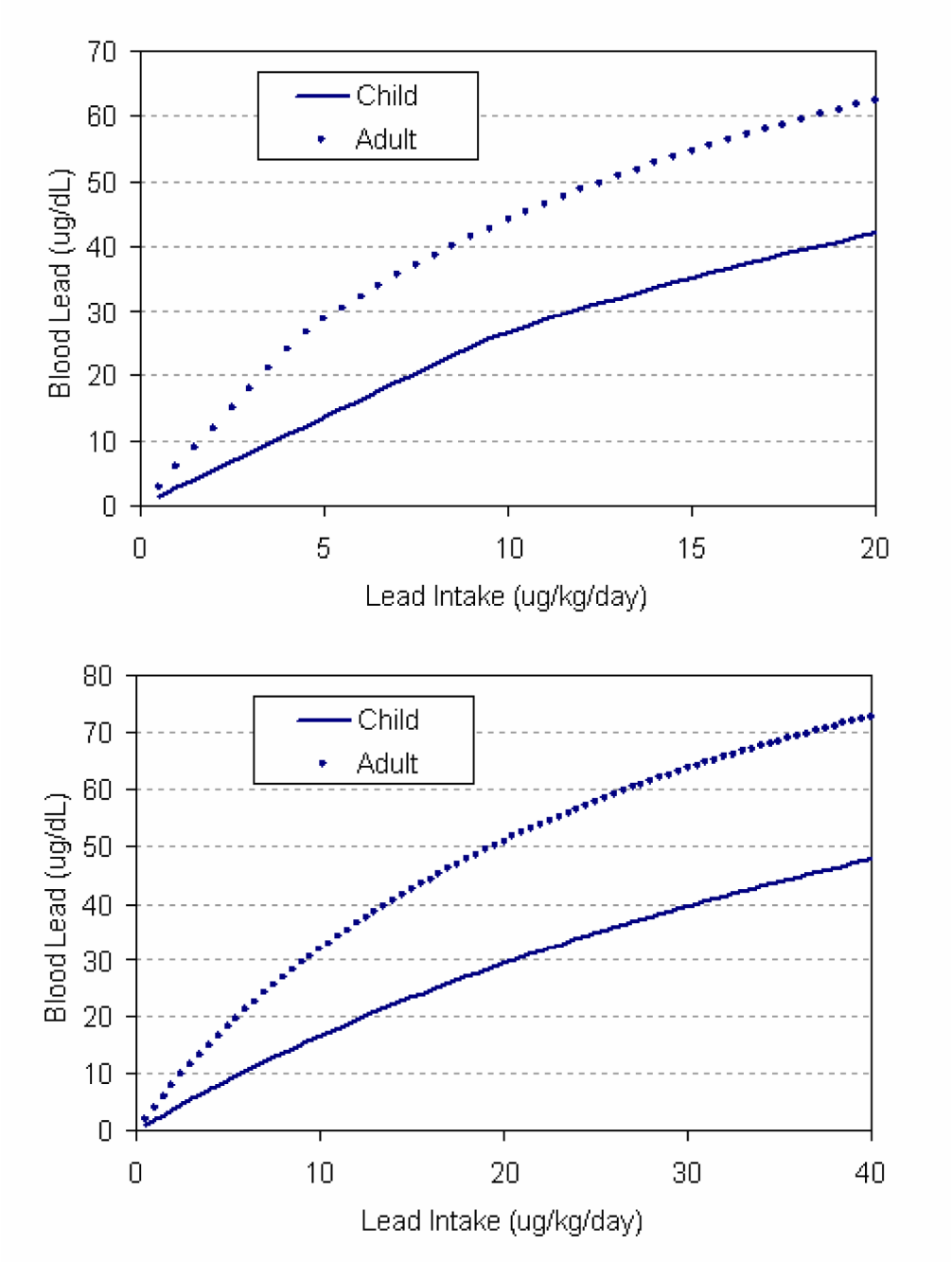


Figure 6-2.5. Simulation of relationships between lead intake and blood lead concentration in adults and children. The relationship between lead intake and blood lead concentration is curvilinear in adults and children. Predictions are for a 2-year-old child and 30-year-old adult, for a constant lead intake (µg/kg/day). Predictions are based on Leggett (1993, upper panel) and O'Flaherty (1993, 1995, lower panel).

duration and intensity of the exposure, age, and various physiological variables (e.g., nutritional status, pregnancy, menopause). Longitudinal measurements of blood lead can be expected to provide a more reliable measure of exposure history of an individual (and will more closely parallel body burden) compared to a single measurement; however, the degree to which this will apply will depend on the sampling frequency with respect to the temporal pattern of exposure.

In general, higher blood lead concentrations can be interpreted as indicating higher exposures (or lead uptakes); however, they do not necessarily predict appreciably higher body burdens. Similar blood lead concentrations in two individuals (or populations) do not necessarily translate to similar body burdens or similar exposure histories.

6.2.2 Lead in Bone

6.2.2.1 Summary of Key Findings from the 1986 Lead AQCD

In the 1986 Lead AQCD, the discussion on the distribution of lead in bone was fairly limited and mostly based on postmortem studies. The distribution between the two major compartments of cortical and trabecular bone were addressed especially based on the pioneering isotopic work of Rabinowitz et al. (1977). Estimates of the amount of lead in bone were also provided. There was limited discussion of the half-life of lead in bone as being on the order of several decades.

One of the major conclusions of the 1986 Lead AQCD regarding bone lead was that the traditional view that the skeletal system was a total sink for body lead was now giving way to the notion that there were at least several bone compartments for lead, with different mobility profiles. The possibility of bone lead serving as a source of long-term internal exposure was also considered.

Since 1986, the main focus of lead in bone studies has been on occupationally-exposed subjects, because of concern, until more recent times, about the ability to measure lower levels of lead in bone from environmentally-exposed subjects. Furthermore most of the focus has been on adult males, with very few studies on females and children. The newly available studies of lead in bone are discussed in the following sections.

6.2.2.2 Methodology of Bone Lead Analysis

6.2.2.2.1 Analytical Methods for Measuring Lead in Bone

Bone is comprised of two main types (cortical and trabecular) that have distinct rates of turnover and lead release, resulting in potential differences in implications with respect to toxicity aspects (further discussed in Section 6.2.2.3). The most commonly measured bones are the tibia, calcaneus, patella, and finger bone. For cortical bone, the midpoint of the tibia is measured. For trabecular bone, both the patella and calcaneus are measured. Recent studies favor measurement of the patella, because it has more bone mass and may afford better measurement precision than the calcaneus. The advantages and disadvantages of patella and calcaneus sites have not been thoroughly investigated. Bone lead measurements in cadavers, environmentally-exposed subjects, and occupationally-exposed subjects are presented in Annex Tables AX6-2.3, AX6-2.4, and AX6-2.5, respectively.

Bone analysis methods for in vivo measurements have included AAS, ASV, ICP-AES, ICP-MS, laser ablation inductively coupled plasma mass spectrometry (LAA ICP-MS), thermal ionization mass spectrometry (TIMS), synchrotron radiation induced X-ray emission (SRIXE), particle induced X-ray emission (PIXE), and X-ray fluorescence (XRF). Since the 1986 Lead AQCD, there have been many new papers published on bone lead using XRF. The upsurge in popularity of the XRF method has paralleled a decline in the use of the other methods.

In the past, two main approaches for XRF measurements have been used to measure lead concentrations in bone, the K-shell and L-shell methods. The K-shell method is now the most widely used, as there have been no further developments in L-shell devices since the early 1990s. The K-shell methods using ^{57}Cd and ^{109}Cd have been described in detail by Somervaille et al. (1989). Briefly, the K-shell XRF method uses 88.034 keV gamma rays from ^{109}Cd to fluoresce the K-shell X-rays of lead.

Since 1986, several investigators have reported refinements to hardware and software to improve the precision and accuracy of XRF measurements and there have been a number of investigations into the precision, accuracy and variability in XRF measurements (e.g., Aro et al., 2000; Todd et al., 2000, 2001, 2002). Todd et al. (2000) provided a detailed discussion of factors that influence the variability and measurement uncertainty, including repositioning, sample measurement duration, overlying tissue, operator expertise, detector resolution, and changes to measurement process over time. Some of these aspects were also discussed by

Hu et al. (1995). From their cadaver and in vivo measurements, Todd et al. (2000) concluded that the uncertainty in an individual measurement was an underestimate of the standard deviation of replicate measurements, suggesting a methodological deficiency probably shared by most current ^{109}Cd-based K-shell XRF lead measurement systems. In examining the reproducibility of the bone lead measurements over a 4½ month period, Todd et al. found the average difference between the XRF results from short term and longer term measurements was 1.2 μg/g, indicating only a small amount of variability in the XRF results over a sustained period of time.

6.2.2.2.2 Statistical Methods for Analyzing Bone Lead Concentrations in Epidemiologic Studies

In the literature, XRF bone data has typically been reported in two ways: one involving a methodological approach to assessing the minimum detection limit and the other termed an epidemiologic approach by Rosen and Pounds (1998). In the methodological approach, a minimum detection limit is defined using various methods, including two or three times the square root of the background counts; one, two, or three times the SD of the background; and two times the observed median error. This approach relies upon the minimum detection limit to define a quantitative estimate that is of sufficient precision to be included in the statistical analysis. The following are examples of methodological minimum detection limits for bone lead analyses. Bellinger et al. (1994) observed minimum detection limits, equivalent to the SD, of 5.4 μg/g for tibia and 9.2 μg/g for patella. Using twice the median observed error, Gerhardsson et al. (1993) observed minimum detection limits of 9.8 μg/g for tibia and 19.1 μg/g for calcaneus. For finger bone lead measurements, Christoffersson et al. (1986) observed a minimum detectable limit of 20 μg/g, which was equivalent to three times the square root of the background counts.

With the epidemiologic approach, to determine the minimum detection limit of an instrument all values are used (including negative values), which results in extremely low detection limits. Rosen and Pounds (1998) noted that this approach yields population bone lead averages that they considered artificially low and inconsistent with observations from many other earlier studies. However, not including values that are negative or below the detection limit, or assigning these values a fixed number for the statistical analysis is also of concern. To examine and compare the two methods used to analyze data at low levels of bone lead concentration,

Kim et al. (1995) performed serial measurements on phantoms containing spiked amounts of lead. The results demonstrated that the use of methodological minimum detection limits to recode low-level observations reduced the efficiency of the analysis and the ability to distinguish between the phantoms. Using the epidemiologic approach of retaining all point estimates of measured bone lead concentrations provided less bias and greater efficiency in comparing the mean or median levels of bone lead of different populations.

6.2.2.3 Bone Lead as a Biomarker of Lead Body Burden

6.2.2.3.1 Uptake of Lead in Bone

The dominant compartment for lead in the body is in bones. In human adults, more than 90% of the total body burden of lead is found in the bones, whereas bone lead accounts for ~70% of the body burden in children (Barry, 1975). Bone is comprised of two main types, cortical and trabecular. The tibia consists of more than 95% cortical bone, the calcaneus and patella comprise more than 95% trabecular bone, and finger bone is a mixed cortical and trabecular bone although the second phalanx is dominantly cortical. The cortical and trabecular bones have distinct rates of turnover and lead release, as well as potentially different associated toxicity implications (Hu et al., 1998). For example, adult tibia has a turnover rate of about 2% per year whereas trabecular bone has a turnover rate of more than 8% per year (Rabinowitz, 1991). The proportion of cortical to trabecular bone in the human body varies by age, but on average is about 80 to 20 (International Commission on Radiological Protection, 1973). Although not so important for certain types of measurements, the periosteum is of limited dimension and may reflect a bone compartment of more rapid deposition and turnover of lead than the other two types (Skerfving et al., 1993), which would also likely have implications for toxicity, especially for chelation therapy.

Much of the understanding of bone structure and metal deposition comes from studies of radioactive elements (e.g., International Commission on Radiological Protection, 1996). Durbin (1992, page 823) suggests that there is "an initial deposition of lead on anatomical bone surfaces with some skewing to the well nourished trabecular surfaces in red marrow, intense deposits at bone growth sites, and later on, a nearly diffuse labeling throughout the bone volume. For constant intake of lead during growth, it is expected that lead will be nearly uniformly distributed in the mineralized bone. Single or irregular intakes during growth are expected to result in

residual buried lines and hotspots superimposed on a relatively uniform diffuse concentration in bone mineral volume. . . For example, periosteal and subperiosteal lead deposits in the long bones, including those of the hands and feet, are likely to be greater than at many other sites, since bone growth continues at the periosteal surface while the endosteal surface is resorbed."

The importance of bone marrow was also stressed by Salmon et al. (1999), with a key factor affecting lead uptake into bone being the fraction of bone surface in trabecular and cortical bone adjacent to active bone marrow. The fraction of total marrow that is red and active decreases from 100% at birth to about 32% in adulthood (Cristy, 1981). Early lead uptake is greater in trabecular bone due to its larger surface area and higher metabolic rate. Of the total bone surface against red marrow, 76% is trabecular and 24% is cortical endosteal (Salmon et al., 1999). Bone marrow has much lower lead concentrations than bone matrix (Skerfving et al., 1983).

6.2.2.3.2 Half-Life of Lead in Bone

Estimates of the half-life of lead in trabecular bone are partly dependent on the tissue analyzed and the "purity" of the trabecular component (e.g., patella, calcaneus, and phalanx). Earlier estimates of the half-life of lead in trabecular bone ranged from 12 to 19 years (Bergdahl et al., 1998; Gerhardsson et al., 1993). For cortical bone, estimates for the half-life of lead were on the order of 13 to 27 years (Bergdahl et al., 1998; Gerhardsson et al., 1993; Rabinowitz, 1991).

With respect to half-lives in bone, recent K-shell XRF bone studies have indicated that earlier concepts of a constant rate of removal of lead from bone throughout adulthood assumed in models of human metabolism (Leggett, 1993; O'Flaherty, 1993) may be incorrect. In a study of active and retired smelter workers, Brito et al. (2001) suggested that people less than 40 years old had a shorter half-life for the release of lead from the tibia than those older than 40 years, 4.9 years (95% CI: 3.6, 7.8) compared to 13.8 years (95% CI: 9.7, 23.8), respectively. Also, they suggested that less intensely exposed subjects with a lifetime averaged blood lead of ≤25 µg/dL had a shorter half-life in the tibia (6.2 years [95% CI: 4.7, 9.0]) than those with a lifetime averaged blood lead >25 µg/dL (14.7 years [95% CI: 9.7, 29.9]).

Even by the end of the sixth decade, ~35 to 40% of skeletal mass consists of unremodelled first generation bone acquired during childhood and adolescence (International

Commission on Radiological Protection, 1973). This statement contrasts with that of O'Flaherty (1993) who suggested that because of the relatively short half-life of lead in the bones of children that much of the lead incorporated during active growth would not persist into adulthood. In a comparison of lead in tooth dentine and the tibia from young adults who were followed up after a period of 13 years, Kim et al. (1996) suggested that "pockets" of lead acquired in childhood may persist into adults. Likewise, McNeill et al. (2000) compared tibia lead levels and cumulative blood lead indices in a population of 19 to 29 year olds who had been highly exposed to lead in childhood from the Bunker Hill, Idaho smelter. They concluded that lead from exposure in early childhood had persisted in the bone matrix until adulthood.

6.2.2.3.3 Changes in Bone Lead Concentrations with Age

Conventional and XRF analyses of bone have shown significant increases in bone lead with age (Hu et al., 1990, 1996; Kosnett et al., 1994; Morgan et al., 1990). Kosnett et al. (1994) observed no significant change in bone lead concentrations up to age 20 years, but found an increasing trend with the same slope for men and women between the ages of 20 to 55 years and an increase to a faster rate in men older than 55 years. Kosnett et al. reanalyzed earlier cadaver cortical bone data of Drasch et al. (1987) and found that male bone lead values increased significantly after age 40 years, whereas female values slightly declined. A similar analysis of the post-mortem data of Barry (1975) showed an upward inflection for all males after age 35 years. Kosnett et al. (1994) found no significant slope to the relationship between age and bone lead for the 10 to 20 year old subjects, in contrast to Barry (1975) and Drasch et al. (1987).

Annual increments of lead to bone vary although no attempt has been made to determine whether the differences are significant. For example, the annual increment of 0.46 μg/g bone mineral/year found by Gordon et al. (1993) was slightly lower than that found by Somervaille et al. (1989), but the difference was not significant. After age 20 years, Kosnett et al. (1994) found the annual increment to be 0.38 μg/g bone mineral/year. Hu et al. (1990) reported a value of 0.31 μg/g bone mineral/year for subjects ranging in age from 20 to 58 years.

6.2.2.4 Distribution of Lead from Bone into Blood and Plasma

6.2.2.4.1 Contribution of Bone Lead to Blood Lead

Although the skeleton was recognized as a potentially significant contributor to blood lead in the 1986 Lead AQCD, there have been several investigations using both bone lead XRF and stable lead isotope methods which have helped quantify the contribution. The earlier estimation of skeletal contribution to blood lead was 70% by Manton (1985) and ~65% ranging up to 100% by Schütz et al. (1987). The more recent isotope studies confirmed these estimates. Using female immigrants to Australia and their children, Gulson et al. (1995, 1997, 1999a) found a mean value of 50% (range 16-73%) deriving from the skeleton. Smith et al. (1996) found a range of 40–70% in five patients who underwent total hip or knee joint replacement. Gwiazda et al. (2005) observed a range of 40-65% in two children and >90% in one child. Studies examining the bone lead contribution to blood lead are presented in Annex Table AX6-2.6.

The contribution of skeletal lead to blood lead was further examined in females from varying environments. In middle-aged to elderly subjects (46-74 years), an increase of 19 μg/g of lead in tibia bone mineral was associated with an increase in blood lead of 1.7 μg/dL, which corresponds to a 0.09 μg/dL increase in blood lead per 1 μg/g bone mineral (Korrick et al., 2002). A study of 108 former workers at the Bunker Hill smelter in northern Idaho and 99 referents from the Spokane, WA area examined the endogenous bone lead release rate of postmenopausal and premenopausal women (Popovic et al., 2005). The results indicated that the endogenous release rate in postmenopausal women (0.13 μg/dL per μg/g bone) was greater than the rate found in premenopausal women (0.07 μg/dL per μg/g bone). In a Mexico City study, the endogenous bone lead release rate in postmenopausal women also was observed to be double that in premenopausal women (Garrido-Latorre et al., 2003). A change of 10 μg/g bone mineral was associated with an increase in blood lead of 1.4 μg/dL in postmenopausal subjects, compared to an increase of 0.8 μg/dL in premenopausal women. Lactation was also found to affect the endogenous bone lead release rate. After adjusting for patella lead concentration, an increase in blood lead levels of 12.7% (95% CI: 6.2, 19.6) was observed for women who practiced partial lactation and an increase of 18.6% (95% CI: 7.1, 31.4) for women who practiced exclusive lactation compared to those who stopped lactation (Téllez-Rojo et al., 2002).

The mean cortical leads to current blood lead ratios for occupationally-exposed subjects are shown in Figure 6-2.6. Box plots were calculated using data from the following studies:

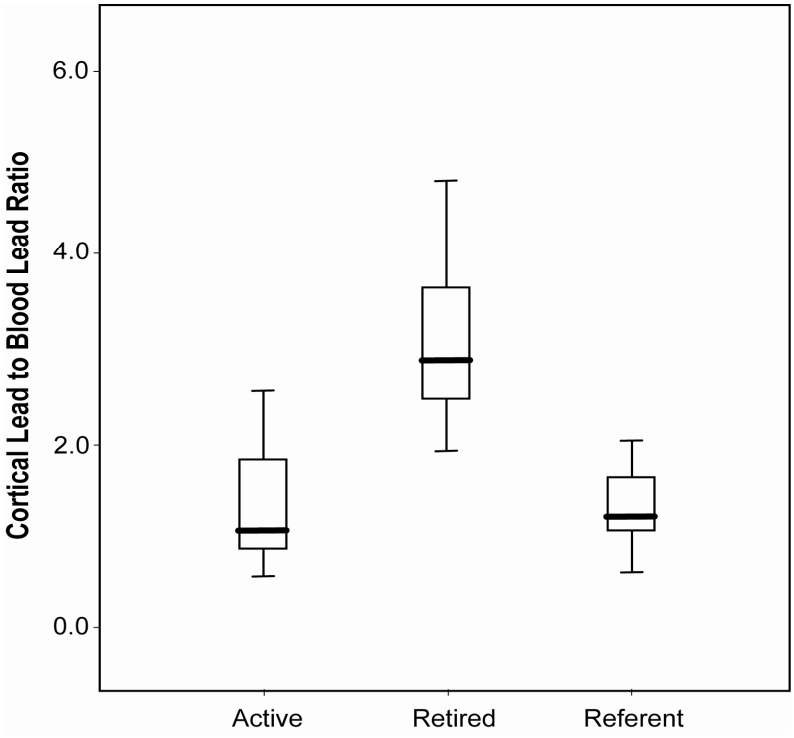


Figure 6-2.6. Cortical lead to blood leads ratios for occupationally-exposed subjects (both active and retired) and referents. Data compiled from several studies. See text for more details.

Bergdahl et al., 1998; Brito et al., 2002; Christoffersson et al., 1984; Erfurth et al., 2001; Erkkilä et al., 1992; Fleming et al., 1998; Gerhardsson et al., 1993; Hänninen et al., 1998; Juarez-Perez et al., 2004; Popovic et al., 2005; Roels et al., 1995; Schwartz et al., 2000a, 2000b; Somervaille et al., 1988, 1989; Todd et al., 2001. The mean cortical lead to current blood lead ratio is about 1.2 (range 0.4-2.6) for active employees (n = 17). For retired employees (n = 7), the mean is 3.2 (range 2.0-5.3), while for environmentally-exposed referent subjects from these industries (n = 7) the mean ratio is about 1.3 (range 1-2.2). The differences in the cortical lead to blood lead ratio between active and retired employees and retired employees and referents are significant ($p < 0.01$) but not between active employees and referents. Several investigators have pointed out the weak association between bone lead and blood lead in active employees in comparison with the stronger association with retired employees (e.g., Erkkilä et al., 1992; Fleming et al., 1997; Gerhardsson et al., 1993). This is likely because circulatory lead of active employees

reflects mainly ongoing exposure whereas that in retired employees is more dependent on lead released from the skeleton.

The mean tibia lead to current blood lead ratios for environmentally-exposed subjects is shown in Figure 6-2.7. The box plot for pregnancy-related subjects was calculated using data from the following studies: Brown et al., 2000; Chuang et al., 2001; Ettinger et al., 2004; Gomaa et al., 2002; Gonzalez-Cossio et al., 1997; Hernandez-Avila et al., 1996, 1998, 2002, 2003; Hu et al., 1996; Moline et al., 2000; Rothenberg et al., 2000; Sanin et al., 2001; Téllez-Rojo et al., 2002, 2004. The box plot for middle-aged and elderly subjects included the following studies: Berkowitz et al., 2004; Cheng et al., 1998a; Garrido-Lattore et al., 2003; Hu et al., 1996, 2001; Korrick et al., 2002; Kosnett et al., 1994; Oliveira et al., 2002; Schafer et al., 2005; Tsaih et al., 2004; Webber et al., 1995. The box plot for the younger subjects (age range 1-30 years) included Farias et al., 1998; Kim et al., 1996; Rosen et al., 1989; Stokes et al., 1998. The mean tibia lead to blood lead ratio for pregnancy-related subjects ($n = 21$) is 1.5 (range 1.0-4.2) and is statistically significantly different ($p < 0.001$) from the mean ratio of 3.4 (range 1.6-5.4) for middle-aged to elderly subjects ($n = 27$). Similar relationships are observed for the patella lead to blood lead ratios for pregnancy-related subjects and middle-aged to elderly subjects.

In several other studies of environmentally-exposed subjects, there is a stronger relationship between patella lead and blood lead than tibia lead and blood lead (e.g., Hernandez-Avila et al., 1996; Hu et al., 1996, 1998). Hu et al. (1998) suggest that these relationships indicate that trabecular bone is the predominant bone type providing lead back into circulation under steady-state and pathologic conditions.

6.2.2.4.2 Partitioning of Bone Lead into Plasma

Although most of the lead in whole blood is associated with erythrocytes (~99%), it has been suggested that the small fraction of lead in plasma (<0.3%) may be the more biologically labile and toxicologically active fraction of the circulating lead. Several authors have proposed that lead released from the skeleton was preferentially partitioned into serum compared with red cells (Cake et al., 1996; Hernandez-Avila et al., 1998; Tsaih et al., 1999) with one explanation being that the lead from endogenous sources was in a different form to that from exogenous sources. However, this concept has been withdrawn by its main proponents. In contrast to using

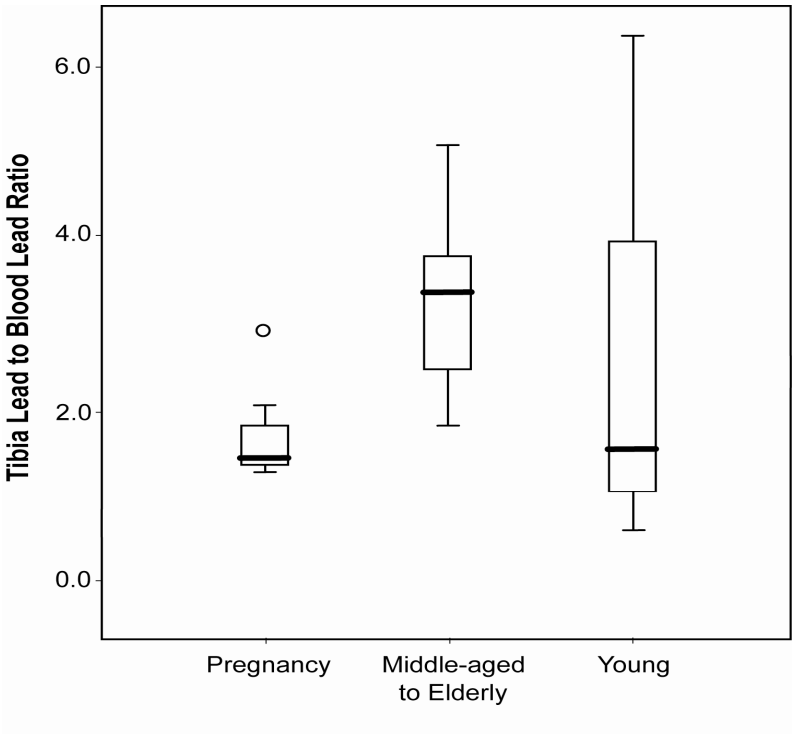


Figure 6-2.7. Tibia leads to blood lead ratios for environmentally-exposed pregnancy-related subjects, middle-aged to elderly subjects, and younger subjects. Data compiled from several studies. See text for more details.

urine as a proxy for serum and measuring lead isotopes, Gulson et al. (2000) concluded that there was no evidence for preferential partitioning of lead into serum compared with whole blood.

6.2.2.5 Mobilization of Lead From Bone

Although earlier investigators such as Brown and Tompsett (1945), Ahlgren et al. (1976) and Christoffersson et al. (1984) suggested that the skeleton was a potential endogenous source of lead poisoning, the opposing concept of the skeleton as a "safe" repository for lead persisted until the mid-1980s and early 1990s. Potential mobilization of lead from the skeleton could occur at times of physiological stress associated with enhanced bone remodeling such as during pregnancy and lactation (Hertz-Picciotto et al., 2000; Manton, 1985; Silbergeld, 1991), menopause or in the elderly (Silbergeld, 1991; Silbergeld et al., 1988), extended bed rest (Markowitz and Weinberger, 1990), hyperparathyroidism (Kessler et al., 1999), and weightlessness. The lead deposited in the bone of adults can serve to maintain blood lead levels

long after exposure has ended (Fleming et al., 1997; Gulson et al., 1995; Inskip et al., 1996; Kehoe, 1987; Manton, 1985; Nilsson et al., 1991; O'Flaherty et al., 1982; Schütz et al., 1987; Smith et al., 1996).

In the 1986 Lead AQCD, there was a comprehensive summary of chelation therapies and the recognition that there was limited release of lead from bones. The potential role of bone lead as an endogenous source of lead in blood, resulting in elevated levels for former lead employees, was mentioned although data to support this hypothesis were limited.

6.2.2.5.1 Mobilization of Lead from Bone during Pregnancy and Lactation

Bone lead studies of pregnant and lactating subjects are summarized in Annex Table AX6-2.7. Most of the bone XRF studies on pregnancy and lactation have focused on subjects from Mexico City and Latin subjects from Los Angeles, California. Relationships and/or health outcomes from these investigations include: patella bone as a significant contributor to blood lead (Brown et al., 2000; Hernandez-Avila et al., 1996); a positive association between plasma lead and bone lead in the highest bone lead group of pregnant women (Téllez-Rojo et al., 2004); a positive association of tibia and calcaneus lead with prenatal lead concentration, and calcaneus lead with postnatal lead (Rothenberg et al., 2000); a positive association of tibia lead and seasonal variations in blood lead (Rothenberg et al., 2001); maternal tibia and patella lead as significant predictors of fetal exposure determined using cord blood (Chuang et al., 2001); a positive association of calcaneus lead and increased systolic and diastolic blood pressure in the third trimester (Rothenberg et al., 2002); an inverse relationship between maternal tibia and patella lead, and birth weight (Gonzalez-Cossio et al., 1997; Sanin et al., 2001); an inverse association between tibia lead and birth length, and patella lead and head circumference (Hernandez-Avila et al., 2002); an inverse association of maternal patella bone and Mental Development Index (Gomaa et al., 2002); increased bone resorption during lactation (Téllez-Rojo et al., 2002); increased lead in breast milk with an increase in patella and tibia lead (Ettinger et al., 2004).

Lead isotope studies on immigrant women to Australia (Gulson et al., 1997, 1998a) confirmed the earlier work of Manton (1985) of increased blood lead during pregnancy. Gulson et al. reported that, during pregnancy, blood lead concentrations in the first immigrant cohort (n = 15) increased by an average of about 20% compared to non-pregnant migrant controls

(n = 7). The percentage change in blood lead concentration was significantly greater during the postpregnancy period than during the second and third trimesters ($p < 0.001$). Skeletal contribution to blood lead, based on the isotopic composition for the immigrant subjects, increased in an approximately linear manner during pregnancy. The mean increases for each individual during pregnancy varied from 26% to 99%. Skeletal lead contribution to blood lead was significantly greater during the postpregnancy period than during the second and third trimesters. The contribution of skeletal lead to blood lead during the postpregnancy period remained essentially constant at the increased level of lead mobilization. In a follow-up study using a different immigrant cohort of 12 women with calcium supplementation at the recommended level of approximately 1,000 mg/day (National Institutes of Health, 1994), Gulson et al. (2004) found increased mobilization of lead occurred in the third trimester rather than in the second trimester as observed with first cohort. In addition, the extra flux released from bone during late pregnancy and postpartum varied from 50 to 380 μg (geometric mean 145 μg) compared with 330 μg in the previous cohort.

In an extended monitoring of 7 subjects for up to 22 months postpartum, Gulson et al. (1999a) found that blood lead concentrations in some of the subjects decreased to about half the earlier levels almost immediately after cessation of breastfeeding. However, in 4 of the 7 cases there was a rebound in blood lead concentrations that exceeded the earlier levels in 3 cases. The authors interpreted these results to indicate that there is ongoing increased mobilization of lead from the maternal skeleton for much longer than predicted, probably associated with remodeling processes. Also using lead isotopes, Manton et al. (2003) observed that blood lead concentrations decreased in early pregnancy and rose during late pregnancy. They attributed these results to changes in bone resorption with decoupling of trabecular and cortical bone sites.

6.2.2.5.2 Transplacental Transfer of Lead and Transfer through Breast Milk

Transplacental transfer of lead in humans has been suggested in a number of studies based on cord blood to maternal blood lead ratios ranging from about 0.6 to 1.0 at the time of delivery. Maternal-to-fetal transfer of lead appears to be related partly to the mobilization of lead from the maternal skeleton. Evidence for transfer of maternal bone lead to the fetus has been provided from stable lead isotope studies in cynomolgus monkeys (*Macaca fascicularis*). Approximately 7 to 39% of the maternal lead burden that is transferred to the fetus appears to derive from the

maternal skeleton (Franklin et al., 1997; O'Flaherty et al., 1998). Further evidence for maternal-to-fetal transfer of lead in humans can be gained from stable lead isotope measurements. For example, a 0.99 correlation in lead isotopic ratios for maternal and cord blood (Manton, 1985; Gulson et al., 1998b) and the similarity of isotopic ratios in maternal blood and in blood and urine of newly-born infants provide strong evidence for placental transfer of lead to the fetus (Gulson et al., 1999b).

Breast milk can also be a pathway of maternal excretion of lead. However, given the very low lead concentrations and analytical difficulties arising from high fat contents in breast milk, their analyses require careful attention. Selected studies appear to show a linear relationship between breast milk and maternal whole blood with the percentage of lead in breast milk compared with whole blood of <3% in subjects for blood lead concentrations ranging from 2 to 34 μg/dL. Blood lead concentrations in breastfed newborn infants decreased in spite of the maternal blood lead concentrations having risen or remained elevated postpartum compared to lower levels during prepregnancy or in the first trimester (Gulson et al., 1999b). Similar trends were noted by Manton et al. (2000). However, in a Mexico City study, an association between patella lead and blood lead concentrations was higher for women with partial lactation than for those who stopped lactation, and it was increased among women who breastfed exclusively (Téllez-Rojo et al., 2002). In another Mexico City study, Ettinger et al. (2004) concluded that an interquartile increase in patella lead was associated with a 14% increase in breast milk lead, whereas for tibial lead the increase was ~5%.

In conclusion, there is evidence that maternal-to-fetal transfer of lead occurs, likely resulting from the mobilization of lead from the maternal skeleton during pregnancy. Breast-fed infants appear to be at greater risk only if the mother is exposed to high lead concentrations either from exogenous sources or endogenous sources such as the skeleton.

6.2.2.5.3 Mobilization of Lead in Bone During Menopause and in the Elderly

Increases in blood lead for postmenopausal women have been attributed to release of lead from the skeleton associated with increased bone remodeling during menopause. Many of the studies have been based on blood lead concentration. Bone lead studies of menopausal and middle-aged to elderly subjects are summarized in Annex Table AX6-2.8.

Overall, the various studies of bone and blood lead levels, as well as hormone replacement therapy, have provided conflicting outcomes. Hormone replacement therapy alone or combined with calcium supplementation prevents bone resorption and increases the bone mineral density in trabecular and cortical bones of women with or without metabolic bone disease. The effect of hormone replacement therapy may result in a decrease of lead mobilization from bone along with a reduction in blood lead concentration levels. Several studies have found that tibia bone lead levels were higher in women who used hormone replacement therapy (Popovic et al., 2005; Webber et al., 1995). In contrast, other investigators have found no association between bone lead and use of estrogens (Berkowitz et al., 2004; Korrick et al., 2002). In addition, some studies observed a decrease in blood lead concentrations associated with hormone replacement therapy (Garrido-Latorre et al., 2003), whereas others observed no association (Webber et al., 1995).

The endogenous release rate of lead from bone in postmenopausal women was double the rate in premenopausal former smelter employees (Popovic et al., 2005) and environmentally-exposed women from Mexico (Garrido-Latorre et al., 2003). In middle-aged to elderly males from the Normative Aging Study, patella lead accounted for the dominant portion of variance in blood lead (Hu et al., 1996).

6.2.2.5.4 Effect of Nutritional Status on Mobilization of Lead from Bone

Most studies that investigated the effect of nutritional status on the mobilization of lead from the skeleton have examined the effects of calcium supplementation. Several studies have suggested that dietary calcium may have a protective role against lead by decreasing absorption of lead in the gastrointestinal tract and by decreasing the mobilization of lead from bone stores to blood, especially during periods of high metabolic activity of the bone such as pregnancy, lactation, and menopause. An inverse association between patella lead and low calcium intake in postpartum women has been found (Hernandez-Avila et al., 1996). In contrast, Rothenberg et al. (2000) observed that dietary calcium intake had no effect on calcaneus lead in women monitored during the third trimester and 1 to 2 months postpartum. Likewise, no effect from calcium supplementation on bone lead was found amongst lactating women from Mexico City (Téllez-Rojo et al., 2002), although in a follow-up study, Hernandez-Avila et al. (2003) reported a 16.4% decrease in blood lead concentration among women with the highest patella bone lead levels who

were taking supplements. Gulson et al. (2004) observed that calcium supplementation was found to delay increased mobilization of lead from bone during pregnancy and halved the flux of lead release from bone during late pregnancy and postpartum. In another study, women whose daily calcium intake was 850 mg per day showed lower amounts of bone resorption during late pregnancy and postpartum than those whose intake was 560 mg calcium per day (Manton et al., 2003). Téllez-Rojo et al. (2004) observed that plasma lead levels were inversely related to dietary calcium intake. Results for whole blood lead were similar but less pronounced.

Some researchers have noted concerns regarding potential lead toxicity resulting from calcium supplementation. However, Gulson et al. (2001) observed that lead in calcium or vitamin supplements did not appear to increase blood lead concentrations. No information was available on the effects of other nutritional supplements (e.g., iron or zinc) on lead body burden.

6.2.2.6 Summary of Bone Lead as a Biomarker of Lead Body Burden and Exposure

Bone accounts for more than 90% of the total body burden of lead in adults and 70% in children. In addition, the longer half-life of lead in bone, which largely depends on the bone type but is generally estimated in terms of years compared to days for blood lead, allows a more cumulative measure of lead dose. The more widespread use of in vivo XRF lead measurements in bone and indirect measurements of bone processes with stable lead isotopes since the 1986 Lead AQCD have enhanced the use of bone lead as a biomarker of lead body burden.

In addition to considering bone lead as an indicator of cumulative lead exposure, lead in the skeleton can also be regarded as a source of lead. Key studies have examined the contribution of bone lead to blood lead; the preferential partitioning of bone lead into plasma; mobilization of lead from bones during pregnancy, lactation, and menopause; and the role of nutritional supplementation in bone mobilization.

6.2.3 Lead in Teeth

6.2.3.1 Summary of Key Findings from the 1986 Lead AQCD

The importance of dentine as a potential indicator of lead exposure was noted in the 1986 Lead AQCD. There was more emphasis and optimism on using dentine to assess lead exposure in this document as the bone XRF method was in its infancy. The issue of deciduous tooth type was addressed but there was little information on permanent teeth. The portion of the tooth

analyzed (i.e., whole tooth or circumpulpal dentine) was also addressed. In the 1990 Addendum, the use of tooth lead as an exposure metric was described in a number of the longitudinal and cross-sectional studies.

6.2.3.2 Analytical Methods for Measuring Lead in Teeth

Analytical methods for tooth analysis vary from the most widely used AAS, to energy-dispersive XRF, laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS), and high precision lead isotopes.

As a standard analytical method has yet to be established for tooth lead analysis, some of the discrepancies in findings between studies could arise from several factors, including differences in tooth type, part of the tooth analyzed, and tooth location. Any real differences among populations are unlikely to be the result of physiological factors such as blood supply to teeth or mineralization rates. As enamel and dentine in different teeth calcify at overlapping but different times (Orban, 1953), they could retain varying amounts of lead.

In a systematic evaluation of the magnitude of random errors associated with dentine lead measurements, Fergusson et al. (1989) measured lead concentrations in two samples of dentine from 996 New Zealand children. They estimated that 15 to 20% of the variance was unexplained. Tests of differences of means and variances showed no significant differences between the two samples.

Lead measurements in deciduous teeth in individuals from urban and remote environments and from polluted environments are presented in Annex Tables AX6-2.9 and AX6 2.10, respectively. Based on the limited number of studies, it would appear that the range in whole deciduous tooth lead for environmentally exposed subjects is about 1–10 μg/g, but the most likely levels are <5 μg/g and probably even <2 μg/g. Studies of whole deciduous teeth from industrial environments, including those in urban settings, are also commonly much less than 10 μg/g.

The utility of circumpulpal dentine (Shapiro et al., 1973) as the metric of lead exposure in deciduous teeth has not been enthusiastically received. This is likely due to the separation difficulties, as well as the limited amount of circumpulpal dentine that may be present when the teeth are resorbed, prior to exfoliation.

In another approach to gain more information about exposure during pregnancy and early childhood, the teeth may be sectioned into dominantly enamel or dominantly dentine. These samples can then be analyzed for lead isotopic ratios and lead concentrations (Gulson and Wilson, 1994). Even for children living in lead mining and smelting communities, levels of lead in the enamel are generally low (<5 μg/g) and are consistent with other studies of whole teeth. However, higher levels are observed in the dentine samples (e.g., 32 μg/g), which likely reflect the early childhood exposure. Permanent teeth tend to have up to three times the level of lead compared with deciduous teeth, but the number of studies is very limited.

6.2.3.3 Tooth Lead as a Biomarker of Lead Body Burden

Compared with the amount of lead in the skeleton, tooth lead is a minor contributor to the body burden of lead. Most of the tooth lead information is based on analyses of deciduous teeth. There is still controversy over the amounts of lead in different whole teeth but it appears that the highest concentrations are in central incisors, with decreasing amounts in lateral incisors, canines, first molars, and second molars. Teeth from the upper jaw tend to have higher lead concentrations than those from the lower jaw.

As teeth accumulate lead, tooth lead levels are generally considered an estimate of cumulative lead exposure. Rabinowitz et al. (1993) found that tooth lead was a better measure of exposure than current blood lead levels; however, it was not a good measure of the child's cumulative exposure from birth to exfoliation due to the mobilization of lead from dentine.

Teeth are composed of several tissues formed over the years. Therefore, if a child's lead exposure during the years of tooth formation varied widely, different amounts of lead would be deposited at different rates (Rabinowitz et al., 1993). This may allow investigators to elucidate the history of lead exposure in a child.

Gulson and Wilson (1994) advocated the use of sections of enamel and dentine to obtain additional information compared with analysis of the whole tooth (e.g., Fosse et al., 1995; Tvinnereim et al., 1997). For example, deciduous teeth lead in the enamel provides information about in utero exposure whereas that in dentine from the same tooth provides information about postnatal exposure until the tooth exfoliates at about 6 to 7 years of age.

6.2.3.4 Relationship between Tooth Lead and Blood Lead

As with bone lead-blood lead relationships, there is interest in understanding more about potential relationships between tooth lead and blood lead. The tooth lead-blood lead relationship is more complex than the bone lead-blood lead relationship because of differences in tooth type, location, and analytical method.

Rabinowitz (1995) used studies which reported values for dentine, whole shed teeth, or crowns, but discarded those measuring circumpulpal dentine because of the higher values in this medium. The mean tooth lead levels varied from 2.8 to 12.7 μg/g and blood lead levels from 6.5 to 17 μg/dL. In a plot of blood versus tooth lead, Rabinowitz found a good fit ($R^2 = 0.97$; $p < 0.0001$) with the relationship:

$$\text{Tooth Lead } (\mu g/g) = \beta \times [\text{Blood Lead } (\mu g/dL)], \text{ where } \beta = 0.49 \text{ (SE } 0.04).$$

In an earlier Boston study, Rabinowitz et al. (1989) found that the association between tooth and blood lead increased with age, first achieving statistical significance at 18 months; by 57 months, the correlation coefficient was 0.56. A correlation of 0.47 was found between current blood lead and incisors amongst 302 German children (Ewers et al., 1982).

6.2.3.5 Mobilization of Lead from Teeth

Although mobilization of lead from bone appears well established, this is not the case for lead in teeth. Conventional wisdom has lead fixed once it enters the tooth. Although that may be the case for the bulk of enamel, it is not true for the surface of the enamel and dentine.

In evaluating deciduous teeth data, Rabinowitz et al. (1993) suggested that their data were compatible with a model that allows lead to be slowly removed from dentine. Such a process may be associated with resorption of the root and dentine that precedes exfoliation, which allows reequilibration of dentine lead with blood lead.

In children exposed to lead sources from mining, paint, or petrol in communities such as the Broken Hill lead mining community, Gulson and Wilson (1994) and Gulson (1996) showed that the source of lead from the incisal (enamel) sections was different from the source of lead in the cervical (dentine) sections of deciduous teeth, reflecting the change in lead from in utero exposure to early childhood. Based on changes in the isotopic composition of enamel and

dentine in deciduous teeth sections from the Broken Hill mining community children, Gulson (1996) estimated that lead is added to dentine at a rate of approximately 2-3% per year.

Stable lead isotopes and lead concentrations were measured in the enamel and dentine of permanent (n = 37) and deciduous teeth (n = 14) from 47 European immigrants to Australia to determine whether lead exchange occurs in teeth and how it relates to lead exchange in bone (Gulson et al., 1997). The authors concluded that enamel exhibited no exchange of its European-origin lead with lead from the Australian environment, whereas dentine lead exchanged with Australian lead to the extent of ~1 ± 0.3% per year.

6.2.3.6 Summary of Tooth Lead as a Biomarker of Lead Body Burden and Exposure

Tooth lead is a minor contributor to the total body burden of lead. Moderate-to-high correlations have been observed between tooth lead levels and blood lead levels. Differences in tooth type, part of the tooth analyzed, and tooth location may contribute to some of the discrepancies in findings between studies of tooth lead. As teeth are composed of several tissues formed over the years, if a child's lead exposure during the years of tooth formation varied widely, different amounts of lead would be deposited at different rates. Deciduous teeth lead in the enamel provides information about in utero exposure, whereas that in dentine provides information about postnatal exposure until the tooth exfoliates.

6.2.4 Lead in Urine

6.2.4.1 Summary of Key Findings from the 1986 Lead AQCD

The 1986 Lead AQCD provided an extensive discussion of the physiological basis for "chelatable" urinary lead. Also discussed was lead excretion provoked by EDTA, including the pools of lead in the body that might be mobilized in the EDTA provocation test, and the relationship between the outcome and blood lead concentration. The 1986 Lead AQCD noted observations that formed the basis for application of the EDTA provocation test for detecting elevated lead body burden.

6.2.4.2 Analytical Methods for Measuring Lead in Urine

Standard methods that have been reported for urine lead analysis are summarized in Annex Table AX6-2.1 and are, in general, the same as those analyses noted for determination of

lead in blood. Reported detection limits are approximately 50 µg/L for AAS, 5–10 µg/L for ICP-AES, and 4 µg/L for ASV for urine lead analyses. Sample preparation usually consists of wet ashing; however, chelation and solvent extraction has also been reported (National Institute for Occupational Safety and Health, 1994, 1977a).

6.2.4.3 Levels of Lead in Urine

A summary of selected measurements of urine lead levels in humans can be found in Annex Table AX6-2.11. Urine lead concentrations in the U.S. general population have been monitored in NHANES. Data from the most recent survey (NHANES IV, Centers for Disease Control, 2005) for subjects ≥6 years of age are shown in Table 6-2.4. The geometric mean for the entire sample (n = 2,689) was 0.64 µg/g creatinine (95% CI: 0.60, 0.68). The geometric means for males (n = 1,334) and females (n = 1,335) were 0.64 µg/g creatinine (95% CI: 0.61, 0.67) and 0.64 µg/g creatinine (95% CI: 0.59, 0.69), respectively. These values correspond to approximately 1-1.3 µg lead/day for an adult, assuming a daily creatinine excretion rate of approximately 1.5 g/day in adult females, a body weight of 70 kg for males and 58 kg for females, and a lean body mass fraction of 0.88 for males and 0.85 for females (Forbes and Bruining, 1976; International Commission on Radiological Protection, 1981).

Table 6-2.4. Urine Lead Concentrations in U.S. by Age, NHANES IV (1999–2002)

Age	6–11 years		12–19 years		≥20 years	
Survey Period	1999–2000	2001–2002	1999–2000	2001–2002	1999–2000	2001–2002
n	340	368	719	762	1406	1559
Urine Lead (µg/g)[a]	1.17 (0.98, 1.41)	0.92 (0.84, 1.00)	0.50 (0.46, 0.54)	0.40 (0.38, 0.43)	0.72 (0.68, 0.76)	0.66 (0.62, 0.70) (µg/g)[2]

[a]Urine lead concentrations presented are geometric means (95% CI) of µg lead/g creatinine.

Geometric mean urinary lead excretion rates of 7-10 µg/g creatinine (maximum 43) have been reported in groups of children living in areas impacted by lead smelting operations (Brockhaus et al., 1988). Daily urinary lead excretion can exceed 200 µg/day in association with

occupational exposures (Biagini et al., 1977; Cramer et al., 1974; Lilis et al., 1968; Lin et al., 2001; Wedeen et al., 1975).

6.2.4.4 Urine Lead as a Biomarker of Lead Body Burden

Urine is a major route of excretion of absorbed lead (Chamberlain et al., 1978; Griffin et al., 1975; Kehoe, 1987; Rabinowitz et al., 1976). The kinetics of urinary excretion following a single dose of lead is similar to that of blood (Chamberlain et al., 1978), likely due to the fact that lead in urine derives largely from lead in blood plasma. Evidence for this is the observation that urinary lead excretion is strongly correlated with the rate of glomerular filtration of lead (i.e., glomerular filtration rate × plasma lead concentration; Araki et al., 1986). Estimates of urinary clearance of lead from serum (or plasma) range from 13-22 L/day, with a mean of 18 L/day (Araki et al., 1986; Chamberlain et al., 1978; Manton and Cook, 1984; Manton and Malloy, 1983). Estimates of blood-to-urine clearance, on the other hand, range from 0.03-0.3 L/day with a mean of 0.12 L/day (Araki et al., 1990; Berger et al., 1990; Chamberlain et al., 1978; Gulson et al., 2000; Koster et al., 1989; Manton and Malloy, 1983; Rabinowitz et al., 1976, 1973; Ryu et al., 1983; see Diamond, 1992 for an analysis of these data), consistent with a plasma to blood concentration ratio of approximately 0.005–0.01 L/day (U.S. Environmental Protection Agency, 2003). Based on the above, urinary excretion of lead can be expected to reflect the concentration of lead in plasma and variables that affect delivery of lead from plasma to urine (e.g., glomerular filtration and other transfer processes in the kidney).

Plasma lead makes a small contribution (<1%) to the blood lead concentration and a negligible contribution to total lead body burden. Furthermore, the kinetics of elimination of lead from plasma is fast, relative to lead in bone, where most of the lead burden resides. Therefore, the basic concepts described for blood as a biomarker for body burden also apply to urine. A single urine lead measurement, or a series of measurements taken over short-time span, is likely a relatively poor index of lead body burden (Figure 6-2.8). On the other hand, long-term average measurements of urinary excretion can be expected to be a better index of body burden. In the hypothetical simulation shown in Figure 6-2.8, both the long-term average urinary lead excretion rate and the body burden have approximately doubled.

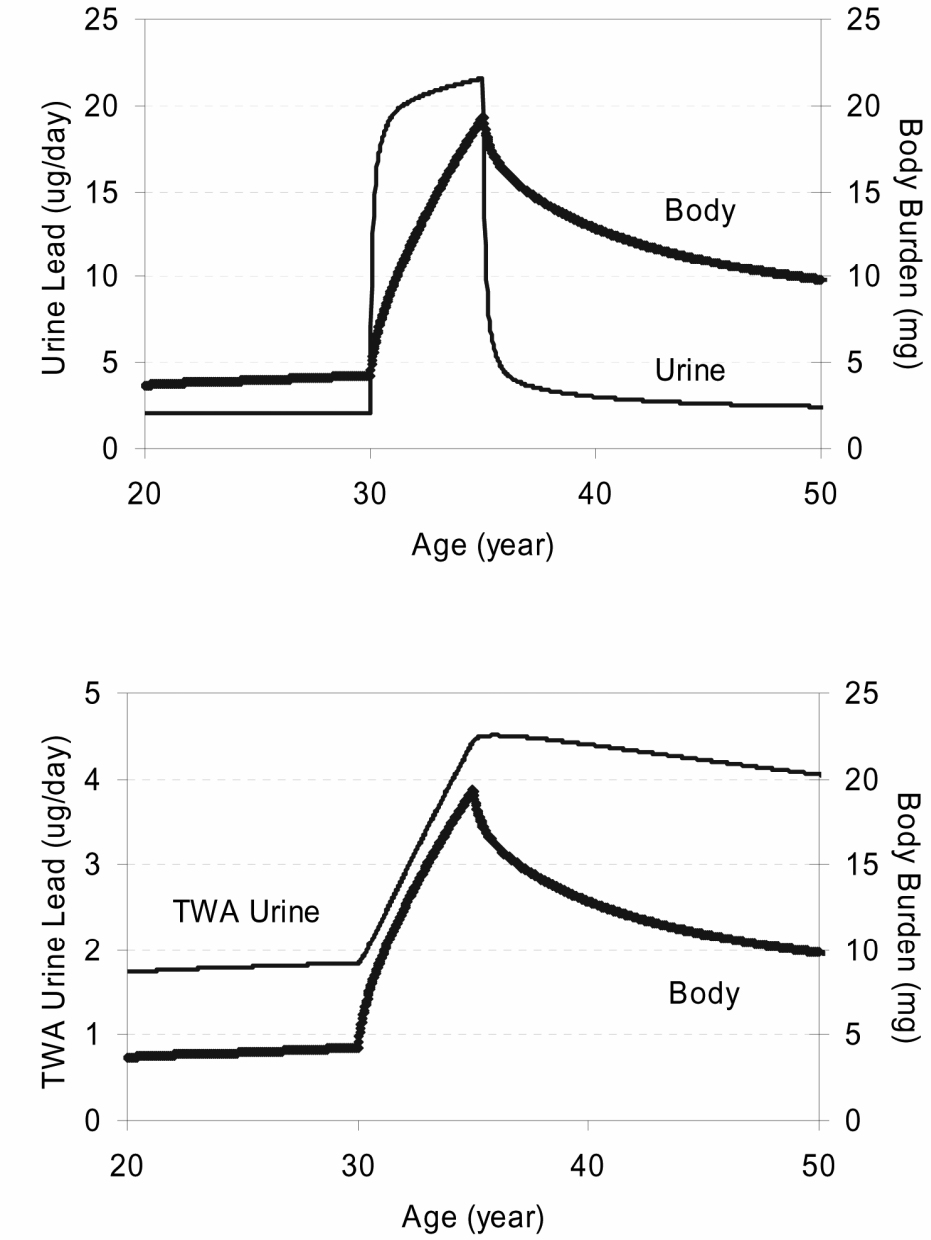


Figure 6-2.8. Simulation of relationship between urinary lead excretion and body burden in adults. An abrupt change in lead uptake gives rise to a relatively rapid change in urinary excretion of lead, to a new quasi-steady state, and a relatively small change in body burden (upper panel). The long-term average urinary lead excretion more closely tracks the pattern of change in body burden (lower panel). Simulation based on Leggett (1993) lead biokinetics model.

6.2.4.5 Urine Lead as a Biomarker of Lead Exposure

Assuming first-order kinetics, a plasma-to-urine clearance (UClP) of 13-22 L/day corresponds to half-time for transfer of lead from plasma to urine of 0.1-0.16 day for a 70 kg adult who has a plasma volume (VP) of approximately 3 L:

$$t_{1/2} = \frac{\mathrm{In}(2) \cdot V_P}{ICl_P}$$

This translates to a very rapid steady-state, much faster than observed for blood lead after a change in exposure level. The kinetics of change in urinary lead excretion in response to a change in exposure, therefore, will be determined by variables that affect the plasma lead level, including partitioning of lead into erythrocytes and exchanges with lead in soft tissues and mobile pools within bone (e.g., bone surface). Here again, the basic concepts that apply to blood lead as a biomarker of exposure also apply to urine lead. Urinary lead excretion reflects, mainly, the exposure history of the previous few months; thus, a single urinary lead measurement cannot distinguish between a long-term low level of exposure or a higher acute exposure. The relationship between urinary lead concentration and lead uptake is thought to be linear, unlike that for blood lead concentration, although there are no direct empirical tests of this assumption in humans. This assumption predicts a linear relationship between lead intake (at constant absorption fraction) and urinary lead excretion rate. Figure 6-2.9 presents a simulated relationship between lead intake and urinary lead excretion in adults and children using both the Leggett (1993) model and O'Flaherty (1993, 1995) model. The major difference between the Leggett model and the O'Flaherty model is in the assignment of the time dependence of bone lead residence. The Leggett model assumes a slow accumulation of a nonexchangable lead pool, whereas the O'Flaherty model assumes a gradual distancing of lead from bone surfaces by diffusion throughout the bone volume (O'Flaherty, 1998).

It is important to emphasize that the above concepts apply to urinary lead excretion rate, not to urinary lead concentration. The concentration of lead in urine (U_{Pb}) is a function of the urinary lead excretion (UE_{Pb}) and the urine flow rate (UFR, L/day):

$$UE_{Pb} = U_{Pb} \cdot UFR$$

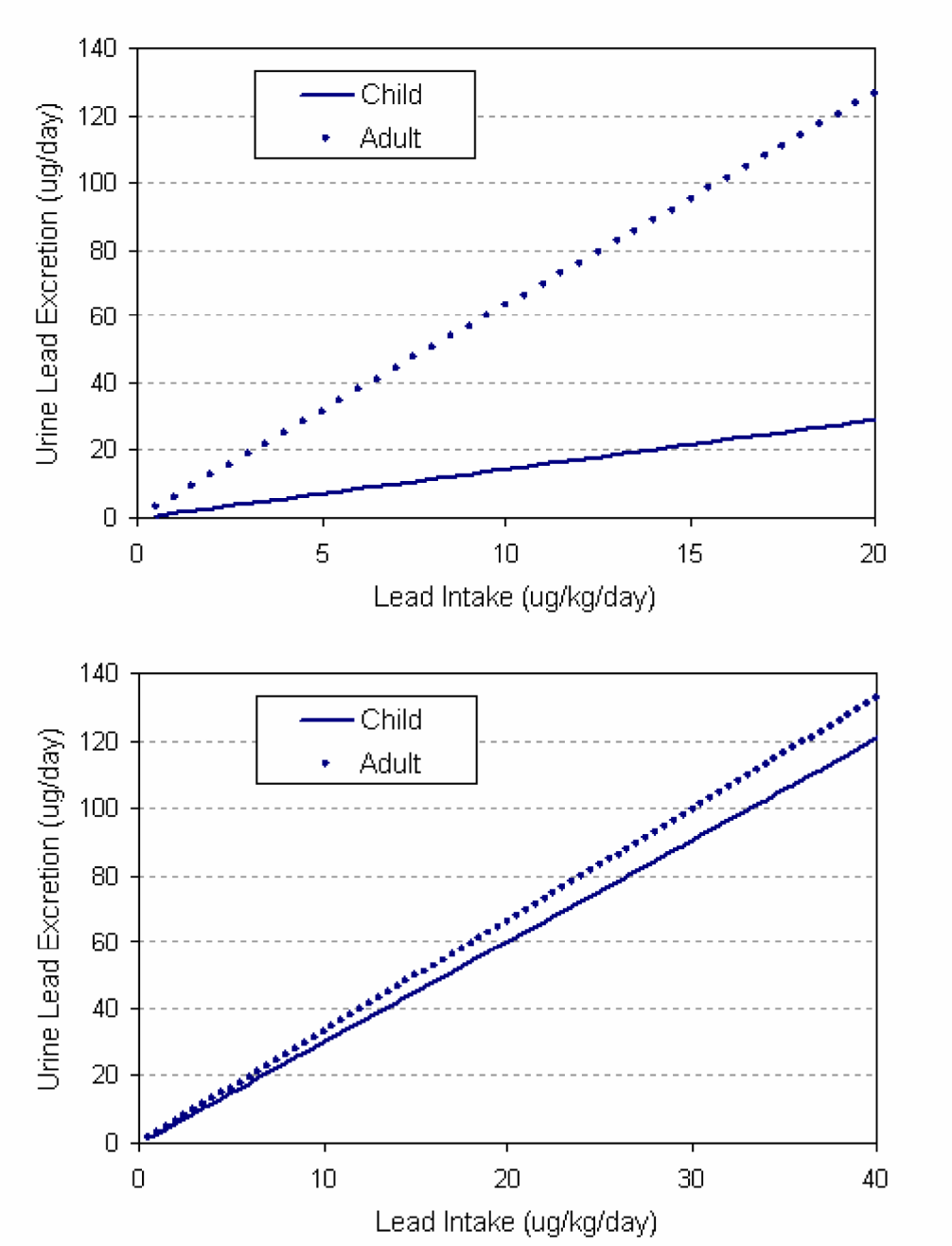


Figure 6-2.9. Simulation of relationship between lead intake and urinary lead excretion in adults and children. Predictions are for a 2-year-old child and 30-year-old adult, for a constant lead intake (µg/kg/day). The relationship is linear, for intake and plasma lead concentration (not shown). Predictions are based on Leggett (1993, upper panel) and O'Flaherty (1993, 1995, lower panel).

Urine flow rate can vary by a factor or more than 10, depending on the state of hydration and other factors that affect glomerular filtration rate and renal tubular reabsorption of the glomerular filtrate. All of these factors can be affected by lead exposure at levels that produce nephrotoxicity (i.e., decreased glomerular filtration rate, impaired renal tubular transport function; see Section 6.4 for discussion of effects of lead on the renal system). Therefore, urine lead concentration measurements provide little reliable information about exposure (or lead body burden), unless they can be adjusted to account for unmeasured variability in urine flow rate (Araki et al., 1990).

A determination of urinary lead excretion rate requires measurement of two variables, urine lead concentration, and urine flow rate; the later requires collection of a timed urine sample, which is often problematic in epidemiologic studies. Collection of un-timed ("spot") urine samples, a common alternative to timed samples, requires adjustment of the lead measurement in urine to account for variation in urine flow (Diamond, 1988). Several approaches to this adjustment have been explored, including adjusting the measured urine lead concentration by the urine creatinine concentration, urine osmolality, or specific gravity (Araki et al., 1990).

The measurement of lead excreted in urine following an injection (intravenous or intramuscular) of the chelating agent calcium disodium EDTA (EDTA provocation) has been used to detect elevated body burden of lead in adults (Biagini et al., 1977; Lilis et al., 1968; Wedeen, 1992; Wedeen et al., 1975) and children (Chisolm et al., 1976; Markowitz and Rosen, 1981). EDTA-provoked urinary lead excretion has been shown to correlate with tibia bone lead measurements (Wedeen, 1992). Given the difficulties associated with the parenteral administration of EDTA, XRF measurements of bone lead, offer a more feasible alternative to the EDTA provocation test for assessment of bone lead stores in epidemiologic studies. More recently, DMSA (DMSA-provocation) has been used as an orally-effective alternative to EDTA and has been applied to epidemiologic studies as dose metric for lead body burden (e.g., Lee et al., 2001; Schwartz et al., 2001a, 2000a, 2000b).

6.2.4.6 Summary of Urine Lead as a Biomarker of Lead Body Burden and Exposure

Similar to blood lead concentration measurements, urinary lead excretion measured in an individual at a single point in time will reflect the recent exposure history of the individual and

physiological variables that determine the plasma lead concentration time profile. Longitudinal measurements of urinary lead excretion can be expected to provide a more reliable measure of exposure history of an individual and will more closely parallel body burden than will single measurements; however, the degree to which this will apply will depend on the sampling frequency with respect to the exposure temporal pattern.

Although, in general, higher urinary lead excretion can be interpreted as indicating higher exposures (or lead uptakes), it does not necessarily predict appreciably higher body burdens. Similar urinary lead excretion rates in two individuals (or populations) do not necessarily translate to similar body burdens or similar exposure histories.

Measurement of the urinary lead excretion rate requires either a timed urine sample, or an approach to adjusting measured urinary lead concentrations for variability in urine flow rate, which by itself may be affected by lead exposure (i.e., lead-induced nephrotoxicity). Both approaches, timed urine samples or adjustment of concentration, introduce complications into the assessment and uncertainties into the interpretation of urinary lead measurements as biomarkers of lead body burden or exposure. The EDTA-provocation test provides a more reliable indicator of elevated body burden than do measurements of basal lead excretion; however, it is not feasible to apply this test for epidemiologic investigations. The DMSA-provocation test may provide a more feasible alternative.

6.2.5 Lead in Hair

6.2.5.1 Summary of Key Findings from the 1986 Lead AQCD

The 1986 Lead AQCD did not discuss applications of hair lead measurements for assessing lead body burden or exposure.

6.2.5.2 Analytical Methods for Measuring Lead in Hair

Methods used for hair lead analysis are summarized in Annex Table AX6-2.1. Wilhelm et al. (1989) reported a detection limit of 0.16 μg/g for GFAAS; use of GFAAS for hair lead measurements has been reported elsewhere (Annesi-Maesano et al., 2003). Gerhardsson et al. (1995a) reported a detection limit of 0.5 μg/g for XRF of the hair shaft; but Campbell and Toribara (2001) found XRF to be unreliable for hair root lead determinations. Use of other

methods has been reported, including ICP (Tuthill, 1996), ET/AAS (Drasch et al., 1997), and AAS (Sharma and Reutergardh, 2000; Esteban et al., 1999).

6.2.5.3 Levels of Lead in Hair

A summary of selected measurements of hair lead levels in humans can be found in Annex Table AX6-2.12. Reported hair lead levels vary considerably. Esteban et al. (1999) reported a geometric mean levels of 5.4 ng/g (range 1-39) for a sample of 189 children (aged 1.9 to 10.6 years) residing in Russian towns impacted by smelter and battery plant operations. By contrast, Tuthill (1996) reported much higher levels in a sample of Boston, MA children (aged 6.5 to 7.5 years, n = 277). Approximately 41% had levels that ranged from 1 to 1.9 µg/g. DiPietro et al. (1989) reported a geometric mean hair lead level of 2.42 µg/g (10–90th percentile range <1.0-10.8) in a general population sample of U.S. adults (aged 20 to 73 years, n = 270). In a post-mortem sample of the general population from Germany (aged 16 to 93 years, n = 150), the median hair lead level was 0.76 µg/g (range 0.026-20.6) (Drasch et al., 1997). Also, Gerhardsson et al. (1995a) reported median values for postmortem samples of 8.0 µg/g (range 1.5-29,000) in active workers (n = 6), 2.6 µg/g (range 0.6-9.3) in retired workers (n = 23), and 2.1 µg/g (range 0.3-96) in a reference group (n = 10).

6.2.5.4 Hair Lead as a Biomarker of Lead Body Burden

Lead is incorporated into human hair and hair roots (Bos et al., 1985; Rabinowitz et al., 1976) and has been explored as a possibly noninvasive approach for estimating lead body burden (Gerhardsson et al., 1995a; Wilhelm et al., 1989, 2002). Hair lead measurements are subject to error from contamination of the surface with environmental lead and contaminants in artificial hair treatments (i.e., dyeing, bleaching, permanents) and are a relatively poor predictor of blood lead concentrations, particularly at low levels (<12 µg/dL) (Campbell and Toribara, 2001; Drasch et al., 1997; Esteban et al., 1999). Studies evaluating quantitative relationships between hair lead and lead body burden have not been reported. Nevertheless, hair lead levels have been used as a dose metric in some epidemiologic studies (e.g., Annesi-Maesano et al., 2003; Esteban et al., 1999; Gerhardsson et al., 1995a; Powell et al., 1995; Sharma and Reutergardh, 2000; Tuthill, 1996).

6.2.5.5 Hair Lead as a Biomarker of Lead Exposure

Rabinowitz et al. (1976) measured hair lead levels in two adult males who received a stable lead isotope supplement to their dietary intake for 124–185 days. Approximately 1% of the daily lead intake was recovered in hair. Temporal relationships between exposure levels and kinetics and hair lead levels, and kinetics of deposition and retention of lead in hair have not been evaluated. Higher hair lead levels were observed in lead workers than in reference subjects with lower blood lead levels (Mortada et al., 2001).

6.2.5.6 Summary of Hair Lead as a Biomarker of Lead Body Burden and Exposure

Although hair lead measurements have been used in some epidemiologic studies, an empirical basis for interpreting hair lead measurements in terms of body burden or exposure has not been firmly established. Hair lead measurements are subject to error from contamination of the surface with environmental lead and contaminants in artificial hair treatments (i.e., dyeing, bleaching, permanents) and, as such, are relatively poor predictor of blood lead concentration, particularly at low levels (<12 μg/dL).

6.3 NEUROTOXIC EFFECTS OF LEAD

This section assesses epidemiologic evidence for neurotoxic effects of lead exposure in children and adults. First presented are studies of the neurotoxic effects of lead on children, with a focus on several prospective studies examining neurocognitive ability. Other topics include measures of academic achievement, cognitive abilities, disturbances in behavior, mood, and social conduct, measures of brain anatomical development and activity, gene-environmental interaction, and reversibility of neurodevelopmental deficits. Then, neurotoxic effects of environmental and occupational lead exposure of adults are discussed.

6.3.1 Summary of Key Findings on Neurotoxic Effects of Lead in Children from 1986 Lead AQCD and Addendum, and 1990 Supplement

The 1986 Lead AQCD stated that children were particularly susceptible to lead-induced neural damage. In particular, human infants and toddlers below that age of 3 years were considered to be at special risk due to their in-utero exposure, increased opportunity for exposure

because of normal mouthing behavior of lead-containing objects, and increased rates of lead absorption due to factors such as iron and calcium deficiencies.

Effective blood lead levels for producing encephalopathy or death in children were noted in the 1986 Lead AQCD as starting at 80–100 µg/dL. Various types of neural dysfunction were stated as being evident at lower blood lead levels. Behavioral (e.g., reaction time, psychomotor performance) and electrophysiological (e.g., altered electrophysiological patterns, evoked potential measures, and peripheral nerve conduction velocities) effects were observed at blood levels as low as 15-30 µg/dL and possibly lower. A concentration-response relationship between blood lead levels and IQ also was observed; a 1-2 point difference in IQ was generally seen with blood lead levels in the 15-30 µg/dL range. However, a study by Schroeder and Hawk (1987) reported a highly significant linear relationship between a measure of IQ and blood lead levels over the range of 6 to 47 µg/dL in a cohort of all African American children of low SES, suggesting that IQ effects might be detected even at these low levels.

The 1986 Addendum discussed the newly published results of several prospective cohort studies on the developmental effects of lead in children. These studies improved upon the previous studies with longitudinal study design that followed children from the prenatal stage, a larger number of subjects, and better analytic techniques to more accurately measure blood lead levels. The four prospective studies (conducted in Boston, MA; Cincinnati, OH; Cleveland, OH; and Port Pirie, Australia) reported significant associations between prenatal and postnatal blood lead levels and neurobehavioral deficits, after adjusting for various potential confounding factors such as maternal IQ and HOME (Home Observation for Measurement of Environment) scores (Bellinger et al., 1984; Dietrich et al., 1986; Ernhart et al., 1985, 1986; McMichael et al., 1986; Vimpani et al., 1985; Wolf et al., 1985). In these studies, the observed maternal and cord blood lead levels were fairly low, with mean levels of approximately 10 µg/dL. These results led the 1986 Addendum to conclude that neurobehavioral deficits, including declines in Bayley Mental Development Index (MDI) scores and other assessments of neurobehavioral function, are associated with prenatal blood lead exposure levels on the order of 10 to 15 µg/dL and possibly even lower, as indexed by maternal or cord blood lead concentrations.

The 1990 Supplement updated evidence from the above-mentioned longitudinal cohort studies and summarized results from other more recent prospective cohort studies conducted in Glasgow, Scotland; Kosovo, Yugoslavia; Mexico City; and Sydney, Australia. Results from

several other international cross-sectional studies also were discussed. The collective evidence from the various prospective cohort and cross-sectional studies reaffirmed the conclusions from the 1986 Addendum that neurobehavioral effects were related to blood lead levels of 10 to 15 µg/dL and possibly lower. Further analyses of the Boston data indicated that deficits in MDI could be detected in relation to cord blood lead levels of 6-7 µg/dL in children within the lower strata for SES (Bellinger et al., 1988). In the Port Pirie study, the relationship between postnatal blood lead levels and MDI at two years of age provided little evidence of a threshold effect (Wigg et al., 1988). Restricting the analysis to children with blood lead levels below 25 µg/dL yielded an even stronger association between integrated postnatal blood lead and McCarthy General Cognitive Index (GCI) scores in the Port Pirie study (McMichael et al., 1988).

Impaired neurobehavioral development was associated with blood lead measures in pregnant women, umbilical cords, and infants up to at least 2 years of age; thus, no distinction could be made as to whether this level of concern applied to only fetuses or infants or preschool-age children. The issue of the persistence of the neurobehavioral effects from low-level lead exposure also was considered. Although the Boston and Cincinnati studies provided limited evidence suggesting that the effects of prenatal lead exposure on neurobehavioral development were not permanent, the evidence available to support this conclusion was inadequate.

6.3.2 Neurotoxic Effects of Lead in Children

Several major developments have occurred in lead research on child neurodevelopment following the 1986 Lead AQCD/Addendum and the 1990 Supplement. First, there has been an attempt to broaden outcome assessments beyond neurocognitive deficits. The earlier emphasis on neurocognitive measures (e.g., MDI, GCI, IQ) in previous studies is understandable from the perspectives of the strong psychometric properties of most of these rigorously standardized measures as well as the immediate pubic health concerns. Examples of other outcomes used to assess neurodevelopment include the number of errors on tests of visual-motor integration, the time required to complete a task assessing manual dexterity, the number of errors and false alarms on a continuous performance test, and the efficiency of short term memory. Additional neurodevelopment outcomes include those which elucidate brain-behavior relationships or the potential real life consequences of early exposure to lead, such as academic and vocational failure and maladjustment to the daily demands of living in a complex society. Thus,

epidemiologic studies of lead neurotoxicity have been expanded to adopt measures of academic achievement, specific cognitive abilities, behavior and mood, sensory acuities, neuromotor function, and direct measures of brain anatomical development and activity. Another development has been the initiation of nutritional and pharmacological intervention studies to assess the impact of treatment on reducing blood lead levels and preventing or moderating the degree of harm to the central nervous systems of young children. Also, in addition to blood and tooth lead, bone lead has emerged as a reliable biomarker of lead exposure. The technology for the assessment of lead in cortical (tibial) and trabecular (patellar) bone using K-shell X-ray fluorescence (XRF) has advanced to the point where it could be applied as a reliable and valid index of cumulative lead dose in neuroepidemiologic studies (Aro et al., 1994).

In recent years, more studies have investigated the impact of blood lead levels below 10 µg/dL on the developing brain. Average blood lead levels in U.S. children ages one to five years decreased from 15 µg/dL to approximately 3 µg/dL between 1976-1980 and 1991-1994, allowing newer studies to examine the effects of low level lead on the neurodevelopment of children (Centers for Disease Control, 2000; Pirkle et al., 1998).

At the time of the last previous criteria review, it was recognized that estimating a threshold for toxic effects of lead on the central nervous system entailed difficulties. As discussed in the 1990 Supplement, insults to the human brain may be irreversible, making it difficult to determine whether any measured insult is the result of current or past exposures. An observed effect concurrent with a measured blood lead concentration may be the result of exposure in the child's earlier life in the womb or infancy. There is also the critical question of reversibility or the persistence of lead effects identified in infants and preschoolers into school age and later. A given effect observed at younger ages may not persist due to functional compensation or a return to a normal neuromaturational trajectory (Dietrich et al., 1990). Another problem is that it is sometimes difficult to distinguish between neurobehavioral effects due to lead and effects owing to the many social, economic, urban-ecological, nutritional, and other medical factors that are known to have important effects on neurobehavioral development. Equally important is the high probability that the concentration-response relationship and even the neurobehavioral lesion associated with childhood lead exposure may vary as a function of these cofactors (Bellinger, 1995).

In the following sections, prospective cohort studies and cross-sectional studies of neurocognitive ability published since the 1990 Supplement are presented first. Then, studies examining the effect of lead on a variety of neurodevelopmental outcomes, including academic achievement; specific cognitive abilities; disturbances in behavior, mood, and social conduct; sensory acuities; neuromotor function; and brain anatomical development and acuity, are discussed. This is followed by a presentation of issues involved in understanding lead neurotoxicity in children, including gene-environment interactions, reversibility of lead effects, times of vulnerability, and potential threshold levels for effects.

6.3.2.1 Neurocognitive Ability

6.3.2.1.1 Prospective Longitudinal Cohort Studies of Neurocognitive Ability

Several prospective longitudinal cohort studies were initiated in the 1980s because it became widely recognized that the cross-sectional study design was inadequate to address a number of research issues (U.S. Environmental Protection Agency, 1986; World Health Organization, 1977). These longitudinal studies were characterized by serial measures of dose (blood lead levels) spanning (in most cases) the prenatal and postnatal periods of central nervous system development, thus helping to clarify the temporal association between exposure and insult. Also, developmental assessments that extended into the school-age period were planned to determine if early lead associated neurobehavioral impairments were permanent or reversible in the fullness of time. It was also determined that assessment of potential confounding factors should be comprehensive and include measures of perinatal health, nutrition, maternal consumption of other neurotoxicants during pregnancy, parental intelligence, and direct observations of parenting behavior. These studies were also characterized by very careful attention to biostatistical issues and strategies (Bellinger, 1995; Ernhart, 1995).

At the time of the 1990 Supplement, studies were underway or planned in the U.S., Australia, Scotland, the former Yugoslavia, and Mexico. These cohorts differed in the source and degree of lead exposure and in other important aspects, notably ethnicity and SES. Nevertheless, the early results from several of these studies have been largely responsible for the emergence of the current perspective that blood lead concentrations as low as 10 μg/dL, or perhaps even lower, may pose a risk for neurodevelopmental toxicity (Davis and Svendsgaard, 1987; U.S. Environmental Protection Agency, 1990). Most of the prospective studies underway

in 1990 continued to follow their subjects into the later preschool and school age years with age-appropriate measures of intelligence. Continued follow-up of these cohorts was important due to the following: (1) greater reliability and precision of measurements attained with assessments of older children; (2) high predictability of adult intellectual functioning from measures of IQ in the older child; and (3) examination of potential effects of lead on important abilities that cannot be easily tapped during infancy such as executive functions and higher order reasoning (McCall, 1979).

A unique aspect of this research was that most investigators agreed during the formative stages of their projects to develop somewhat similar assessment protocols (Bornschein and Rabinowitz, 1985). This has facilitated comparison of results across studies and allowed for sophisticated meta- and pooled-analyses of these data (e.g., Pocock et al., 1994; Schwartz, 1994; World Health Organization, 1995; Lanphear et al., 2005; Rothenberg and Rothenberg, 2005).

In the following sections, further updates on the individual prospective cohort studies are presented in chronological order of study initiation. The prospective cohort studies reviewed are summarized in Annex Table AX6-3.1. Results of the meta- and pooled-analyses are presented later in this section.

Boston Study

In the 1986 Addendum, the most advanced investigation at that time was the Boston Prospective Study (Bellinger et al., 1984). The subjects were 216 middle-to upper-middle-class Boston children, 90% of whom had cord blood lead levels below 16 µg/dL (maximum 25 µg/dL). Cord blood lead levels in the "high" group (mean 14.6 µg/dL) were associated with lower covariate-adjusted scores on the Mental Development Index (MDI) of the Bayley Scales of Infant Development at 6 months of age. It was concluded that although lower level lead exposure in utero may result in delays in early sensorimotor development, the Boston results did not allow estimation of the persistence of these effects nor the public health significance of the findings. The association between higher cord blood lead and lower MDI persisted to 24 months; however no association was observed between postnatal blood lead levels and MDI (Bellinger et al., 1985, 1986).

Particular attention was focused on the Boston study, which was among the more mature in terms of follow-up, in the 1990 Supplement (Bellinger et al., 1987; Bellinger et al., 1991).

With respect to the effects of cord blood lead concentrations on MDI assessed longitudinally from 6 to 24 months, the lead associated deficits were evident across the entire range of blood lead levels starting at 10 μg/dL, which reinforced the previous designation of 10-15 μg/dL as a blood level of concern for early neurodevelopmental deficits. At approximately 5 years of age, cord blood lead levels were not significantly associated with the McCarthy GCI, but blood lead level at 2 years of age (mean 6.8 μg/dL [SD 6.3]) was significantly associated with lower scores. Although cord blood lead concentrations were not independently associated with deficits in 5-year neurocognitive status, the risk of obtaining lower GCI scores was greater among subjects with higher prenatal and postnatal blood lead concentrations. Boston investigators also examined the relationship between lead measured in shed deciduous teeth obtained from 102 children in their cohort (mean 2.8 ppm [SD 1.7]) and GCI at 5 years of age. Prior to covariate-adjustment, there was a very strong and significant relationship amounting to a loss of more than 10 points in GCI for each log increment in dentine lead. However, in the multivariable analysis the tooth lead coefficient, although negative, was no longer statistically significant. Reduced sample size should be taken into consideration in interpreting this null finding.

Since the 1990 Supplement, the Boston investigators reexamined 148 of their subjects at 10 years of age with the Wechsler Intelligence Scale for Children-Revised (WISC-R) and other neurobehavioral assessments (Bellinger et al., 1992). They examined the association of WISC-R scores at 10 years of age with blood lead concentrations in the cord blood and at 6 months, 12 months, 18 months, 24 months, 57 months, and 10 years. Only blood lead levels at 24 months were significantly associated with full scale and verbal IQ and marginally associated with performance IQ, after adjusting for HOME score, maternal age, birth weight, and maternal IQ. The integrated average blood lead level in this cohort over the first 2 years was 7.0 μg/dL (range 4-14 μg/dL). An increase of 10 μg/dL in blood lead level at age 2 was associated with a decrement of 5.8 points (95% CI: 1.8, 9.9) in full scale IQ. These findings indicated that children's performance was much more strongly associated with blood lead levels at age 2 than with blood lead levels at other ages. It is unclear whether this reflects a special vulnerability of the nervous system during this period or simply the fact that blood lead level tends to peak in the second year.

A reanalysis involving the total Boston cohort that employed nonparametric smoothing revealed that the inverse association persisted at blood lead levels below 5 µg/dL (Schwartz, 1994). Bellinger and Needleman (2003) reanalyzed data on 48 children whose measured blood lead concentrations never exceeded 10 µg/dL. Reduction in full scale IQ at 10 years was significantly associated with blood lead levels at 2 years of age following covariate adjustment. A larger deficit of 15.6 points (95% CI not presented) per 10 µg/dL increase in blood lead levels was observed in this cohort, compared to the 5.8 point deficit observed in the entire cohort. These findings indicated that the inverse slope might be steeper at blood lead levels below 10 µg/dL.

Cincinnati Study

Interim results on a partial sample of 185 subjects from a cohort of 305 were available from the Cincinnati prospective study in the 1986 Addendum and the 1990 Supplement (Dietrich et al., 1986, 1987a). The Cincinnati study investigators reported an inverse relationship between prenatal maternal blood lead levels (mean 8.3 µg/dL) and 6 month Bayley MDI. This effect was mediated, in part, through lead-associated reductions in birth weight and gestational maturity. A more complete analysis of the full Cincinnati cohort confirmed these interim findings (Dietrich et al., 1987b).

Further updates of the Cincinnati study appeared after the 1990 Supplement. The Kaufman Assessment Battery for Children (KABC) was administered to approximately 260 children at 4 and 5 years of age (Dietrich et al., 1991; 1992). The principal findings at 4 years were that higher neonatal blood lead concentrations were associated with poorer performance on all KABC subscales. However, this relationship was confined to children from the poorer families. Following full covariate adjustment, few statistically significant relationships remained. At 5 years of age, postnatal blood lead levels were associated with performance on all subscales of the KABC; however, few statistically significant relationships remained after adjustment for covariates. Nevertheless, it is of interest that at both 4 and 5 years the KABC subscale that assessed visual-spatial skills was among those that remained the most highly associated with various indices of postnatal exposure following covariate adjustment. At the age of approximately 7 years, 253 children in the Cincinnati cohort were administered the WISC-R (Dietrich et al., 1993a). In this cohort, approximately 35% had at least one blood lead

concentration ≥25 µg/dL while 95% exceeded 10 µg/dL sometime during the first 5 years of life. Postnatal blood lead concentrations were inversely associated with full scale and performance IQ, after adjusting for HOME score, maternal IQ, birth weight, birth length, child gender, and cigarette consumption during pregnancy. Figure 6-3.1 presents the unadjusted and adjusted concentration-response relationship between lifetime average blood lead concentrations and performance IQ. Following covariate adjustment, a statistically significant relationship was observed between postnatal blood lead levels at 5 and 6 years of age and full scale IQ. Postnatal blood lead levels at nearly all ages (including the integrated average blood lead level) were inversely associated with performance IQ. Blood lead levels at 6 years of age were most strongly associated with performance IQ – a 5.2 point [95% CI: 2.3, 8.1] decline was observed for each 10 µg/dL increase in blood lead level. A 10 µg/dL increase in lifetime average blood lead concentration was associated with a 2.6 point (95% CI: 0.2, 5.0) decline in performance IQ.

At 15-17 years of age, the Cincinnati subjects were administered a comprehensive neuropsychological battery (Ris et al., 2004). Variables derived from the Cincinnati neuropsychological battery were subjected to a principal components factor analysis that yielded five factors, including a learning/IQ factor that had high loadings for the Vocabulary and Block Design subtests from the WISC-III as well as the Reading, Spelling, and Arithmetic subscales of the Wide Range Achievement Test-Revised (WRAT-R). Prenatal, Average Childhood, and 78 month blood lead levels were used in a series of multiple regression analyses. Following covariate-adjustment, there was a trend towards significance for higher blood lead concentrations in later childhood (e.g., 78 months) to be associated with lower learning/IQ factor scores, but this was largely observed in subjects from the lower end of the socioeconomic scale in the sample. This finding is consistent with previous reports that children in the lower social strata may be more vulnerable to general effects on cognitive development and learning (Bellinger, 2000; Winneke and Kraemer, 1984).

Cleveland Study

Early results of the Cleveland prospective study also were reviewed in the 1986 Addendum and 1990 Supplement. By selection, about half of the mothers had histories of alcohol abuse as measured by the Michigan Alcoholism Screening Test. The other women were matched controls. The initial cohort included 389 infants with a mean cord blood lead level of

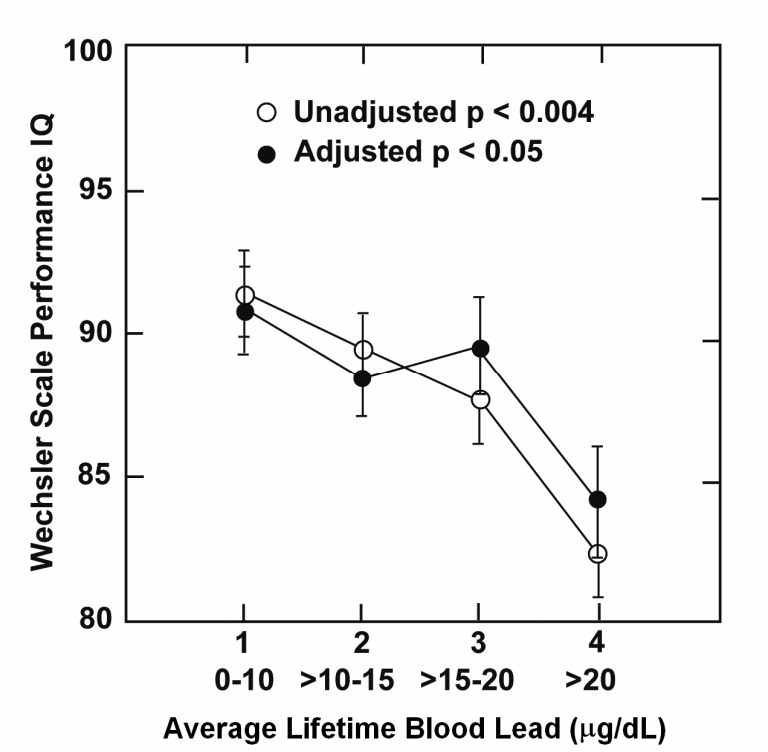


Figure 6-3.1. Unadjusted and adjusted relationships between average lifetime blood lead concentrations and Wechsler Scale performance IQ. Mean ± SD lifetime average blood lead concentrations within each category were as follows: 0-10 µg/dL, 7.7 ± 1.4 µg/dL (n = 68); >10-15 µg/dL, 12.3 ± 1.4 µg/dL (n = 89); >15-20 µg/dL, 17.1 ± 1.2 µg/dL (n = 53); and >20 µg/dL, 26.3 ± 5.0 µg/dL (n = 41).

Source: Dietrich et al. (1993a).

5.84 µg/dL (maximum 14.7). In addition to size, minor morphological anomalies, and 1- and 5-minute Apgar performances, infants were evaluated on the Brazelton Neonatal Behavioral Assessment Scale (NBAS) and part of the Graham-Rosenblith Behavioral Examination for Newborns (G-R). Of the 17 neonatal outcomes examined, the NBAS Abnormal Reflexes scale and neurological soft signs assessed by G-R were associated with cord blood lead levels in the range of 3 to 15 µg/dL following covariate adjustment (Ernhart et al., 1986). A follow-up study observed a significant effect of the neurological soft signs measure on Bayley MDI scores at 12 months; however, prenatal lead exposure was not associated with MDI scores at 6-24 months or Stanford-Binet IQ (S-B IQ) scores at 36 months (Wolf et al., 1985).

In 285 children from the original cohort, maternal and cord blood lead levels, as well as postnatal blood lead levels at 6 months, 2 years, and 3 years were examined in relation to Bayley MDI, Psychomotor Index (PDI), and Kent Infant Development Scale (KID) at 6 months, MDI at 1 year and 2 years, and S-B IQ at 3 years of age (Ernhart et al., 1987, 1988). After covariate adjustment, only maternal blood lead level at delivery (mean 6.5 μg/dL [maximum 11.8]) was inversely associated with MDI, PDI, and KID scores at 6 months. No other indices of prenatal or postnatal lead exposure were inversely associated with assessments of global intellectual functioning. Language development also was assessed in the Cleveland cohort at 1, 2, and 3 years of age. Few significant associations remained after covariate adjustment (Morrow-Tlulak and Ernhart, 1987).

At 4 years and 10 months, 242 children from the Cleveland cohort were administered the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) test. Significant negative correlations were observed between full scale, verbal, and performance IQ, and prenatal (both maternal and cord) and postnatal (at 2 years and 3 years) blood lead levels (Ernhart and Morrow-Tlulak, 1987). However, these associations were no longer significant after adjustment for various covariates, including HOME score, maternal IQ, parent education, race, medical problems, maternal alcohol use in pregnancy, Michigan Alcoholism Screening Test score, maternal use of marijuana, and several categories of psychosocial trauma scale. The authors reported a large contribution of these covariates to the variance of the WPPSI scores; the smaller effects of lead may have been suppressed by these other social factors. In particular, the HOME score was found to most strongly contribute to the child's IQ. In 164 children, shed deciduous incisor were collected between ages 5 and 7. Circumpulpal dentine lead levels were found to be significantly associated with full scale, verbal and performance IQ, assessed using the WPPSI test, at 4 years and 10 months, after adjustment for various covariates except for HOME score. After additional adjusting for HOME score, the lead effects on all three IQ measures diminished, but remained statistically significant for verbal IQ ($p = 0.01$) and marginally significant for full scale IQ ($p = 0.06$). An increase in dentine lead from the 10th percentile to the 90th percentile level (13.5 μg/g to 129.4 μg/g) was associated with a 6.0 point (95% CI: 1.4, 10.6) decrease in verbal IQ and a 4.5 point (95% CI: −0.2, 9.2) decrease in full scale IQ. The estimated lead effect increased as a function of the level of measurement error in the dentine lead variable. This finding of an adverse effect for dentine lead is not consistent with previous analyses of the

Cleveland study showing that blood lead levels are, generally, not associated with cognitive outcomes after covariate adjustment.

Port Pirie, Australia Study

Preliminary results from the Port Pirie, Australia study also were described in the 1986 Addendum (Vimpani et al., 1985). Lower Bayley MDI scores at 2 years from 592 children were significantly associated with higher integrated postnatal blood lead levels (approximately 20% of the sample had blood lead levels >30 μg/dL at the time of assessment), but not with maternal prenatal, delivery, or cord blood lead levels. Results of this interim analysis were interpreted with caution since important covariates such as maternal IQ and HOME scores were not available for the entire cohort at the time of the analyses.

The Port Pirie cohort study had reported results out to 4 years when the 1990 Supplement was released (McMichael et al., 1988). Following adjustment for covariates, lead concentrations at most postnatal sampling points as well as an integrated average for the 4-year postnatal period were significantly and inversely associated with scores on the McCarthy Scales of Children's Abilities. The GCI scores declined by approximately 4.5 points (95% CI: 0.2, 8.8) for a doubling in blood lead levels. Similar deficits occurred in the perceptual-performance and memory scores. The integrated postnatal blood lead levels among the 537 children in this cohort were among the highest of the prospective studies (geometric mean 19 μg/dL). However, further analyses indicated that the effects observed did not depend on children with the more extreme levels of exposure. The concentration-response relationship between blood lead and GCI was stronger among children with blood lead levels below 25 μg/dL than it was overall.

Of all of the prospective studies of lead and child development, the Port Pirie cohort study was probably among the best positioned to reliably detect effects of low level lead exposure into later childhood owing to its wide range of exposure, large sample size, and lack of extremes in terms of sample social advantage or disadvantage. The WISC-R was administered to 494 children between 7 and 8 years of age (Baghurst et al., 1992). IQ scores were examined in relation to ln-transformed blood lead concentration. Following adjustment for covariates there was little association with pre- and perinatal lead exposure assessments. However, significant decrements in full scale and verbal IQ were found to be associated with postnatal blood lead levels. The estimated effect size was a loss of 3.3 points (95% CI: 0.2, 6.5) in full scale IQ and

4.0 points (95% CI: 0.7, 7.2) in verbal IQ in association with a doubling of the integrated postnatal blood lead concentration up to three years. In light of the Cincinnati findings, it is of interest that the Block Design subtest of the WISC-R (a measure of visual-spatial abilities), exhibited the strongest association with lead exposure. Port Pirie investigators also collected deciduous central upper incisors from 262 children in their cohort (McMichael et al., 1994). After covariate adjustment, a significant inverse association was observed between tooth lead concentration and WISC-R full scale IQ at 7 years of age. The adjusted estimated decline in full scale IQ across the tooth lead range from 3 to 22 μg/g (range for 90% of population) was 5.1 points (90% CI: 0.2, 10.0). Once again, the Block Design subtest was among the most highly sensitive.

Port Pirie children were assessed again at 11-13 years of age to examine the persistent relationship between exposure to environmental lead and intelligence (Tong et al., 1996). At that age, Port Pirie investigators were able to recall 375 children for IQ assessments. At 11-13 years of age, the geometric mean lifetime average blood lead concentration was 14.1 μg/dL. WISC-R scores were significantly and inversely associated with integrated lifetime average blood lead concentrations out to 11-13 years. Later blood lead concentrations after 3 years of age were more predictive of lower IQ. Mean full scale IQ declined by 3.0 points (95% CI: 0.1, 5.9) for a doubling of lifetime average blood lead concentrations. The authors could find no clear evidence of a threshold level in their data.

Sydney, Australia Study

Unlike Port Pirie, the reports on the Sydney cohort study were consistently negative with respect to the effects of exposure on neurodevelopment (Cooney et al., 1989a,b; McBride et al., 1989). In the 298 mothers and infants sampled, geometric mean blood lead levels at delivery were 9.1 μg/dL and 8.1 μg/dL, respectively, with less than 2% in excess of 15 μg/dL. Mean postnatal blood lead levels peaked at 16.4 μg/dL when children reached 18 months and then declined to 10.1 μg/dL at 48 months. No significant, inverse relationships were reported between prenatal or postnatal blood lead concentrations and neurodevelopmental assessments conducted from 6 months through 4 years of age. The McCarthy Scales of Children's Abilities was administered to 207 children at 4 years of age but no associations with blood lead levels were observed prior to or following covariate-adjustment. As in the case of the Cleveland study,

the authors noted that the HOME score was a strong contributor to the neurodevelopmental assessments at all ages. As stated in the 1990 Supplement, this raises the questions of whether lead exposure might have covaried with HOME scores. If so, adjusting for HOME scores would reduce the statistical power to examine the effect of postnatal blood lead levels on the neurocognitive measures. Also note that the interpretation of the Sydney findings has been complicated by concerns about possible contamination of capillary blood lead samples collected during the early phases of the investigation (Cooney et al., 1989b).

The Sydney prospective study further assessed 175 subjects that remained in the study at 7 years of age (Cooney et al., 1991). Geometric mean blood lead concentrations peaked at 2 years of age (15.2 µg/dL). The geometric mean blood lead level at 7 years of age was 7.7 µg/dL. The WISC-R and other neurobehavioral assessments were administered. The adjusted correlations between postnatal blood lead levels and WISC-R scores were consistently negative but nonsignificant at the $p = 0.05$ level. The r value (units = SD of IQ per SD of blood lead) for the correlation between full scale IQ and concurrent blood lead at age 7 years was −0.06 (95% CI: −0.20, 0.09). The correlation coefficient is not significantly different form Bellinger et al. (1992) for 57-month-old children, −0.07 (95% CI: −0.23, 0.08), or from Lanphear et al. (2005) for children aged 4.8 to 10 years, −0.20 (95% CI: −0.28, −0.12). All correlation coefficients are for full scale IQ and concurrent blood lead concentrations.

Results from this follow-up study were consistent with their earlier reports of no association between blood lead levels <15 µg/dL and developmental deficits. However, the authors noted that their study was not designed to examine small deficits associated with blood lead levels at this magnitude. They reported that the size of their cohort did not provide sufficient power to detect effects less than 5%. Cooney et al. concluded that results from their study indicate that if developmental deficits do occur at blood lead levels below 25 µg/dL, the effect size is likely to be less than 5%.

Mexico City Study

Preliminary results of the Mexico City cohort prospective study were presented in the 1990 Supplement (Rothenberg et al., 1989). Blood lead levels from 42 mother-infant pairs were measured at 36 weeks of pregnancy (mean 15.0 µg/dL) and delivery (mean 15.4 µg/dL), and in the cord blood (mean 13.8 µg/dL). The Brazelton NBAS was administered to infants at

48 hours, 15 days, and 30 days after birth. None of the lead measures were associated with the NBAS outcomes; however, several differential lead measures (i.e., maternal blood lead at 36 weeks of pregnancy minus cord blood lead) were found to be associated with several outcome variables. Increases in the blood lead of the mother during the last month of pregnancy or a cord blood lead level higher than the mother's blood lead level were associated with adverse changes in Regulation of States, Autonomic Regulation, and Gestation Age.

Schnaas et al. (2000) further examined the effect of postnatal blood lead level on cognitive development in 112 children with complete data from the Mexico City study. Lead was measured in blood every 6 months from 6 to 54 months. Intellectual status was assessed with the McCarthy GCI. The purpose of the study was to estimate the magnitude of the effect of postnatal blood lead level on the GCI and describe how the effect varies with the time between blood lead measurements and the neurocognitive assessments. The geometric mean blood lead level between 24-36 months was 9.7 µg/dL (range 3.0-42.7). A number of significant interactions were observed between blood lead levels and age of assessment. The greatest effect was found at 48 months, with a decrease of 4.0 points (95% CI not presented) in adjusted GCI score being observed for a doubling of the 24-36 month blood lead level. The authors concluded that 4 to 5 years of age (when children are entering school) appears to be a critical period for the manifestation of earlier postnatal blood lead level effects.

In a related study, Gomaa et al. (2002) examined prenatal and postnatal lead exposure effects on the neurodevelopment of 197 children aged 2 years residing in Mexico City. Lead was measured in the umbilical cord and maternal venous blood samples at delivery. Maternal body burden was measured by obtaining cortical (tibial) and trabecular (patellar) bone lead measurements using K-shell XRF within 4 weeks of delivery. At 2 years of age, the Bayley MDI and PDI were administered. The major objective of this study was to compare lead levels in umbilical cord blood and maternal bone as independent predictors of infant mental development. Mean blood lead concentrations in the cord blood, at 12 months of age, and at 24 months at age were 6.7 µg/dL (SD 3.4), 7.2 µg/dL (SD 2.8), and 8.4 µg/dL (SD 4.6), respectively. Mean maternal patella and tibia bone lead levels were 17.8 µg/g (range <1-76.6) and 11.5 µg/g (range <1-85.9), respectively. Following covariate adjustment, postnatal blood lead concentrations were not significantly associated with MDI; however, lead levels in cord blood and trabecular bone were found to be significantly associated with lower scores on the

Bayley MDI. Maternal trabecular bone lead levels predicted poorer sensorimotor functioning in children 2 years of age independent of the cord blood lead level. The authors concluded that higher maternal trabecular bone lead concentrations constitute an independent risk factor for impaired mental development in infants at 2 years of age and that this is likely due to the mobilization of maternal bone lead stores over the course of gestation.

Kosovo, Yugoslavia Study

The neurodevelopment results of a large birth cohort study of 577 children in two towns in Kosovo, Yugoslavia were not available at the time of the 1990 Supplement. The study took place in Titova Mitrovica, near the site of a longstanding lead smelter, refinery, and battery plant, and in Pristina, a less exposed community 25 miles to the south. A unique characteristic of this cohort was the high prevalence of anemia secondary to iron deficiency (34% with hemoglobin concentrations <10.5 μg/dL at 2 years of age). The investigators began providing iron-fortified multivitamin supplements to the entire cohort when the children were between 18 to 38 months of age (Wasserman et al., 1994).

Like Port Pirie, this was one of the more highly exposed cohorts. Blood lead levels were obtained during the second trimester, at delivery, from the umbilical cord and postnatally at 6-month intervals to 90 months. At birth, geometric mean cord blood lead levels were nearly 21 μg/dL in the smelter area (Wasserman et al., 1992). At age 2 years, geometric mean blood lead concentrations were 35.5 μg/dL and 8.4 μg/dL among infants from Titova Mitrovica and Pristina, respectively.

Neurocognitive measures of mental abilities were administered at 2, 4, 7, and 10-13 years of age. The relationships between these neurocognitive outcomes and log-transformed blood lead levels were assessed. A doubling of blood lead levels at 2 years of age was associated with a covariate-adjusted decline of 1.6 points (95% CI: 0.2, 3.0) in Bayley MDI. Statistically nonsignificant decrements in MDI were associated with blood lead levels measured at all other time points. Iron deficiency anemia also was an independent predictor of lower MDI (Wasserman et al., 1992). When examined at 4 years of age, the geometric mean blood lead concentration of children from the smelter area was 39.9 μg/dL, while the geometric mean for children in the "unexposed" area was 9.6 μg/dL (Wasserman et al., 1994). Children were administered the McCarthy Scales of Children's Abilities. Higher prenatal and cord blood lead

concentrations were associated with lower GCI scores. Following covariate-adjustment, children of mothers with prenatal blood lead levels greater than 20 μg/dL scored a full standard deviation below children in the lowest exposure group (<5 μg/dL prenatal blood lead). A statistically significant association also was observed between nearly every blood lead measurement (at 6-month intervals since birth) and GCI. At 4 years of age, a doubling of blood lead levels was associated with a reduction of 2.8 points (95% CI: 1.4, 4.3) on the GCI. The Perceptual-Performance subscale of the McCarthy was found to be most sensitive to lead exposure.

When 301 children were examined at 7 years of age with the WISC-III, significant associations were observed between postnatal blood lead concentrations and IQ, with consistently stronger associations between performance IQ and later blood lead measures (Factor-Litvak, 1999). The adjusted intellectual loss associated with a doubling in lifetime average blood lead was 2.7 points (95% CI: 1.7, 3.7) in full scale IQ, 2.8 points (95% CI: 1.7, 4.0) in performance IQ, and 2.1 points (95% CI: 1.1, 3.2) in verbal IQ. By 7 years, measures of iron status were no longer significantly associated with IQ.

At age 10-12 years, 290 subjects with complete data on exposure and covariate factors were assessed again with the WISC-III (Wasserman et al., 2003). However, in addition to well-characterized exposure histories based on serial blood lead assessments, tibial bone lead was measured using ^{109}Cd based K-shell XRF (Todd et al., 2001) on a representative subsample of 167 subjects from both communities. Blood lead and bone lead measures were highly correlated in Titova Mitrovica, but not in Pristina. Following covariate-adjustment, average lifetime blood lead level was significantly and negatively related to all components of WISC-III IQ. A doubling of average blood lead concentration was associated with a decrease in full scale, performance, and verbal IQ of 1.6 points (95% CI: 0.4, 2.8), 1.5 points (95% CI: 0.3, 2.8), and 1.5 points (95% CI: 0.3, 2.6), respectively. The relationships between bone lead and IQ scores were stronger than those for blood lead, at least in the more highly exposed smelter community. For each doubling of tibial bone lead concentrations, full scale, performance, and verbal IQ decreased by an estimated 5.5, 6.2, and 4.1 points, respectively. The authors also reported that significant associations between tibial lead concentrations and IQ scores persisted despite inclusion of blood lead into the model. The inference drawn from these findings was that associations between bone lead and IQ outcomes may be stronger than those between blood lead measures and IQ.

Shanghai, China Study

A prospective study of low-level prenatal and postnatal exposure was initiated in 1993 by Shen et al. (1998) in Shanghia, China. Pregnant women were recruited from a maternal and child health care facility in the community. Lead levels were determined on 348 cord blood samples. The geometric mean cord blood lead level was 9.2 μg/dL (range 1.6-17.5); 40.8% of the infants had cord blood lead levels ≥10 μg/dL. Infants were further selected for study on the basis of their cord blood lead concentrations – the low lead group (n = 64) had levels <30th percentile while the high lead group (n = 69) had levels >70th percentile. Mean cord blood lead concentrations in the high lead group and low lead group were 13.4 μg/dL (SD 2.0) and 5.3 μg/dL (SD 1.4), respectively. At 3, 6, and 12 months, infants were administered the Chinese version of the Bayley Scales of Infant Development. Capillary blood samples were collected at each visit to ascertain levels of postnatal exposure. Mean blood lead at 1 year of age was 14.9 μg/dL (SD 8.7) in the high lead group and 14.4 μg/dL (SD 7.7) in the low lead group. Postnatal blood lead levels were not significantly different in the high and low lead groups.

At all three ages, the Bayley MDI, but not PDI, was associated with cord blood lead groupings following adjustment for covariates, which included a wide range of perinatal, demographic, social, and environmental factors. Postnatal blood lead concentrations were not associated to any Bayley measures. Differences in mean MDI between cord blood lead groups were 3.4 points at 3 months ($p = 0.02$), 6.3 points at 6 months ($p = 0.03$), and 5.2 points at 12 months ($p = 0.03$). The early results of this prospective study are generally in accord with similar investigations in Boston, Cincinnati, and Cleveland. The authors concluded that the adverse effects of prenatal lead exposure on early neurobehavioral development are readily discernible and stable over the first year of life.

Rochester Study

The Rochester prospective study, initiated in 1994, examined the relationship between blood lead levels and IQ at 3 and 5 years of age in 172, predominantly African-American, lower SES children (Canfield et al., 2003a). Participants were enrolled when children were 5 to 7 months of age in what was originally a study of lead dust control methods (Lanphear et al., 1999). Blood lead concentrations were assessed at 6-month intervals until 2 years and annually thereafter. No data were available on prenatal exposure. The measure of IQ was the abbreviated

Stanford-Binet Intelligence Scale-4th Edition (SBIS-4). Potential confounders assessed included gender, birth weight, iron status, HOME scores, maternal IQ, SES, and tobacco use during pregnancy.

Blood lead concentrations in the Rochester cohort were quite low for an urban population as this study was conducted after public health measures to reduce blood lead levels in children were already having a dramatic impact in the U.S. population. Blood lead levels peaked at 2 years of age (mean 9.7 μg/dL). The mean lifetime average blood lead concentration was 7.7 μg/dL at the age of 3 years and 7.4 μg/dL at the age of 5 years. At 5 years of age, 56% of the children had a peak blood lead concentration below 10 μg/dL. Following adjustment for covariates, there were significant inverse associations with full scale IQ at both 3 and 5 years of age for all blood lead variables, including lifetime average up to age of behavioral assessment.

The effect of lead on IQ was estimated in all children using lifetime average, peak, concurrent, and average in infancy (6-24 months) blood lead levels. Lead effects on IQ for the subgroup of children whose peak lead concentration never exceeded 10 μg/dL also was estimated. Table 6-3.1 shows the covariate-adjusted changes in IQ for each 1 μg/dL increase in blood lead concentration for all children and children with peak blood lead concentrations below 10 μg/dL. In all cases, the effect estimates were larger in the subsample of children with peak blood lead concentrations below 10 μg/dL. For example, the overall estimate including all children indicated that an increase in the lifetime average blood lead concentration of 1 μg/dL was associated with a decrease of 0.46 points (95% CI: 0.15, 0.76) in IQ. In comparison, a 1 μg/dL increase in lifetime average lead concentration was associated with a decline of 1.37 points (95% CI: 0.17, 2.56) in children with peak blood lead concentrations below 10 μg/dL. In an accompanying editorial of the Canfield et al. (2003a) study, Rogan and Ware (2003) noted that the steepness in the concentration-response relationship below 10 μg/dL might have been influenced by 10 children with blood lead concentrations at or below 5 μg/dL and IQs above 115. However, they added that it was unlikely that the associations reported by Canfield et al. were solely due to these values. Regression diagnostics performed by Canfield et al. identified only one potential outlier (a child who had a low IQ and low lead concentration); however, this value was retained in all analyses as it did not pass the discordancy test.

In the Rochester study, the relationship between children's IQ score and their blood lead level was found to be nonlinear. A semiparametric analysis indicated a decline of IQ of

Table 6-3.1. Covariate-Adjusted Changes in IQ for Each 1 µg/dL Increase in Blood Lead Concentration[a]

Type of Blood Lead Measurement	n	At 3 Years of Age		At 5 Years of Age		Overall	
		β (95% CI)	p	β (95% CI)	p	B (95% CI)	p
All Children							
Lifetime average	172	−0.35 (−0.69, 0.00)	0.05	−0.57 (−0.93, −0.20)	0.003	−0.46 (−0.76, −0.15)	0.004
Peak	172	−0.19 (−0.39, 0.01)	0.06	−0.26 (−0.47, −0.05)	0.02	−0.23 (−0.40, −0.05)	0.01
Concurrent	171	−0.31 (−0.60, −0.01)	0.04	−0.61 (−0.99, −0.24)	<0.001	−0.46 (−0.74, −0.18)	0.002
Average in infancy (6-24 mo)	172	−0.32 (−0.71, 0.07)	0.10	−0.53 (−0.93, −0.13)	0.01	−0.43 (−0.77, −0.09)	0.02
Children with Peak Blood Lead Concentrations below 10 µg/dL[b]							
Lifetime average	101	−1.22 (−2.53, 0.09)	0.07	−1.52 (−2.94, −0.09)	0.04	−1.37 (−2.56, −0.17)	0.03
Peak	101	−1.36 (−2.46, −0.27)	0.002	−1.44 (−2.55, − 0.33)	0.01	−1.40 (−2.37, −0.44)	0.005
Concurrent	101	−1.36 (−2.37, −0.35)	0.009	−1.79 (−3.00, −0.60)	0.004	−1.58 (−2.50, −0.65)	0.001
Average in infancy (6-24 mo)	105	−0.58 (−1.75, 0.59)	0.32	−0.92 (−2.09, 0.25)	0.12	−0.75 (−1.78, 0.28)	0.15

[a] Estimates were adjusted for maternal IQ, race, level of education, use of tobacco during pregnancy, household income, HOME score, child's gender, birth weight, and iron status.

[b] A total of 71 children were found to have a peak blood lead concentration below 10 µg/dL at both ages; an additional 15 children had a peak concentration below 10 µg/dL at 3 years of age but at 5 years of age had a higher concentration or were not tested, and another 15 children had a peak concentration below 10 µg/dL at 5 years but were not tested at 3 years. The total number of children in the analysis of the average concentration in infancy is 105, because in 4 children the peak blood lead concentration occurred after the age of 24 months.

Source: Canfield et al. (2003a).

7.4 points for a lifetime average blood lead concentration of up to 10 µg/dL, while for levels between 10 to 30 µg/dL a more gradual decrease of approximately 2.5 points IQ was estimated. The authors concluded that the most important aspect of their findings was that effects below 10 µg/dL that have been observed in previous cross-sectional studies (e.g., Chiodo et al., 2004; Fulton et al., 1987; Lanphear et al., 2000; see Section 6.3.2.1.2) have been confirmed in this rigorous prospective longitudinal investigation.

Pooled-Analyses of Prospective Longitudinal Cohort Studies

Investigators have collectively analyzed the results of multiple independent studies using the methods of meta- and pooled data analyses. A powerful approach involves pooling the raw data from several high quality studies to examine concentration-response relationships in a large sample of children with diverse sociodemographic backgrounds and levels of exposure. The studies reviewed here are summarized in Annex Table AX6-3.2.

Lanphear et al. (2005) reported on a pooled analysis of seven prospective studies that were initiated prior to 1995. The analysis involved 1,333 children with complete data on confounding factors that were essential in the multivariable analyses. The participating sites included Boston, MA; Cincinnati, OH; Cleveland, OH; Rochester, NY; Mexico City; Port Pirie, Australia; and Kosovo, Yugoslavia. A prospective cohort study conducted in Sydney, Australia was not included because the authors were unable to contact the investigators (Cooney et al., 1989b, 1991). The sample size of 175 for children at age 7 years in the Sydney cohort and the wide confidence intervals of the effect estimates, as implied by the lack of significant associations, indicate that the nonavailability of this study is unlikely to influence the results of the pooled analysis by Lanphear et al.

The primary outcome measure was full scale IQ measured at school age (mean age at IQ testing was 6.9 years). All children were assessed with an age-appropriate version of the Wechsler scales. Four measures of lead exposure were examined: concurrent blood lead (blood lead level closest in time to the IQ test), maximum blood lead level (peak blood lead measured at any time prior to the IQ test), average lifetime blood lead (mean blood lead from 6 months to the concurrent blood lead test), and early childhood blood lead (defined as the mean blood lead from 6 to 24 months). A pooled analysis of the relationship between cord blood lead levels and IQ also was conducted in the subsample for which cord blood lead tests were available.

Multivariate regression models were developed adjusting for site as well as ten common covariates assessing factors likely to be confounders of the relationship between lead and cognitive development, including HOME scores, birth weight, maternal education and IQ, and prenatal substance abuse. A thorough statistical analytic strategy was employed to determine the linearity or nonlinearity of the relationship between blood lead levels and full-scale IQ. Regression diagnostics also were performed to ascertain whether lead coefficients were affected by collinearity or influential observations. The fit of all four measures of postnatal blood lead levels was compared using the magnitude of the model R^2. The blood lead measure with the largest R^2 (adjusted for the same covariates) was nominated a priori as the preferred blood lead index relating lead exposure to IQ in subsequent inspections of the relationships. Results were evaluated by applying a random-effects model (with sites random) rather than a fixed-effects model. The authors also examined the impact of any one site on the overall model by calculating the blood lead coefficient in seven identical models, each omitting one of the seven prospective cohort studies. Similar models were fitted for verbal and performance IQ as well.

The median lifetime average blood lead concentration was 12.4 µg/dL (5th-95th percentile 4.1-34.8) with about 18% of the children having peak blood lead levels below 10 µg/dL. The 5th to 95th percentile concurrent blood lead levels ranged from 0.8 to 4.7 µg/dL in the individual studies. The mean IQ of all children was 93.2 (SD 19.2) but this varied greatly between studies. All four measures of postnatal exposure were highly correlated. However, the concurrent blood lead level exhibited the strongest relationship with IQ, as assessed by R^2. Nevertheless, the results of the regression analyses for all blood lead measures were very similar. Multivariable analysis resulted in a six-term model including log of concurrent blood lead, study site, maternal IQ, HOME Inventory, birth weight, and maternal education. As illustrated in Figures 6-3.2 and 6-3.3, the shape of the log-linear model and the spline function indicated that the steepest declines in IQ were at blood lead concentrations below 10 µg/dL. The log-linear model estimated a decrement of 1.9 points (95% CI: 1.2, 2.6) in full scale IQ for a doubling of concurrent blood lead. Due to the log-linear relationship, the slope of the lead effect on IQ was greater in the lower ranges of exposure. The IQ point decrements associated with an increase in blood lead from <1 to 10 µg/dL compared to 10 to 20 µg/dL were 6.2 (95% CI: 3.8, 8.6) versus 1.9 (95% CI: 1.2, 2.6).

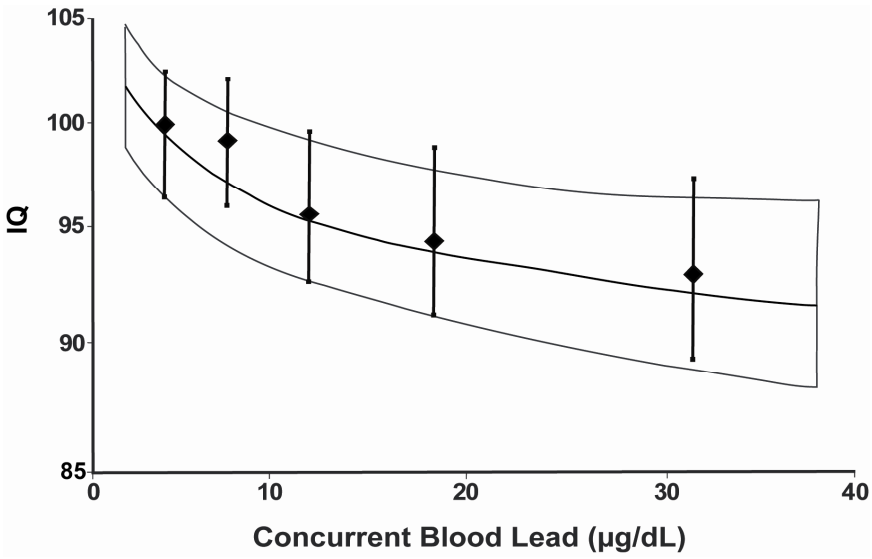


Figure 6-3.2. Log-linear model (95% CI shaded) for concurrent blood lead concentration adjusted for HOME score, maternal education, maternal IQ, and birth weight. The mean IQ (95% CI) for the intervals <5, 5-10, 10-15, 15-20, and >20 µg/dL are shown.

Source: Lanphear et al. (2005).

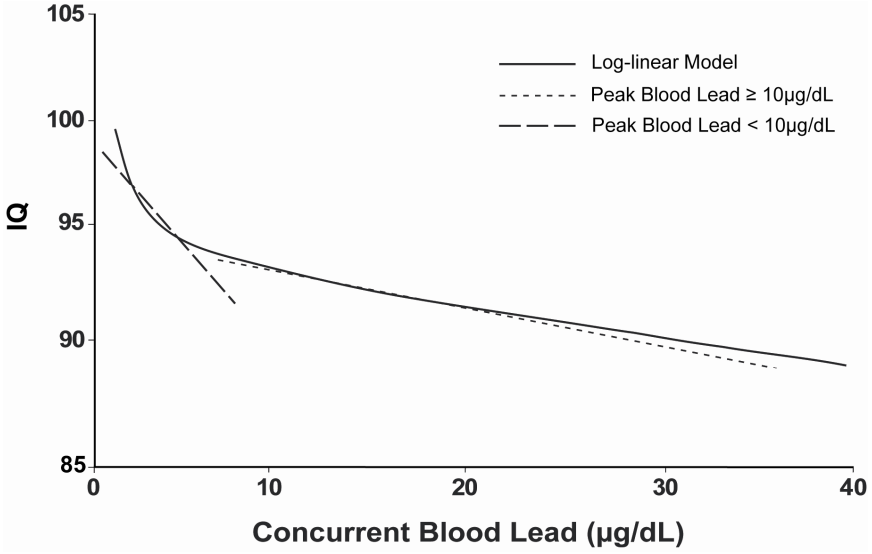


Figure 6-3.3. Log-linear model for concurrent blood lead concentration along with linear models for concurrent blood lead levels among children with peak blood lead levels above and below 10 µg/dL.

Source: Lanphear et al. (2005).

Rothenberg and Rothenberg (2005) reanalyzed the Lanphear et al. (2005) pooled study to examine the form of the concentration-response function for the lead exposure effect on child IQ. This further analysis also focused on concurrent blood lead levels. Rothenberg and Rothenberg reported that a log-linear relationship between blood lead and IQ was a significantly better fit within the ranges of the blood lead levels than was a linear-linear relationship ($p = 0.009$), with little evidence of residual confounding from included model variables. However, a segmented linear model also offers an appropriate alternative since limited data is available at lower levels.

The log-linear model in Lanphear et al. estimated a decline of 6.2 points in full scale IQ for an increase in concurrent blood lead levels from <1 to 10 μg/dL. This effect estimate was comparable to the 7.4 point decrement in IQ for an increase in lifetime mean blood lead levels up to 10 μg/dL observed in the Rochester study (Canfield et al., 2003a), as well as other studies reviewed above.

6.3.2.1.2 Cross-sectional Studies of Neurocognitive Ability

Among the cross-sectional studies reviewed in the 1986 Lead AQCD and the 1990 Supplement, the most thorough and methodologically rigorous were those of Needleman et al. (1979) and Fulton et al. (1987). Needleman et al. (1979) measured lead in the dentin of deciduous teeth in elementary school children from two Boston area communities. After statistical adjustment for a number of potential confounding factors, children in the higher tooth lead group performed significantly less well on full scale and verbal IQ. Differences in full scale IQ between the high and low tooth lead groups was on the order of 4.5 points.

The general population study by Fulton et al. (1987) studied 501 children aged 6-9 years in Edinburgh, Scotland who were at risk for lead exposure owing to a plumbosolvent water supply and a large number of houses with lead plumbing. Blood lead levels averaged 11.5 μg/dL (range 3-34). Following covariate adjustment, there were statistically significant relationships between concurrent blood lead levels and total scores on the British Ability Scale and the Quantitative and Reading subscales. Data showed a clear concentration-response relationship with no evidence of a threshold.

Recent cross-sectional studies of neurocognitive ability are summarized in Annex Table AX6-3.3. Key studies are further discussed in this section. Lanphear et al. (2000) examined the relationship between blood lead concentrations and cognitive deficits in a

nationally representative sample of 4,853 children aged 6 to 16 years children who participated in the third National Health and Nutrition Examination Survey (NHANES III). The purpose of the study was to examine the relationship between low blood lead concentrations (especially those below 10 μg/dL) and two subtests of the WISC-R, Block Design (a measure of visual-spatial skills) and Digit Span (a measure of short-term and working memory). Academic achievement tests also were administered but are discussed in a later section. A number of potential confounders were assessed and included in multivariable analyses including gender, racial/ethnic background, child's serum ferritin level, serum cotinine level, region of country, marital status and education level of primary caregiver, and a poverty index ratio (the ratio of total family income, as reported by the adult informant, to the federal poverty level for the year of the interview). Other potential confounders such as in utero and postnatal exposure to tobacco smoke, birth weight, and admission to the neonatal intensive care unit were only available for children between 6 and 11 years of age. Therefore, the authors conducted a secondary analysis of the data on these children to verify that inclusion of these potentially important variables did not alter the findings of the main analysis using the larger sample.

The geometric mean blood lead concentration for children in the study sample was 1.9 μg/dL (SE 0.1). Only 2.1% of the NHANES III sample in this analysis had blood lead concentrations greater or equal to 10 μg/dL. In multivariate analyses, a significant covariate-adjusted relationship was found between blood lead level and scores on both WISC-R subtest for all children as well as among those children with blood lead levels <10 μg/dL. Blood lead concentration also was significantly associated with Block Design when the multivariate analysis was restricted to children with blood lead levels <7.5 μg/dL. For a 1 μg/dL increase in blood lead level, Block Design scores declined by 0.10 points (SE 0.04) for all children, 0.13 points (SE 0.06) for children with blood lead levels <10 μg/dL, and 0.11 points (SE 0.06) for children with blood lead levels <7.5 μg/dL. The authors concluded that deficits in intellectual functioning were associated with blood lead levels <10 μg/dL. While a large number of potential confounding factors were controlled in these analyses, interpretation of results must be tempered by the fact that no data on maternal IQ or direct observations of caretaking quality in the home were available. Furthermore, it is not clear whether the cognitive deficits observed were due to lead exposure that occurred during early childhood or a function of concurrent exposure.

Chiodo et al. (2004) studied the relationship between blood lead concentrations and IQ, assessed using WISC-III, in a sample of 237 African-American inner-city children from Detroit, MI at 7.5 years of age. This cohort was derived from a larger study of the effects of prenatal alcohol exposure on child development. However, approximately 83% of children for whom blood lead levels were obtained had either low or no gestational exposure to alcohol. Blood lead levels were low with a mean of 5.4 µg/dL (SD 3.3, range 1-25). Following covariate adjustment, there was a statistically significant association between blood lead concentrations and full scale, verbal and performance IQ, with the strongest relationship observed for performance IQ. Significant effects of lead on full scale and performance IQ were still evident at blood lead concentrations below 7.5 µg/dL. Nonparametric smoothing analyses confirmed that these effects were linear in nature.

Walkowiak et al. (1998) conducted a cross-sectional study examining the relationships of low-level lead and mercury exposure, and various measures of neurocognitive and neuromotor functioning in 384 children aged 6 years in three German cities. Lead was measured in blood at the time of testing and mercury burden was estimated from urine samples. As their measure of IQ, they administered two subtests of the German WISC, Vocabulary and Block Design. These subtests were treated separately as well as a summed index, which served as a surrogate for full scale IQ. Blood lead concentrations were low (geometric mean 4.3 µg/dL [95th percentile 8.9]). Following covariate-adjustment, Vocabulary and the combined index, but not Block Design, exhibited negative associations with blood lead of statistical or borderline statistical significance; no associations were observed for mercury. The authors concluded that these findings roughly correspond with those of other studies that find effects of lead exposure on measures of intelligence at blood lead concentrations below 10 µg/dL. However, they also caution that some important covariates and potential confounding variables were not measured, including parental IQ and home environment (e.g., HOME score).

Rabinowitz et al. (1991) studied the relationship between lead measured in shed deciduous teeth (central incisors) and psychometric intelligence in 443 children in grades 1 to 3 in Taiwan. Two of the primary schools included in the study were in proximity to primary lead smelters. The Ravens Colored Progressive Matrices (RCPM), a test of nonverbal reasoning that is widely used in studies of non-western populations because of its more culturally neutral properties, was administered. Studies on a subsample of 60 children residing near the lead

smelters revealed mean blood lead level of 13.0 µg/dL (SD 4.4). Scores on the RCPM were negatively correlated with tooth lead concentrations. In multivariate analyses, parental education was a particularly important predictor of RCPM scores, but tooth lead concentrations still significantly predicted lower scores on the RCPM in families occupying the lowest social strata and among female subjects.

Kordas et al. (2004) examined the relationship between lead exposure and various indices of psychometric intelligence in a cohort of 602 first grade children attending public schools in Torreon, a highly industrialized city in northern Mexico. This study investigated whether lead-associated deficits in intellectual attainment might be explained by correlated nutritional factors such as iron status, anemia, and growth. The mean blood lead concentration was 11.5 µg/dL (SD 6.1). Approximately half of the children had blood lead concentrations below 10 µg/dL and only 20% of the subjects had blood lead levels in excess of 15 µg/dL. Subjects were administered Spanish or Mexican versions of the Peabody Picture Vocabulary Test-Revised (PPVT-R), the Cognitive Abilities Test (CAT), and subtests of the WISC-R (Coding, Digit Span, and Arithmetic subtests). Letter and Number Sequencing tests (adapted from the Trail Making Test, Trails A) also were administered. Following adjustment for sociodemographic variables, anemia, iron status, and growth, higher blood lead levels were significantly associated with poorer performance on the PPVT, WISC-R Coding, and Number and Letter Sequencing. The authors concluded that lead's association with iron deficiency anemia or growth retardation could not explain the relationship between lead and cognitive performance. The authors acknowledged that a major limitation of their study is the lack of earlier measures of lead exposure and nutritional status, and information on potentially confounding variables such as parental intelligence and quality of caretaking in the home.

Bellinger et al. (2005) reported on a study of the relationship between blood lead levels and IQ in 55 children aged 4 to 14 years in Chennai, India. This is the first published study that has investigated neurodevelopmental morbidities associated with undue lead exposure in Indian children. Children were recruited from a rural primary school on the outskirts of the city. The mean blood lead concentration was 11.1 µg/dL (SD 5.6, range 2.5-38.3). The Binet-Kamath Intelligence test along with other measures of neurobehavior were administered. The covariate-adjusted blood lead coefficient was negative but nonsignificant, perhaps due to the small sample size and highly variable performance of subjects with the lowest blood lead concentrations.

For example, the mean IQ of children in the highest blood lead quartile was 95.6 with a SD of 13.3 compared to 102.0 with a larger SD of 22.5 for children in the lowest blood lead quartile.

The cross-sectional studies examining the effect of lead on neurocognitive abilities varied widely in study location, population, age of testing, and outcomes measured. Collectively, they generally concluded that blood or tooth lead levels were significantly associated with declines in intelligence and other neurocognitive outcomes. In addition, these associations were consistently observed in studies with mean blood lead levels <10 μg/dL.

6.3.2.1.3 Meta-Analyses of Studies of Neurocognitive Abilities

The meta-analyses of studies investigating the association between lead and neurocognitive abilities included results from both prospective cohort studies and cross-sectional studies. The studies reviewed here are summarized in Annex Table AX6-3.2. Needleman and Gatsonis (1990) conducted a meta-analysis of 12 studies that used multiple regression techniques to assess the relationship between lead levels in tissues (blood or teeth) while adjusting for potentially confounding variables. Studies were weighted based on sample sizes, which ranged from 75 to 724 children. The authors divided studies into two groups according to the type of tissue analyzed for lead (blood or teeth). Joint p-values and average effect sizes as measured by partial correlation coefficients were calculated using two different methods by Fisher and by Mosteller and Bush (Rosenthal, 1984). The joint p-values for the blood lead studies were <0.0001 for both methods while joint p-values of <0.0006 and <0.004 were obtained for tooth lead studies. The partial correlations ranged from −0.27 to −0.0003. Sensitivity analyses revealed that no single study was responsible for the significance of the final findings. The authors concluded that the hypothesis that lead lowers children's IQ at relatively low dose was strongly supported by their quantitative analysis.

Another meta-analysis conducted by Schwartz (1994) took a different approach. Only studies relating blood lead to IQ were chosen for quantitative review since the concentration of lead in the bloodstream is the only index of exposure that has been used as the basis for public health policy. Three longitudinal and four cross-sectional studies relating blood lead to IQ were examined. Furthermore, while the work of Needleman and Gatsonis (1990) essentially involved combining partial correlations, the measure of effect used in the Schwartz analysis was the predicted change in full scale IQ as blood lead increased from 10 to 20 μg/dL. For the

prospective longitudinal studies, blood lead levels at 2 years of age or average blood lead levels up to 3 years of age were selected for the analysis. This approach by Schwartz may be related to the belief at the time of the analysis that blood lead levels during the first 3 years of life were the most critical in determining the severity of neurodevelopmental toxicity. The exclusion of blood lead levels from other time points may be of issue as it appears that later blood lead levels may be more predictive of mental deficits (Baghurst et al., 1992; Canfield et al., 2003a; Chen et al., 2005; Dietrich et al., 1993a; Factor-Litvak et al., 1993). Studies were weighted by the inverse of the variances using a random-effects modeling procedure. The estimated decrease in IQ for an increase in blood lead from 10 to 20 μg/dL was 2.6 points (95% CI: 1.8, 3.4). Sensitivity analyses indicated that the results were not determined by any individual study. Effect estimates were similar for longitudinal and cross-sectional studies. In another analysis, studies with mean blood lead concentrations below 15 μg/dL and above 15 μg/dL had estimated effect sizes of −3.23 points (95% CI: −5.70, −0.76) and −2.32 points (95% CI: −3.10, −1.54), respectively. When the study with the lowest mean blood lead level was examined in greater detail using nonparametric smoothing, no evidence of a threshold was observed down to a blood lead level of 1 μg/dL.

Pocock et al. (1994) conducted a review of the epidemiologic evidence for lead effects on IQ that included a meta-analysis. For the meta-analysis, the fixed-effect method described by Thompson and Pocock (1992) was used. Five prospective and 14 cross-sectional studies (with both tooth and blood lead measures) were included. For consistency, only blood lead levels at or around 2 years of age were considered for the prospective studies. Their overall conclusion was that a doubling of blood lead levels from 10 to 20 μg/dL, or tooth lead from 5 to 10 μg/g was associated with an average estimated deficit in IQ of around 1 to 2 points.

Other earlier meta-analyses of lead-IQ studies have been published but are not reviewed here, because later work greatly extended these efforts and included more studies, rendering these analyses outdated (Needleman and Bellinger, 1988; Schwartz, 1985; Thacker et al., 1992). The meta-analyses of studies investigating the effect of lead on neurocognitive ability consistently observed significant associations between blood or tooth lead levels and decrements in IQ. The analysis by Schwartz (1994) observed no evidence of a threshold at blood lead levels below 10 μg/dL.

6.3.2.2 Measures of Academic Achievement

There are relatively little data on the relationship between lead exposure and objective measures of academic achievement. A few earlier studies reported an inverse relationship between lead exposure and reading skills (Fergusson et al., 1988a; Fulton et al., 1987; Yule et al., 1981). Since the 1990 Supplement, more studies have focused on the practical consequences of childhood lead exposure by including measures of academic performance in their batteries. Studies reviewed in this section are summarized in Annex Table AX6-3.4.

Lanphear et al. (2000) examined the relationship between blood lead levels and a standardized measure of academic achievement in 4,853 children aged 6 to 16 years. The source of data for this study was the third National Health and Nutrition Examination Survey (NHANES III). This cohort was previously described in Section 6.3.2.1.2. Subjects were administered the Arithmetic and Reading subtests of the Wide Range Achievement Test-Revised (WRAT-R). The WRAT-R Arithmetic subtest includes oral and written problems ranging in level from simple addition to calculus, while the Reading subtest assesses letter recognition and word reading skills. The geometric mean blood lead concentration was 1.9 μg/dL. Only 2.1% of the subjects had blood lead levels equal to or greater than 10 μg/dL. Multiple linear regression revealed a 0.70 point (95% CI: 0.37, 1.03) decrement in arithmetic scores and a 0.99 point (95% CI: 0.62, 1.36) decrement in Reading scores for each 1 μg/dL increase in blood lead concentration ($p < 0.001$). In the next phase of the analysis, the adjusted relationship between performance on WRAT subtests and blood lead concentration for children with blood lead concentrations <10 μg/dL, <7.5 μg/dL, <5 μg/dL, or <2.5 μg/dL were carried out. Statistically significant inverse relationships between blood lead levels and performance for both Reading and Arithmetic subtests were found for children with blood lead concentrations below 5 μg/dL. Secondary analysis limited to younger children with data on all covariates did not alter findings from the main analysis. The authors concluded that results of these analyses suggest that deficits in academic skills are associated with blood lead concentrations lower than 5 μg/dL. However, although the relationship of blood lead concentration and achievement was adjusted for numerous potential confounders, the study lacked information on at least two covariates that have been shown to be important in other lead studies (HOME scores and parental IQ). Failure to adjust for these variables may have underestimated or overestimated the deficits in academic skills related to lead. Furthermore, as with all cross-sectional studies utilizing blood lead as the

index of dose, it is not clear whether the deficits in academic skills were due to lead exposure that occurred sometime during early childhood or due to concurrent exposure. Nevertheless, concurrent blood lead levels likely reflect both ongoing exposure and preexisting body burden.

Needleman et al. (1990) reexamined the Chelsea and Somerville, MA cohort of first and second graders recruited in the 1970s (Needleman et al., 1979). One hundred and thirty-two of the original 270 children were recalled. Neurobehavioral deficits in relationship to the concentration of lead in shed deciduous teeth had persisted into late adolescence. Subjects with dentin lead levels >20 ppm were at higher risk of dropping out of high school (adjusted odds ratio of 7.4, [95% CI: 1.4, 40.7]) and of having a reading disability (adjusted odds ratio of 5.8 [95% CI: 1.7, 19.7]). Higher dentin lead levels also were significantly associated with lower class standing, increased absenteeism, and lower vocabulary and grammatical reasoning scores on the Neurobehavioral Evaluation System (NES). The authors concluded that undue exposure to lead had enduring and important effects on objective parameters of success in real life.

Bellinger et al. (1992) administered a battery of neuropsychological tests to 148 children in the Boston Lead Study cohort at age 10 years. The authors administered the short-form of the Kaufman Test of Educational Achievement (KTEA) in addition to IQ studies. The KTEA assesses reading, math, and spelling skills. The primary outcome was the Battery Composite Score. As previously indicated, exposures in this cohort were low with a peak mean blood lead at 18 months of only 7.8 μg/dL (SD 5.7). The cohort had a high SES that consisted of white intact families with college-educated parents. Average KTEA scores in this cohort were approximately one standard deviation above the population mean. Nevertheless, postnatal blood lead levels measured at virtually all ages were significantly associated with lower KTEA Battery Composite Scores. However, after covariate-adjustment, including full scale IQ in the model, only blood lead levels at 24 months of age were significantly predictive of lower academic achievement. Over the range of approximately 0 to 25 μg/dL, Battery Composite scores declined by approximately 8.9 points (95% CI: 4.2, 13.6) for each 10 μg/dL increase in 24-month blood lead. The specific subscales of the KTEA that were most significantly associated with lead were Spelling and Math. Within the Math subscale, lead appeared to be more strongly associated with performance on the advanced quantitative Concepts/Applications items than on computation. The associations between these early measures of low level exposure to lead and achievement were significant even after adjustment for IQ, suggesting that

lead-sensitive neuropsychological processing and learning factors not reflected in indices of global intelligence may contribute to reduced performance on academic tasks.

Leviton et al. (1993) reported on the relationship between pre- and postnatal lead exposure and academic problems in approximately 2,000 children born in one Boston hospital between 1979 and 1980 using the Boston Teacher Questionnaire (BTQ). A teacher provided an assessment of each child's academic functioning when the child reached the age of 8 years. Mean umbilical cord blood lead was 6.8 μg/dL and mean tooth (dentin) lead concentration was 2.8 μg/g. There was limited information on covariate factors. However, following adjustment for potential confounding variables, elevated dentin lead concentrations were associated with statistically significant reading and spelling difficulties as assessed by the BTQ among girls. The authors concluded that their findings supported the case for lead-associated learning problems at levels prevalent in the general population. However, they added that the inability to assess child-rearing quality in this questionnaire study conducted by mail limits the inferences that came be drawn from the findings.

Fergusson et al. (1993) examined the relationship between dentin lead levels in shed deciduous teeth at 6-8 years and measures of academic attainment and classroom performance in a birth cohort of over 1,200 New Zealand children enrolled in the Christchurch Health and Development Study when they reached 12-13 years of age. This study was an extension of earlier work in these children indicating a relationship between low lead levels and deficits in academic skills around the age of 8 years (Fergusson et al., 1988a). Average dentine lead levels in the cohort were 6.2 μg/g (SD 6.2). Measures of academic performance included word recognition from the Burt Reading Test, reading comprehension from the Progressive Achievement Test, a general measure of scholastic skills based on children's scores on the Test of Scholastic Abilities, and teacher ratings of classroom performance in the areas of reading, written expression, and mathematics. Following adjustment for a wide range of covariates (including residence in potentially lead-hazardous housing), dentin lead levels were significantly associated with virtually every formal index of academic skills and teacher ratings of classroom performance. Statistical treatment of the data included a multivariate analysis of all 12 regression equations simultaneously using LISREL modeling methods. This conservative analysis clearly showed that the probability of observing these results under the null hypotheses that lead was unrelated to all covariate-adjusted test outcomes was extremely small. In an

adjunct analysis, Fergusson and Horwood (1993) examined the effects of low-level lead exposure on the growth of word recognition in this cohort from 8 to 12 years of age. The New Zealand data were analyzed using growth curve modeling methods. After adjustment for potential confounding variables, children with dentin lead levels equal to or greater than 8 μg/g displayed significantly slower growth in word recognition abilities with no evidence of catch up. The authors concluded that these results were consistent with their earlier analyses and suggest that early exposure to very low levels of lead result in small but detectable and enduring deficits in children's cognitive abilities.

Academic achievement in relationship to lead was reexamined in the New Zealand cohort when subjects reached 18 years of age (Fergusson et al., 1997). The sample at 18 years consisted of 881 subjects, or approximately 70% of the original cohort. Measures of educational achievement included the Burt Reading Test, number of years of secondary education, mean number of School Certificate passes (based on results of national examinations), and leaving school without formal qualifications (analogous to failure to graduate from high school in the U.S.). As in previous analyses, a wide range of potentially confounding socioherediatary factors were measured and controlled for in multivariable analyses, which included both linear and logistic regressions. Prior to and following covariate adjustment there were statistically significant concentration-response relationships between dentin lead concentrations and lower reading test scores, having a reading level of less than 12 years, failing to complete 3 years of high school, leaving school without qualifications, and mean number of School Certificates subjects passed. The authors conclude that their results are consistent with the view that there is a relationship between early exposure to low levels of lead and later educational outcomes. The late results of the New Zealand studies confirm the findings of Needleman et al. (1990) in a cohort with lower levels of exposure to environmental lead.

Rabinowitz et al. (1992) examined the relationship between tooth lead concentrations and scores on BTQ clusters in 493 Taiwanese children in grades one through three. Mean lead levels in incisors were 4.6 μg/g (SD 3.5). Factors associated with lead and the BTQ included 13 variables measuring perinatal, familial, and economic parameters. Prior to adjustment for covariates, girls in this sample with higher exposures to lead evinced a borderline significant trend for reading difficulties while boys displayed significantly increased difficulties with respect to activity levels and task attentiveness. In multiple logistic regression models, the tooth lead

terms failed to achieve statistical significance. The authors concluded that lead levels found in the teeth of children in their Taiwanese sample were not associated with learning problems or syndromes as assessed by the BTQ.

Wang et al. (2002) examined the relationship between blood lead levels and class ranking in 934 third graders living in an urban industrial area of Taiwan. The outcome variables were grades for Chinese (reading and writing), Mathematics, History and Society, and Natural Science. To avoid the impact of teacher's bias in grading criteria, the authors converted the children's grades into class rankings. A limited number of potentially confounding factors were measured, including maternal education and father's SES. Mean blood lead level was 5.5 μg/dL (SD 1.89). In multiple regression analyses adjusting for gender, maternal education, and father's SES, blood lead was significantly associated with lower class ranking in all academic subjects. The major shortcoming of this cross-sectional study is the lack of control for potentially important confounding factors such as parental intelligence. However, the strength and consistency of the reported relationships suggest that relatively low levels of lead may play a role in lowering academic performance.

The results of these studies strongly suggest that lead exposure plays a role in the academic performance of children. The effects of lead on academic achievement appear to include children with blood lead levels that do not exceed 10 μg/dL.

6.3.2.3 Measures of Specific Cognitive Abilities

Outcomes of specific cognitive abilities, in particular, the domains of Attention and Executive Functions, Language, Memory and Learning, and Visuospatial Processing have been examined in some detail in recent studies. These studies are summarized in Annex Table AX6-3.5.

In the aggregate, studies suggest that lead exposure impairs a child's ability to regulate attention and engage several related higher order cognitive processes that have come to be termed "executive functions." Executive functions refer to strategic planning, control of impulses, organized search, flexibility of thought and action, and self-monitoring of one's own behavior—activities that help the subject maintain an appropriate mental set in order to achieve an immediate or future goal (Spreen et al., 1995). In some earlier studies, increased lead exposure was found to be associated with a higher frequency of negative ratings by teachers

and/or parents on behaviors such as inattentiveness, impulsivity, distractibility, and impersistence in assigned tasks, as well as slow psychomotor responses and more errors on simple, serial, and choice reaction time tasks (e.g., Hatzakis et al., 1989; Hunter et al., 1985; Needleman et al., 1979; Raab et al., 1990; Winneke et al., 1990). The concept that lead may impact executive functions in particular is biologically plausible. The prefrontal cortex is highly innervated by projections of neurons from the midbrain and has the highest concentration of dopamine of all cortical areas. Dopamine plays a key role in cognitive abilities mediated by the prefrontal cortex. It has been known for some time that the dopamine system is particularly sensitive to lead based upon data from studies of rodents and nonhuman primates (Cory-Slechta, 1995).

Bellinger et al. (1994) examined a portion of the original Chelsea and Somerville cohorts at 19-20 years of age. The principal neurobehavioral outcomes in the investigation were scores on a battery of attentional measures assembled by Mirsky (1987). Higher tooth lead concentrations were significantly associated with poorer scores on the Focus-Execute and Shift factors of the battery leading the authors to conclude that early lead exposure may be associated with poorer performance on executive/regulatory functions, which are thought to depend on the frontal or prefrontal regions of the brain.

Stiles and Bellinger (1993) administered a neuropsychological battery of tests to 10-year-olds in the Boston Lead Study cohort. A large number of assessments were made and, as the authors acknowledge, the number of significant associations was about equal to those that would be expected by chance. However, as in previous studies, tasks that assess attentional behaviors and executive functions tended to be among those for which lead was a significant predictor of performance. For example, higher blood lead concentrations at 2 years were significantly associated with lower scores on the Freedom from Distractibility factor of the Wechsler scales and an increase in the percentage of preservative errors on the Wisconsin Card Sorting Test and the California Verbal Learning Test.

Canfield et al. (2003b) conducted a comprehensive examination of the relationship between low-level lead exposure, executive functioning, and learning in children from the Rochester Lead Study cohort at 48 and 54 months of age. The authors used the Shape School Task (Espy, 1997), which requires only knowing simple shape and primary color names. However, embedded in the tasks are protocols requiring inhibition, attention switching, and a

combination of inhibition and switching mental sets. Following covariate-adjustment, blood lead level at 48 months was negatively associated with children's focused attention while performing the tasks, efficiency at naming colors, and inhibition of automatic responding. Children with higher blood lead concentrations also completed fewer phases of the task and knew fewer color and shape names.

Canfield et al. (2004) also administered portions of the Cambridge Neuropsychological Testing Automated Battery (CANTAB) to 174 children in the Rochester cohort at approximately 66 months. Children were tested with the Working Memory and Planning CANTAB assessment protocols to assess mnemonic and executive functions. Blood lead levels ranged from 0-20 μg/dL in this cohort. Following covariate adjustment, children with higher blood lead levels showed impaired performance on tests of spatial working memory, spatial memory span, cognitive and cognitive flexibility, and planning as indexed by tests of intradimensional and extradimensional shifts and an analog of the Tower of London task.

Ris et al. (2004) administered an extensive neuropsychological battery to 16-17 year old subjects from the Cincinnati Lead Study cohort. In addition to executive functions as assessed by the Wisconsin Card Sorting Test and the Rey-Osterrieth Complex Figure, other domains examined included attention, memory, achievement, verbal abilities, visuoconstructional skills, and fine-motor coordination. A factor analysis of scores selected a priori revealed five factors that included Attention. A strong "executive functions" factor did not emerge. Following covariate-adjustment, the strongest associations between lead exposure and performance were observed for factor scores derived from the Attention component, which included high loadings on variables from the Conners Continuous Performance Test. However, this relationship was restricted to males as indicated by a strong lead by gender interaction. This obtained gender interaction suggests that neuromechanisms sub-serving attention were affected by lead in this cohort for boys but not girls. This is not surprising given the heightened vulnerability of males for a wide range of developmental perturbations. A substantial gender difference in the incidence of Attention Deficit/Hyperactivity Disorder (ADHD) is well established, and one could speculate that early exposure to lead exacerbates a latent potential for such problems.

Visual-spatial skills have also been also been explored in some depth by a few studies. When investigations of lead-exposed children have used global IQ measures and conducted subscale analyses, it has been observed that Performance IQ or subtests contributing to the

performance IQ (i.e., Block Design) are frequently among the most strongly associated with biological indices of exposure (Baghurst et al., 1992; Chiodo et al., 2004; Dietrich et al., 1993a; McMichael et al., 1988; Wasserman et al., 1994). Dietrich et al. (1991, 1992) have also observed that integrated measures of lead exposure over a child's lifetime are most consistently associated with simultaneous processing abilities, cognitive functions closely associated with visual-spatial integration skills and right cerebral functioning (Kaufman and Kaufman, 1983). In addition, studies employing specific measures of visual-motor integration skills such as the Developmental Test of Visual Motor Integration (VMI), the Bender Visual-Motor Gestalt Test and other have found them to be among the most consistently associated with early exposure to lead (Baghurst et al., 1995; Dietrich et al., 1993b; Wasserman et al., 2000a; Winneke et al., 1990). In a follow-up of subjects in the Cincinnati Lead Study cohort at 16 years, Ris et al. (2004) observed a significant association between prenatal maternal blood lead levels and deficits in visual-spatial and constructional skills as indexed by Visual-Constructional factor scores. Variables with high loadings on this factor included scores on the WISC-III Block Design subtests and selected variables from the Rey Osterrieth Complex Figure.

However, it is still unclear whether the domains of attention/executive functions or visual-motor integration per se are specifically sensitive to lead. This is because there is rarely a one-to-one correspondence between performance on a focused neuropsychological test and an underlying neuropsychological process. Thus, for example, a low score on the Berry VMI may reflect singular or multiple neurobehavioral deficits, including difficulties with graphomotor control, visual perception, behavioral monitoring (impulsivity), or planning (executive functions).

6.3.2.4 Disturbances in Behavior, Mood, and Social Conduct

The effects of lead on behavior and mood of children has been an area of recent research. Studies conducted prior to 1990 clearly pointed to behavioral problems as potential sequelae of lower level lead toxicity in children. Several early case control studies linked lead to hyperactivity (David et al., 1972, 1976, 1979). Low levels of lead in blood and/or teeth have been associated with teacher ratings of hyperactive behavior, aggression, and attention problems (e.g., Fergusson et al., 1988b; Hatzakis et al., 1985; Silva et al., 1988; Thomson et al., 1989; Yule et al., 1984). In the seminal study by Needleman et al. (1979), children with higher

concentrations of lead in dentin were more likely to be rated unfavorably by teachers on the dimensions of hyperactivity, impulsivity, and frustration tolerance. New studies reviewed in this section are summarized in Annex Table AX6-3.6.

While there is no compelling evidence that lead is directly related to ADHD, elevated blood or tooth lead levels have been linked to behavioral features of ADHD, including distractibility, poor organization, lacking persistence in completing tasks, and daydreaming (Bellinger and Rappaport, 2002). Bellinger et al. (1994) studied the relationship between early exposure to lead and problem behaviors in the classroom in a cohort of 1,782 children born at one hospital in Boston. Lead levels in umbilical cord blood were low (mean 6.8 µg/dL [SD 3.1]) as were tooth lead levels (mean 3.4 µg/g [SD 2.4]). Teachers filled out the Achenbach Child Behavior Profile (ACBP) which yields both broad and narrow band scales indexing externalizing and internalizing problems. Cord blood lead levels were not associated with the prevalence or nature of behavioral problems reported by teachers. However, tooth lead level was significantly associated with ACBP Total Problem Behavior Scores (TPBS). TPBS scores increased by approximately 2 points for each log unit increase in tooth lead. Statistically significant tooth lead-associated increases in both externalizing and internalizing scores also were noted. Each log unit increase in tooth lead was associated with a 1.5 point increase in scores for these broadband scales assessing under- and overcontrol of behavior. Only weak associations were noted between tooth lead concentrations and the tendency to score in the clinically significant range on these scales. As the authors noted, it was somewhat surprising that lead exposure was not more strongly related to externalizing behavior problems than with internalizing behavior problems. This contradicted several earlier investigations, including one by Sciarillo et al. (1992) described below. It may be that more attention has been accorded under controlled behaviors, because they are more readily visible and disruptive in settings such as the classroom. Therefore, internalizing problems may be part of the full spectrum of behaviors in which lead's developmental neurotoxicity is expressed in children. The authors also cautioned that residual confounding could not be ruled out, because of the lack of covariate information on parental psychopathology or direct observations of the family environment—a problem not unique to this particular study. Nevertheless, these data are in accord with other studies that social and emotional dysfunction may be another expression of increased lead exposure during the early postnatal period.

Sciarillo et al. (1992) examined the relationship between early exposure to lead and child behavior in a cohort of 150 subjects in Baltimore, MD. Children were separated into high exposure (two consecutive blood lead concentrations greater than or equal to 15 µg/dL) and low exposure groups. Blood lead also was treated as a continuous variable in regression analyses. Mothers of 2-5 year old children were administered the Achenbach Child Behavior Checklist (CBCL) and given the Center for Epidemiologic Studies Depression scale (CESD) as a control measure. Mean blood lead concentrations were 28.6 µg/dL (SD 9.3) and 11.3 µg/dL (SD 4.3) in the high and low exposure groups, respectively. When compared to the lower exposed group, children with higher blood lead levels had a significantly higher mean TBPS, and internalizing and externalizing scores. Using regression procedures to control for maternal symptoms on the CESD, blood lead concentrations were still significantly associated with an increase in the TBPS. Children in the high exposure group were also nearly 3 times more likely to have a TBPS in the CBCL's clinical range. A significantly higher percentage of these children scored in the clinical range for CBCL subscales measuring aggressive and destructive behavioral tendencies.

Fergusson et al. (1993) examined the relationship between tooth lead levels and inattention/restlessness in the large national New Zealand study of over 1,000 children at 12 and 13 years of age. Mothers and teachers were asked to respond to a series of items derived from the Rutter and Conners parental and teacher questionnaires. The selected items related to the degree to which the child was restless, inattentive, easily distracted, and lacking in concentration. At each age, an index of the subject's propensity to inattentive and restless behavior was obtained by summing the total reports of attention deficit behaviors made by both teacher and parent respondents. Following adjustment for a wide range of sociodemographic and other covariate factors, a statistically significant, concentration-response relationship was observed between tooth lead concentrations (range 1-12+ µg/g) and the inattention/restlessness variable. The authors concluded that their results were consistent with the view that early mildly elevated lead levels were associated with small but long term deficits in attentional behaviors.

Two prospective studies have also examined measures of early exposure to lead and behavioral problems as assessed by the Achenbach system. Wasserman et al. (1998) studied the relationship between lead exposure and behavior in the Yugoslavian prospective study. The study survey 379 children at 3 years of age with the parent report form of the Achenbach CBCL. Following covariate adjustment, concurrent blood lead levels were significantly associated with

scores on the Destructive Behaviors CBCL subscale, although the variance accounted for by lead was small compared to sociodemographic factors. As blood lead increased from 10 to 20 µg/dL, CBCL subscale scores increased by approximately 0.5 points. The authors concluded that while statistically significant, the contribution of lead to social behavioral problems in this cohort was small compared to the effects of correlated social factors. Burns et al. (1999) examined the relationship between lead exposure and children's emotional and behavioral problems at ages 11-13 years in the Port Pirie, Australia cohort study. After adjusting for a number of confounding variables, including HOME scores, maternal psychopathology and the child's IQ, regression models showed that for an increase in average lifetime blood lead concentrations from 10 to 30 µg/dL, the externalizing behavior problem score increased by 3.5 points (95% CI: 1.6, 5.4) in boys, but only by 1.8 points (95% CI: –0.1, 11.1) in girls. In contrast, internalizing behavior problems were predicted to increase by 2.1 points (95% CI: 0.0, 4.2) in girls, but by only 0.8 points (95% CI: –0.9, 2.4) in boys.

Recently, the question of lead's role in delinquent and criminal behavior has been addressed in several investigations. Previous studies linking attention deficits, aggressive and disruptive behaviors, and poor self-regulation with lead have raised the prospect that early exposure may result in an increased likelihood of engaging in antisocial behaviors in later life.

Denno (1990) surveyed 987 Philadelphia African American youths enrolled in the Collaborative Perinatal Project. Data were available from birth through 22 years of age. The analysis initially considered over 100 predictors of violent and chronic delinquent behavior. Repeat offenders presented consistent features such as low maternal education, prolonged male-provider unemployment, frequent moves, and higher lead intoxication (although Denno does not indicate the level of lead intoxication in her report). In male subjects, a history of lead poisoning was among the most significant predictors of delinquency and adult criminality.

Needleman et al. (1996) examined the relationship between lead exposure and several measures of behavioral disturbance and delinquent behavior in subjects from the Pittsburgh Youth Study. The Pittsburgh Youth Study is a prospective study of the developmental course of delinquency (Loeber et al., 1991). The population consisted of 850 boys who were prescreened with an instrument that measured serious and potentially indictable behaviors extracted from the teachers' and parents' CBCL. Subjects who scored above the 30th percentile on the risk score and an approximately equal number of subjects randomly selected from the remainder of the

distribution formed the sample (n = 503). Body burden of lead was measured in the tibia by K-shell XRF. Measures of antisocial behavior were administered at 7 and 11 years of age and included the Self Reported Antisocial Behavior scale (SRA), the Self Report of Delinquent Behavior (SRD), and the parents' and teachers' versions of the CBCL. Outcome data were adjusted for a number of covariates including mother's IQ, SES, childhood medical problems, and quality of child rearing. Parents of subjects with higher lead levels in bone reported significantly more somatic complaints, more delinquent and aggressive behavior, and higher internalizing and externalizing scores. Teachers reported significant increases in scores on somatic complaints, anxious/depressed, social problems, attention problems, delinquent behavior, aggressive behavior, and internalizing and externalizing problems in the higher lead subjects. At 11 years, subjects SRD scores also were significantly related to bone lead levels. More of the high lead subjects had CBCL scores in the clinical range for the CBCL subscales assessing attention problems, aggression, and delinquency. Odds ratios for these outcomes ranged from 1.5 (95% CI: 0.45, 4.9) for parental reports of aggression to 19.5 (95% CI: 8.9, 41.6) for attention problems. The authors concluded that lead exposure was associated with an increased risk for antisocial and delinquent behavior.

Dietrich et al. (2001) reported on the relationship between early exposure to lead and juvenile delinquency in 195 subjects from the Cincinnati Lead Study. Subjects were between 16 and 17 years of age when examined. As previously described, this is an inner-city cohort of urban children exposed to relatively high levels of lead by virtue of their residence in older, deteriorated housing units. Relationships between prenatal (maternal) and postnatal exposure to lead (through serial blood lead determinations), and antisocial and delinquent behaviors (self- and parental reports) were examined. Parents were administered a questionnaire developed specifically for the study while CLS subjects were given the SRD. A wide range of candidate covariates and confounders were examined, but the only ones predicting antisocial or delinquent behavior were birth weight, HOME scores, SES, and parental IQ. In multiple linear regression analyses, prenatal exposure was significantly associated with a covariate-adjusted increase in the frequency of parent-reported delinquent and antisocial acts, while prenatal and postnatal exposure to lead was significantly associated with a covariate-adjusted increase in frequency of self-reported delinquent and antisocial behaviors, including marijuana use. To clarify the concentration-response relationships, blood lead indices were transformed to categorical

variables and least-square means were calculated from an analysis of covariance procedure. Subjects in the highest prenatal blood lead category (>10 μg/dL) engaged in 2.3 more delinquent acts over the preceding 12 months than subjects in the lowest category (≤5 μg/dL). Using average childhood blood lead levels, subjects in the medium (16-20 μg/dL) and highest (>20 μg/dL) category engaged in approximately 1.5 more delinquent acts compared to the lowest category (≤10 μg/dL). Subjects in the highest 78-month blood lead category (>15 μg/dL) engaged in 4.5 more delinquent acts than subjects in the lowest category (≤5 μg/dL). The authors concluded that lead might play a measurable role in the epigenesis of behavioral problems in inner-city children independent of other social and biomedical cofactors assessed in the study.

Needleman et al. (2002) conducted a case-control study where they examined the levels of lead in bone of 194 adjudicated delinquents and 146 non-delinquent community controls. Subjects were recruited from high schools in the city of Pittsburgh and environs of Allegheny County, PA. Since many delinquents are not arrested or adjudicated, care was taken to ensure that unidentified delinquents did not populate the control group. Potential control subjects were excluded from the analyses if they were found to have a Juvenile Court record or an SRD score above the 90th percentile. Tibial bone lead was measured by K-shell XRF. Covariates included race, parental education and occupation, presence of two parental figures in the home, number of children in the home, and neighborhood crime rate. Logistic regression analyses were undertaken to model the association between delinquent status and bone lead concentration. Cases had significantly higher average concentrations of lead in tibia than controls (11.0 μg/g [SD 32.7] versus 1.5 μg/g [SD 32.1]). Stratified analyses revealed this was true for both white and African American subjects. Following adjustment for covariates, adjudicated delinquents were four times more likely to have bone lead concentration greater than 25 μg/g than controls (odds ratio of 4.0 [95% CI: 1.4, 11.1]). The effect of lead on delinquency was found to be substantial in this study. Bone lead level was the second strongest factor in the logistic regression models, exceeded only by race. In models stratified by race, bone lead was exceeded as a risk factor only by single parent status. The authors concluded that elevated body lead burdens were associated with elevated risk for adjudicated delinquency.

The extension of lead effects into delinquent and criminal behavior is significant for both the individual and society as a whole. The particular biological mechanisms that may underlie

lead's effects on aggression, impulsivity, and poor self-regulation are not clearly understood. However, lead impacts a large number of sites and processes in the brain that are involved in impulse control (Lidsky and Schneider, 2003). Needleman et al. (2002) proposed another pathway. In addition to lead's direct impact on brain development and neuronal function, lead exposure may increase risk of delinquency through a separate, indirect route: impaired cognitive abilities and academic performance. In other words, students who have difficulties in school and fail to achieve academic goals are more likely to become lawbreakers.

6.3.2.5 Sensory Acuities

In comparison to cognitive outcomes, there has been relatively less interest in the effects of lead on sensory functions. However, there are clear indications that lead exposure during the developmental period has an impact on complex aspects of visual and auditory acuities. Much of this work has been carried out in animal models (Otto and Fox, 1993). Epidemiologic studies have typically assessed hearing thresholds and features of auditory processing in lead-exposed children. Studies reviewed in this section are summarized in Annex Table AX6-3.7.

Schwartz and Otto (1987) observed significant lead-associated elevations in pure-tone hearing thresholds at various frequencies within the range of human speech among over 4,500 4-19 year old subjects in NHANES II. In a later study, this finding was replicated in a sample of over 3,000 6-19 year old subjects in the Hispanic Health and Nutrition Examination Survey (HHANES) (Schwartz and Otto, 1991). An increase in blood lead from 6 to 18 µg/dL was associated with a 2 db loss in hearing at all frequencies, and an additional 15% of children had hearing thresholds that were below the standard at 2,000 Hz. These relationships continued at blood lead levels less than 10 µg/dL.

Dietrich et al. (1992) assessed the relationship between scores on a test of central auditory processing (SCAN) and prenatal/postnatal blood lead concentrations in 215 children 5 years of age drawn from the Cincinnati Lead Study. Higher prenatal, neonatal, and postnatal (up to concurrent) blood lead concentrations were associated with more incorrect identification of common monosyllabic words presented under conditions of filtering (muffling). Other variables associated with impaired central auditory processing included the results of pure-tone audiometry testing, social class, HOME scores, birth weight, gestational age, a measure of obstetrical complications, and consumption of alcohol during pregnancy. Following adjustment

for these covariates, neonatal and postnatal blood lead levels remained significantly associated with impaired performance on the Filtered Word subtest, more prominently in the right ear. In the right ear, the Filtered Word subtest score decreased by 0.7 points ($p < 0.05$; 95% CI not presented) for a 10 µg/dL increase in lifetime average blood lead levels.

Osman et al. (1999) examined the relationship between concurrent blood lead levels and hearing loss in 155 children 4-14 years of age living in an industrial region of Poland. Blood lead levels ranged from 1.9 to 28 µg/dL (median 7.2 µg/dL). Hearing thresholds increased significantly with higher blood lead levels at all frequencies (500-8,000 Hz). This relationship remained statistically significant when restricted to children with blood lead levels below 10 µg/dL.

A limited number of epidemiologic studies provide supportive evidence of a relationship between lead exposure and auditory processing. Lead-related deficits in hearing and auditory processing may be one plausible mechanism by which an increased lead burden might impede a child's learning (Bellinger, 1995).

6.3.2.6 Neuromotor Function

Relatively few studies have focused on neuromotor deficits as an outcome of early lead exposure. However, those that have examined motor functions in lead-exposed children often report positive findings. Studies reviewed in this section are summarized in Annex Table AX6-3.8.

In an early study, unsteadiness, clumsiness, and fine-motor dysfunctions were noted in a group of mildly symptomatic lead-poisoned children in Boston, with such effects persisting long after medical treatment (Pueschel et al., 1972). A study of moderately exposed children living in the vicinity of a longstanding lead smelter in Greece found that children with blood lead levels of 35-60 µg/dL had significantly lower scores on both the Gross and Fine Motor Composite scores from the Oseretsky scales when compared to controls (Benetou-Marantidou et al., 1988).

Only two modern prospective studies of lead have assessed motor development in a comprehensive manner. Dietrich et al. (1993b) investigated the association between lead exposure and motor developmental status in 245 children 6 years of age in the Cincinnati Lead Study cohort. Following covariate adjustment, they found that postnatal lead exposure was significantly associated with poorer scores on measures of bilateral coordination, visual-motor

control, upper-limb speed and dexterity, and the fine motor composite from the Bruininks-Oseretsky scales. Neonatal, but not prenatal, blood lead concentrations also were significantly associated with poorer scores on upper-limb speed and dexterity and the fine motor composite. The strongest and most consistent relationships were observed with concurrent blood lead levels (mean 10.1 µg/dL [SD 5.6]). A 10 µg/dL increase in concurrent blood lead levels was associated with a 4.6 point (95% CI: 2.1, 7.1) decline in the fine motor composite score. In the same Cincinnati cohort, postnatal lead exposure was associated with greater postural instability as assessed by a microprocessor-based strain gauge platform system (Bhattacharya et al., 1995). When assessed at 16 years of age, 78-month postnatal blood lead levels were significantly associated with poorer fine-motor skills as indexed by covariate-adjusted factor scores derived from a factor analysis of a comprehensive neuropsychological battery (Ris et al., 2004). The variables loading highly on the fine-motor component came from the grooved pegboard and finger tapping tasks.

Some results of the Cincinnati Lead Study were replicated by Wasserman et al. (2000a) in the Yugoslavian Prospective Study. The authors adapted the Bruininks-Oseretsky Test of Motor Proficiency for use in their population residing in two towns in the province of Kosovo. The measure of exposure was the log of the lifetime average blood lead concentration through 54 months of age. Following covariate-adjustment, average childhood blood lead concentrations were associated with poorer fine motor and visual motor function, but were found to be unrelated to gross motor function.

A recent study by Despres et al. (2005) of multiple exposures including lead, mercury, and polychlorinated biphenyls found that only blood lead concentrations measured at the time of assessment were associated with neuromotor functions in 110 preschool Inuit children residing in Canada. The mean blood lead level was 5.0 µg/dL (range 0.8-27.1). Blood lead levels were significantly associated with increased reaction time, sway oscillations, alternating arm movements, and action tremor. Ten percent of the children had blood lead levels greater than 101 µg/dL. After eliminating these children from the analyses, results remained significant for reaction time, sway oscillations, and alternating arm movements. These findings indicated that neuromotor effects of lead occurred at blood lead concentrations below 10 µg/dL.

6.3.2.7 Brain Anatomical Development and Activity

Electrophysiological evaluations have been conducted on lead-exposed children in attempts to obtain a more direct measure of the toxicant's impact on the nervous system. Much of this work was conducted by Otto and colleagues during the 1980s (e.g., Otto et al., 1985). Studies reviewed in this section are summarized in Annex Table AX6-3.9. These studies have demonstrated effects of lead on neurosensory functioning (auditory and visual evoked potentials) within a broad range of exposures (Otto and Fox, 1993).

Rothenberg et al. (1994) reported that higher maternal blood lead levels at 20 weeks of pregnancy were associated with increased I-V and III-V interpeak intervals in the brainstem auditory evoked response recorded in 1-month-old infants. Mean maternal blood lead level at 20 weeks in this subsample from the Mexico City Prospective Study was only 7.7 μg/dL with a range of 1-30.5 μg/dL. Rothenberg et al. (2000) repeated these measurements with a larger group of 5-7 year old children (n = 133). In contrast to their previous findings, prenatal blood lead levels at 20 weeks were associated with decreased interpeak intervals. However, after fitting a nonlinear model to their data, they observed that I-V and III-V interpeak intervals decreased as blood lead rose from 1 to 8 μg/dL and increased as blood lead rose from 8 to 30 μg/dL. The biphasic effect was only observed with maternal blood leads at 20 weeks of pregnancy. Increasing postnatal blood lead at 12 and 48 months was related to decreased conduction intervals for I-V and III-V interpeak intervals across the entire blood lead range.

The methods of Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) have recently been applied in studies of lead-exposed children. Trope et al. (1998) were the first to apply MRI and MRS in an evaluation of a lead-exposed subject. The subject was a 10 year old boy who had a history of elevated blood lead levels as a toddler (e.g., 51 μg/dL at 38 months). The subject was compared to his 9-year-old unexposed cousin. The investigation was particularly focused on *N*-acetylaspartate, a metabolite shown to decrease in processes that involve neuronal and axonal loss. Both children presented with normal volumetric MRI, MRS revealed a significant alteration in brain metabolites, with a reduction in *N*-acetylaspartate:creatine ratio for both gray an white matter compared to the subject's cousin. Trope et al. (2001) performed identical MRI and MRS studies on a sample of 16 subjects with a history of elevated blood lead levels before five years of age (23 to 65 μg/dL). Average age at time of evaluation was 8 years. These subjects were compared to age-matched controls

composed of siblings or cousins. Control subjects had blood lead levels that never exceeded 10 µg/dL. Although all of the participants had normal MRI examinations, the lead-exposed subjects exhibited a significant reduction in *N*-acetylaspartate:creatine and phosphocreatine ratios in frontal gray matter compared to controls.

Meng et al. (2005) performed MRI and MRS studies on children with blood lead concentrations ≥27 µg/dL (n = 6) and age- and gender-matched controls with blood lead concentrations <10 µg/dL (n = 6). The average age at time of evaluation was approximately 11 years. Subjects came from the Anhui province in China. Lead-exposed children had an average blood concentration of 37.7 µg/dL (SD 5.7) while controls averaged 5.4 µg/dL (SD 1.5). MRS was used to measure *N*-acetylaspartate, choline-containing compounds, and total creatine in the frontal lobes and hippocampus in cases and controls. All children presented with normal MRI with no evidence of structural abnormalities. However, peak values of *N*-acetylaspartate, choline, and creatine in all four brain regions were reduced in lead-exposed children relative to controls. The authors concluded that the reduced brain *N*-acetylaspartate levels they observed in cases may be related to decreased neuronal density or neuronal loss. Furthermore, reduced choline signal may indicate decreased cell membrane turnover or myelin alterations that can lead to central nervous system hypertrophy, while lower creatine may indicate reduced neuronal cell viability.

Using functional MRI (fMRI), Cecil et al. (2005) examined the influence of childhood lead exposure on language function in a subsample of 48 young adults from the Cincinnati Lead Study. At age 20-23 years, subjects performed an integrated verb generation/finger tapping paradigm. Higher childhood average blood lead levels were significantly associated with reduced activation in Broca's area, a recognized region of speech production in the left hemisphere. This association remained statistically significant after adjustment for the subject's latest IQ assessment. Higher childhood blood lead levels also were associated with increased activation in the right temporal lobe, the homologue of Wernicke's area (an area associated with speech production) in the left hemisphere. The results of this study suggest elevated childhood lead exposure strongly influences neural substrates of semantic language function on normal language areas with concomitant recruitment of contra-lateral regions resulting in a striking, dose-dependent atypical organization of language function.

6.3.2.8 Gene-Environment Interactions in the Expression of Lead-Associated Neurodevelopmental Deficits

The discussion of gene-environment interactions with respect to lead exposure encompasses differential susceptibilities with respect to race, gender, and genetic polymorphisms associated with lead metabolism, and neurotransmitter metabolism and function. While the differential effects of lead on neurodevelopment have been studied to some extent with respect to race and gender, very little work has been accomplished with respect to specific genetic polymorphisms.

In the U.S., African-American children are at increased risk for having an elevated blood lead level compared with white children. For example, in the last two NHANES surveys, African-American children were found to have significantly higher blood lead levels than whites, even after adjusting for urban residential status and family income (Brody et al., 1994; Mahaffey et al., 1982). However, reliable differences with respect to lead's effects on neurodevelopmental morbidity as a function of race have not been reported with consistency.

Most surveys find that boys have higher blood lead levels than girls. The data are less clear with respect to gender-related differences in lead-associated neurodevelopmental morbidities. At various assessments from birth to adolescence, a greater male vulnerability has been noted in the Cincinnati Lead Study (e.g., Dietrich et al., 1987b; Ris et al., 2004). Data from a cross-sectional study in England showed that the lead-IQ deficit association was more pronounced in boys at 6 years of age (Pocock et al., 1987). However, in a study of 764 children in Taiwan, it was found that the relationship between lead exposure and IQ scores was substantially stronger in girls (Rabinowitz et al., 1991). In the Port Pirie cohort study, lead effects on cognition were significantly stronger in girls at ages 2, 4, 7, and 11-13 years (Baghurst et al., 1992; McMichael et al., 1992; Tong et al., 2000).

At least two genetic polymorphisms have been identified that can influence the absorption, retention and toxicokinetics of lead in humans (Onalaja and Claudio, 2000). The ALAD gene has been the most studied but, as yet, the consequences of the different alleles for susceptibility to the neurodevelopmental consequences of lead exposure are unclear. Individuals with the ALAD12 or ALAD22 polymorphism tend to have higher blood lead levels than those with ALAD11. ALAD2 could increase vulnerability by raising blood lead levels or decrease it by maintaining lead in a sequestered state in the bloodstream. Only one pediatric study has

examined this directly. Bellinger et al. (1994) found that subjects with the ALAD2 polymorphism tended to have lower dentin levels than those with ALAD1. This is consistent with the concept that increased affinity of the ALAD2 polymorphism inhibits entry of lead from the blood stream into other tissues. After adjustment for exposure level, Bellinger et al. found that adolescents with the ALAD2 polymorphism performed better in the areas of attention and executive functioning assessed in their study when compared to subjects with the ALAD1 polymorphism. However, as there were only 5 subjects with the ALAD2 form, meaningful statistical comparisons could not be made.

The other gene that has been studied is the vitamin D receptor or VDR gene. This gene is involved in calcium absorption through the gut. Research on lead workers has shown that variant VDR alleles modify lead concentrations in bone, and the rate of resorption and excretion of lead over time (Schwartz et al., 2000c). Haynes et al. (2003) examined the relationship between the VDR Fok1 polymorphism and blood lead concentrations in 275 children enrolled in the Rochester Longitudinal Study. It was hypothesized that children homozygous for the *F* allele—a marker for increased calcium absorption—would have higher blood lead concentrations than heterozygotes and children homozygous for the *f* allele, after adjusting for environmental sources of lead (floor dust lead). A statistically significant interaction was found between floor dust lead loading and VDR-*Fok*1 genotypes on blood lead concentration, with the *FF* genotypes having the highest adjusted mean blood lead concentrations at 2 years of age. Consistent with other reports, Haynes et al. (2003) also found that African American children were significantly more likely to have the VDR-*FF* than were non-African American children. The ability of African American children to have increased calcium absorption may partially explain the higher blood lead concentrations observed in African American children. Unfortunately, there have been no studies to indicate which, if any, of the VDR polymorphisms are associated with increased vulnerability to the neurodevelopmental toxicity of lead.

6.3.2.9 Reversibility of Lead-related Neurodevelopmental Deficits Associated with Prenatal and Postnatal Exposure

The apparent persistence of the neurodevelopmental effects of lead observed into later childhood and adolescence has resulted in a widely held view that the damage to the central nervous system and resulting deficits in neurobehavior are irreversible. The ramifications of the

effects of lead on neurodevelopment depend not only on the extent of the initially observable effects in early childhood, but also on their enduring consequences for cognition, attainment, and behavior over the lifetime of the individual. Studies reviewed in this section are summarized in Annex Table AX6-3.10.

Since 1990, several studies attempted to eliminate or at least reduce lead-associated neurodevelopmental damage through nutritional and/or pharmacological interventions. Optimism that such interventions might be effective was raised by a New York study published in the early 1990s (Ruff et al., 1993). In an observational study, children 13 to 87 months old with blood lead levels between 25 and 55 µg/dL were given chelation with EDTA and therapeutic iron when clinically indicated. The children were then followed for 6 months. Those whose blood lead levels fell the most had improved cognitive test scores, independent of whether they had been given iron or chelation therapy. Prior to this publication, the National Institute for Environmental Health Sciences (NIEHS) was already in the process of planning a multicenter clinical trial to determine if a recently licensed oral chelating drug (dimercaptosuccinic acid or "succimer") might diminish the neurodevelopmental impact of lead in children with blood lead levels between 20 and 44 µg/dL (Rogan et al., 1998).

The Treatment of Lead-Exposed Children (TLC) study was originally designed to test the hypothesis that children with moderate blood lead levels who were given succimer would have better scores than children given placebo on a wide range of tests measuring cognition, neuropsychological functions, and behavior at 36 months of follow-up (Rogan et al., 2001). TLC enrolled 780 children from four clinical sites into a randomized, placebo-controlled, double-blind trial of up to three 26-day courses of treatment with succimer. Most children lived in deteriorating inner-city housing. Seventy-seven percent of the subjects were African American. Succimer was effective in lowering the blood lead levels of subjects on active drug during the first 6 months of the trial. However, after 1 year, differences in the blood lead levels of succimer and placebo groups had virtually disappeared. All data analyses were conducted on an intent-to-treat basis. At 36 months of follow-up, the mean IQ score on the WPPSI-R of children given active drug was 1 point lower than that of children administered placebo, and children given succimer evinced more behavioral problems as rated by the primary caregiver on the Conners Parent Rating Scale. Children given succimer scored marginally better on the Developmental Neuropsychological Assessment (NEPSY), a battery of tests designed to measure

neuropsychological deficits that can interfere with learning. However, all of these differences were statistically nonsignificant.

Although results for the first wave of follow-up for TLC were consistently negative for drug effects on cognition and behavior, they were not necessarily conclusive. Lead may affect higher-level neurocognitive processes that are inaccessible, difficult to assess, or absent in the preschool age child. In older children, scores on psychometric measures are more precise and reliable, a wider and more differentiated range of abilities can be examined, and early academic performance and social functioning outside the home environment can be evaluated. Therefore, TLC followed the cohort into the first years of elementary education to determine whether these later emerging neurodevelopmental functions were spared the effects of lead in treated children compared to placebo controls (Dietrich et al., 2004). While remaining within the limits of hypothesis driven inference, a comprehensive battery of tests were administered to TLC subjects at 7 and 7.5 years of age. These included assessments of cognition, learning, memory, global intellectual attainment, attention/executive functions, psychiatric status, behavioral and academic conduct, neurological functioning, and motor speed. However, treatment with succimer resulted in no benefit in cognitive, behavioral, neurological, and neuromotor endpoints. Indeed, children treated with succimer fared worse than children in the placebo group in several areas, including linear growth, hospitalized and outpatient injury events in the first 3 years of follow-up, and neuropsychological deficits as assessed by the Attention and Executive Functions core domain score from the NEPSY. The authors concluded that these latest follow-up data confirmed their previous finding that the TLC regimen of chelation therapy is not associated with neurodevelopmental benefits in children with blood lead levels between 20 and 44 μg/dL. Furthermore, these results emphasize the importance of taking environmental measures to prevent exposure to lead in light of the apparent irreversibility of lead-associated neurodevelopmental deficits.

In addition to pharmacological interventions, a few studies have attempted to remediate or prevent lead-associated neurodevelopmental deficits through nutritional supplementation. Recent studies attempting to reduce lead absorption through mineral hypersupplementation have been disappointing (Sargent et al., 1999). However, to date there has been only one controlled clinical trial involving lead-exposed children where central nervous system outcomes have been the focus of study. Kordas et al. (2005) and Rico et al. (2005) conducted a double-blind

nutritional supplementation trial among 602 first grade children in the city of Torreon in northern Mexico. The city is located near a metal foundry that has been a source of lead contamination in the community. The average blood lead concentration at baseline was 11.5 µg/dL (SD 6.1). About half of the children had blood lead concentrations in excess of 10 µg/dL. Subjects received 30 mg ferrous fumarate, 30 mg zinc oxide, both, or placebo daily for 6 months. In their first report, the principal outcome assessment taken at baseline and at follow-up was the parent and teacher forms of the Conners Rating Scales. There were no consistently significant treatment effects and the authors concluded that this regimen of supplementation did not result in improvements in ratings of behavior in lead-exposed children over 6 months. In addition to behavior, the authors assessed cognitive functioning with 11 tests of memory, attention, visual-spatial abilities, and learning. There were no consistent or lasting differences in cognitive performance among treatment groups confirming the earlier conclusion that nutritional supplementation alone is not effective in eliminating or reducing the impact of early lead exposure on functional neurodevelopment.

Children's blood lead levels generally decline after they peak at somewhere around 2 years of age. However, the degree of decline is a function of a number of factors including previously acquired body burden and sources of continuing exposure. Some observational studies have examined the extent to which the rate of decline in blood lead levels is associated with improvements in neurocognitive status. Tong et al. (1998) assessed the reversibility of the cognitive effects of lead in early childhood in the Port Pirie, Australia cohort study. A total of 375 children were followed to the age of 11-13 years. Average blood lead concentrations decreased from 21.2 µg/dL at 2 years to 7.9 µg/dL at 11-13 years. However, scores on standardized measures of intellectual attainment administered at 2, 4, 7, and 11-13 years of age in children whose blood lead levels declined the most were not significantly improved over those obtained by children with a more shallow decline in body burden.

Liu et al. (2002) made use of the TLC succimer trial data set (Rogan et al., 2001) to examine the question of reversibility. As reviewed above, intent-to-treat analyses revealed no benefits of chelation on neurodevelopmental indices beyond 6 months of treatment. Thus, the scores on the cognitive tests from the two treatment groups could be analyzed either within the treatment groups or as a whole. Data from 741 children were available for analyses. Mean blood lead levels in TLC subjects were 26.2 µg/dL at baseline, 20.2 µg/dL at the 6-month

follow-up, and 12.2 µg/dL at the 36-month follow-up. Mean declines in blood lead levels were 6.0 µg/dL from baseline to 6-month follow-up, 14.1 µg/dL from baseline to 36-month follow-up, and 8.0 µg/dL from 6- to 36-month follow-ups. Blood lead levels declined more quickly in the first 6 months in the succimer group than in the placebo group, but the mean blood lead levels were very similar at baseline and at the 36-month follow-up. Prior to examining changes in blood lead levels in relationship to changes in cognitive test scores, it was verified that baseline and later blood lead levels were indeed significantly associated with deficits on measures administered at specific points in the study after adjustment for socioherediatary factors surveyed in the study including maternal IQ. Unlike in the New York study by Ruff et al. (1993), Liu et al. (2002) found no overall effect of changing blood lead level on changes in cognitive test score from baseline to 6 months. However, during the follow-up from baseline to 36 months and from 6 to 36 months, falling blood lead levels were significantly associated with increased cognitive test scores, but only because of an association in the placebo group. Cognitive test scores increased by 2 points overall and 4 points in the placebo group when blood lead levels declined by 10 µg/dL from baseline to 36 months. There is a possibility that the succimer drug regimen blunted the beneficial effect. Due to the inconsistency in the results, the data do not provide strong supportive evidence that lead-induced cognitive impairments are reversible. Therefore, primary prevention and preventing additional increases in blood lead levels among children whose blood lead levels are high remain the only effective means of dealing with lead toxicity.

6.3.2.10 Periods of Enhanced Developmental Susceptibility to Central Nervous System Effects of Environmental Lead

It has been difficult to identify discrete periods of development when the fetus or child is particularly susceptible to lead's effects on neurodevelopment. When the prospective studies of lead and child development were underway, it was hoped that this methodological approach would be revealing. However, these studies observed that age strongly predicted the period of peak exposure (around 18-27 months when there is maximum hand-to-mouth activity), making it difficult to distinguish whether greater neurotoxic effects resulted from increased exposure or enhanced susceptibility at a particular age. Furthermore, children with the highest blood lead levels tended to maintain their rank order relative to their lower exposed peers throughout these

studies (e.g., Dietrich et al., 1993a; McMichael et al., 1988), limiting the degree to which investigators could identify any particular period of development as critical.

From the perspective of human neurodevelopmental biology, one could argue that the first 3 years of life should represent a particularly vulnerable period. Maximal ingestion of lead coincides with the same period of time when major events are occurring in the development of the central nervous system including some neurogenesis, rapid dendritic and axonal outgrowth, synaptogenesis, synaptic pruning, and programmed apoptosis (see Figure 6-3.4).

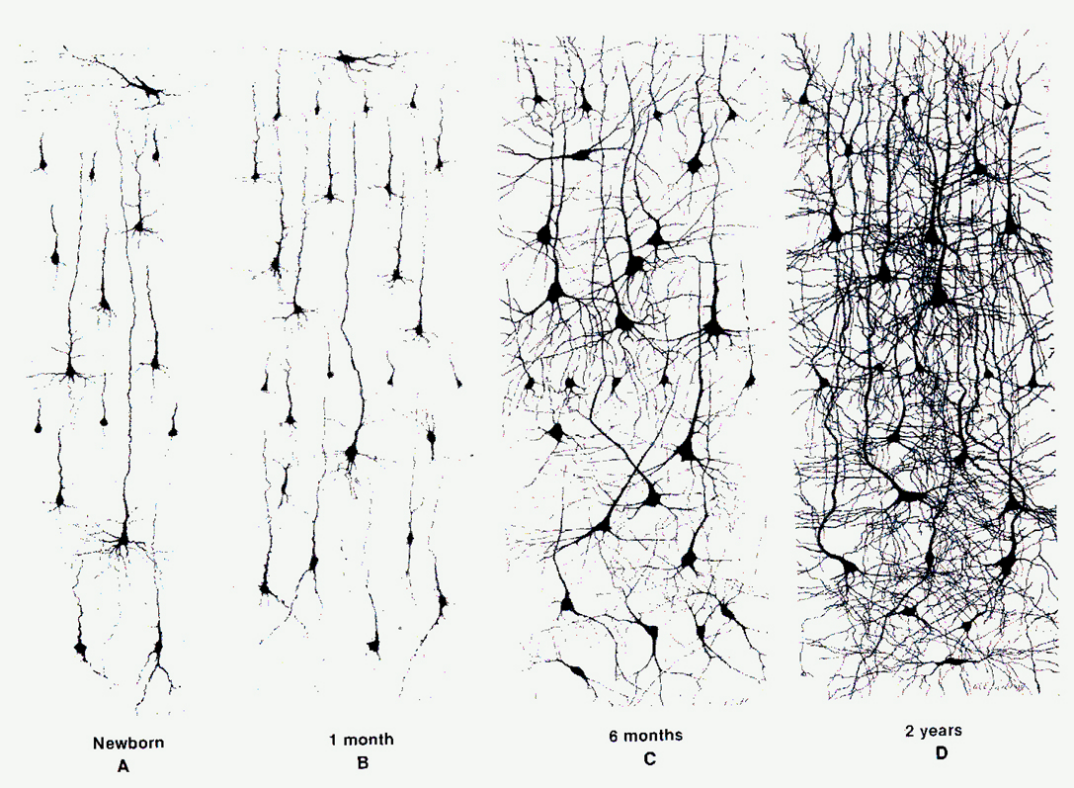


Figure 6-3.4. Golgi-stained section of human cerebral cortex taken from equivalent areas of the anterior portion of the middle frontal gyrus at different ages. Although the packing density of cortical neurons does not appear to change, there is a tremendous increase in the complexity of dendritic arborizations with increasing age with maximal density occurring between two and three years of age.

Source: Nolte (1993).

This belief that the first 3 years represents a critical window of vulnerability is evident in the lead literature (Chen et al., 2005). Two major meta-analyses of the relationships between childhood lead exposure and IQ focused primarily on the strength of the association between IQ at school age and blood lead concentrations at 2 years of age or average blood lead levels up to 3 years of age (Pocock et al, 1994; Schwartz, 1994). Neither meta-analysis considered the importance of concurrent blood lead associations in older children. The focus on these particular age groups implied that the interpretation most consistent with the overall results was that peak blood lead concentration, achieved somewhere between 1 and 3 years of age, was most likely responsible for the cognitive effects observed years later. These meta-analyses were highly influenced by findings from the Boston prospective study where blood lead concentrations at 2 years of age have been exclusively and consistently associated with lower IQ and academic achievement (Bellinger et al., 1992).

This particular interpretation of the lead literature has also influenced screening programs (which focus on 1 and 2 year olds), clinical trials that recruit children during the first 3 years of life, and current interpretation of the cross-sectional literature. For example, the report by Lanphear et al. (2000) that school-age children enrolled in the NHANES III survey displayed a significant inverse relationship between concurrent blood lead concentrations and measures of IQ and academic achievement at blood lead concentrations below 10 μg/dL was interpreted by some to reflect the effects of the children's higher blood lead concentrations when they were between 1-3 years of age.

However, it is not clear that only the period of peak blood lead concentration matters in terms of the risks for neurodevelopmental morbidity. Other prospective studies of children with both high and low lead exposures found concurrent or lifetime average blood lead levels to be more strongly associated with school age IQ and other measures of neurodevelopment (Canfield et al., 2003a; Dietrich et al., 1993a,b; Tong et al., 1996; Wasserman et al., 2000b). One study has recently attempted to address this question directly. Chen et al. (2005) sought to clarify the strength of the association between IQ and blood lead at various time points, to examine whether the cross-sectional associations observed in school age children 84-90 months of age represented residual effects from 2 years of age or "new" effects emerging among these children, and how the change in blood lead over time is related to IQ at later ages. Chen et al. (2005) used data on

780 children from the previously described TLC multicenter clinical trial (Dietrich et al., 2004; Rogan et al., 2001) to examine these relationships. Homogeneity between the two treatment groups was verified. There were no statistical differences between succimer and placebo groups in either blood lead concentrations or cognitive scores at the time points under consideration. At baseline, children were given the Bayley Scales of Infant Development. The children's full scale IQ at the 36-month follow-up was measured with the WPPSI-R. At the 60 month follow-up, IQ was assessed with the WISC-III. All neurodevelopmental outcomes were adjusted for clinical center, race, gender, language, parent's education, parent's employment, single parent family, age at blood lead concentration, and caregiver's IQ.

Figure 6-3.5 displays the mean IQ at current and subsequent ages by quartiles of blood lead measured at 2, 5, and 7 years of age. The concurrent blood lead concentration always had the strongest association with IQ. As the children aged, the relationship grew stronger. The peak blood lead concentration from baseline to 7 years of age was not associated with IQ at 7 years of age. Furthermore, in models including both prior and concurrent blood lead concentrations, concurrent blood lead was always more predictive of IQ. Adjustment for prior IQ did not fundamentally change the strength of the association with concurrent blood lead concentration. Chen et al. (2005) found a stronger relationship between IQ at 7 years of age and blood lead concentration at 7 years compared with blood lead at 2 years of age. A similar relationship was observed between IQ and blood lead at 5 years of age. The strength of the cross-sectional associations increase over time, despite lower blood lead concentrations in older children. These data support the idea that lead exposure continues to be toxic to children as they reach school age, and does not lend support to the interpretation that all of the damage is done by the time the child reaches 2 to 3 years of age. These findings also imply that cross-sectional associations observed in children, such as the study recently conducted by Lanphear et al. (2000) using data from NHANES III should not be dismissed. Chen et al. (2005) concluded that if concurrent blood lead remains important until school age for optimum cognitive development, and if 6 and 7 year olds are as or more sensitive to lead effects as 2 year olds, then the difficulties in preventing lead exposure are magnified but the potential benefits of prevention are greater.

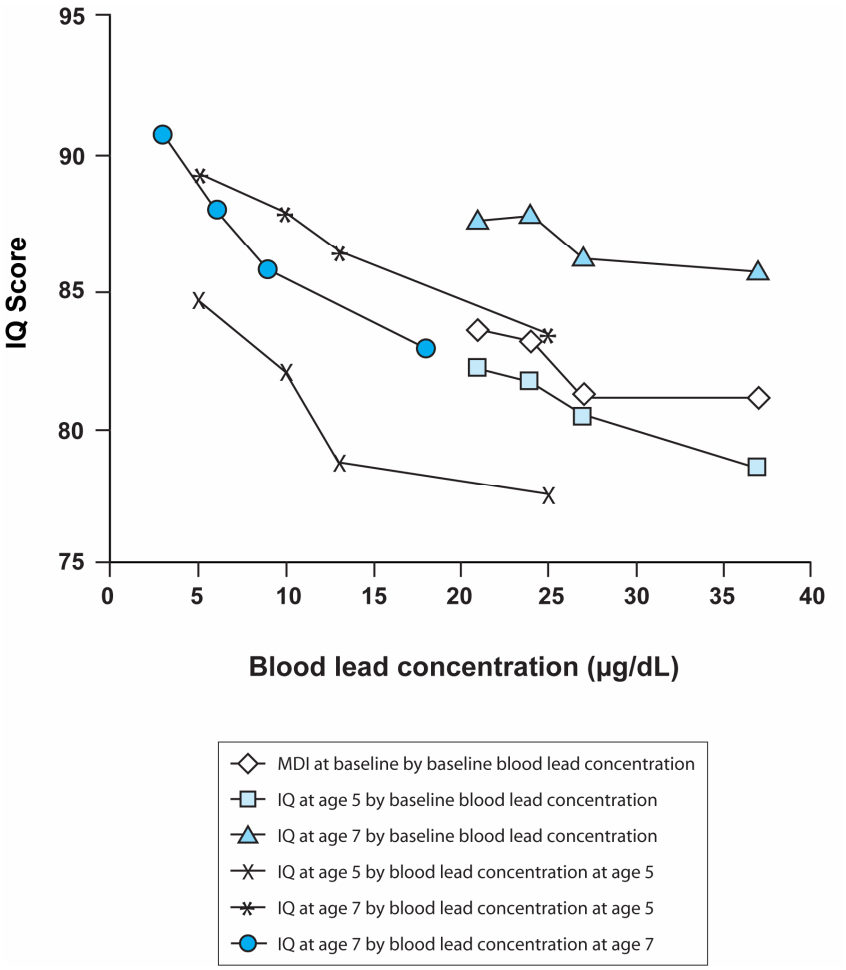


Figure 6-3.5. Full scale IQ test scores by previous or concurrent blood lead concentration. Each data point shows the mean IQ test scores of children measured at baseline or at two follow-ups, grouped by quartiles of blood lead concentration. The abscissa of each point is the middle value of each blood lead concentration category.

Source: Chen et al. (2005).

6.3.2.11 Effect of Environmental Lead Exposure on Neurodevelopment at the Lower Concentration Range

Over the last three decades, epidemiologic studies of lead and child development have demonstrated inverse associations between blood lead concentrations and children's IQ and other outcomes at successively lower levels. The 1986 Addendum and 1990 Supplement concluded that neurobehavioral effects were related to blood lead levels of 10 to 15 µg/dL and possibly

lower. In response to these data, agencies such as the U.S. Centers for Disease Control and Prevention and the World Health Organization have repeatedly lowered the definition of an elevated blood lead concentration, which now stands at 10 μg/dL (CDC, 1991; WHO, 1995). At the time when these policies were put in place, there were too few studies of children with blood lead levels consistently below 10 μg/dL on which to base an opinion as to effects at lower levels of exposure. Since the removal of lead from gasoline, the median blood lead concentration has dropped dramatically in U.S. children, permitting more studies of this nature to be done in recent years. Furthermore, the use of meta- and pooled analytic strategies has permitted investigators to get a clearer picture of effects below 10 μg/dL.

The Rochester Prospective Study (n = 172) by Canfield et al. (2003a) is illustrative. This study extended the relationship between blood lead concentrations and deficits in IQ to levels well below 10 μg/dL. Over half of the children in this study did not have a recorded blood lead concentration above 10 μg/dL. Nonlinear semiparametric smoothing revealed a covariate-adjusted decline of more than 7 points up to 10 μg/dL of childhood average blood lead and a further decline of 2 points associated with an increase from 10 to 20 μg/dL. In response to the Rochester findings, Bellinger and Needleman (2003) reanalyzed data from the Boston Prospective Study focusing on children whose blood lead levels never exceeded 10 μg/dL (n = 48). In their analyses, 10 year IQ was inversely related to blood lead levels at 24 months following adjustment for covariates. Nonparametric smoothing analyses indicated that the inverse association persisted at blood lead levels below 5 μg/dL.

Perhaps the most compelling evidence for effects below 10 μg/dL comes from an international pooled analysis of seven prospective cohort studies (n = 1,333) by Lanphear et al. (2005) described earlier. Although exposures in some cohorts were high, by pooling data from these studies a substantial number (n = 244) of children with blood lead levels that never exceeded 10 μg/dL could be included in the analyses. For the entire pooled data set, the observed decline of 6.2 points in IQ for an increase in blood lead levels from 1-10 μg/dL was comparable to the decrements for an increase in lifetime mean blood lead levels from <1-10 μg/dL observed in the Rochester Longitudinal Study (Canfield et al., 2003a). The pooled analysis of Lanphear et al. also demonstrated that deficits in IQ extended to blood lead levels <7.5 μg/dL. Therefore, recent evidence is suggestive of effects of lead on neurocognitive deficits at blood lead levels below 10 μg/dL, and possibly below 7.5 μg/dL, in children.

6.3.2.12 Selection and Validity of Neuropsychological Outcomes in Children

A fair amount of material has been written about methodologies for neurobehavioral evaluation in studies of environmental chemicals and child development (Bellinger, 2002, 2003; Dietrich et al., 2005). Much of the discussion has centered on the ability of neurobehavioral tests to detect damage to the central nervous system as a result of in utero or early postnatal exposures. In other words, the sensitivity of these tests to toxicity has been in question. The sensitivity of a neuropsychological or any other diagnostic test is defined as the proportion with the abnormality that the test classifies as abnormal (true positives). In the selection of neurodevelopmental measures in studies of lead or any other toxicant, it is clearly advantageous to include tests that have the best prognostic value. This is particularly important in the current context, because the neurobehavioral endpoints reviewed in this document are being incorporated into an assessment of risk (Bellinger, 2002). In addition, it is important to select instruments that tap into neurodevelopmental domains that have shown to be sensitive to particular environmental toxicants. As evident in this review, a large number of neuropsychological instruments, tapping a wide range of domains have proven to be sensitive to lower level lead exposure. Certain domains such as attention, executive functions, visual-spatial skills, fine-motor abilities, academic achievement (reading in particular), and externalizing behaviors appear to be affected by lead with some degree of consistency. However, the identification of behavioral phenotypes for lead has been a largely elusive goal. There are a number of plausible reasons for this. The sample's SES; level, pattern and timing of exposures; nutritional intake; general health; educational opportunities; and the particular instruments that were employed in a given study probably play an important role in between-study differences (Bellinger, 1995; Schantz, 1996). This may be one reason why the broad net provided by global, multiple domain assessments of cognition such as IQ have proven to be the most consistently sensitive across studies of various design and sample characteristics. These measures combine subscales that are representative of a broad number of underlying cognitive functions; thus, they are likely to pick up exposure-related deficits across cohorts that differ in their functional expressions of toxicity (Dietrich et al., 2005).

The validity of neuropsychological tests as indices of neurodevelopment in lead studies also is of concern. In psychometrics, there are various types of validity. But the validity lead researchers are usually most concerned about is "construct validity." If a measure has construct

validity it measures what it purports to measure. Most lead researchers utilize assessments with proven construct validity. This means that the instruments utilized by the investigator have proven that they possess concurrent and predictive "criterion" validity (i.e., it relates to other manifestations of the construct the instrument is supposed to be measuring and predicts an individual's performance in the future in specific abilities). It also means that the instrument possesses good "convergent validity." This means that the test returns similar results to other tests that purport to measure the same or related constructs. Finally, the instrument should demonstrate "discriminant validity." That is, the instrument is not measuring a construct that it is not supposed to measure, it discriminates.

Bellinger (2003) states that the general literature attests to robust observations between IQ and important measures of life success, such as grades in school, years of education, job success, social status, and income (Neisser et al., 1996; Salkever, 1995). Testing is difficult depending on examined age, especially for infants who are in a period of rapid developmental change. Also, the way an infant's cognitive function can be probed is restricted. The lack of continuity between their response modalities and ones that can be exploited as a child gets older is also a factor. Still neurobehavioral tests scores in infancy do possess strong concurrent validity.

There many potential sources of invalidity which researchers take steps to avoid. These include unreliability (an instrument that, all other things being equal, yields scores that are unrepeatable and inconsistent) and bias (e.g., due to factors such as culture, gender). Most modern standardized measures of development and cognitive attainment have taken steps to reduce these sources of invalidity and must meet certain minimum requirements such as those formulated by the American Educational Research Association, American Psychological Association, and the National Council on Measurement in Education (American Educational Research Association et al., 1999). One reason that global measures of IQ have been used so widely is because of their outstanding psychometric properties. The Wechsler series has excellent reliability and validity (Groth-Marnat, 2003). For example, the average internal consistency for the Wechsler children's scales across all age groups is 0.96. Test-retest reliability is similarly very high. The underlying factor structure of these scales has also been strongly confirmed. The validity of so-called experimental measures of learning and cognition is sometimes less certain.

All measurement procedures have the potential for error, so the goal of the researcher is to minimize it. In elementary psychometric theory, any observed test score is made of the "true" score plus measurement error. It is assumed that measurement errors are essentially random (the child's true score may not be reflected in the observed score because of errors of administration, inconsistency of administration across examiners, the child's health, or aspects of the testing environment that are not conducive to performance). This does not mean that lead researchers cannot take pains to reduce these sources of error. In fact, most modern lead researchers do minimize measurement error through attention to training, establishing inter-examiner reliability, attention to child factors, site factors, and vigilant monitoring of examiner performance throughout the course of a study (Dietrich et al., 2005).

6.3.2.13 Confounding, Causal Inference, and Effect Modification of the Neurotoxic Effect of Lead in Children

The major challenge to observational studies of lead's impact on parameters of child development has been the assessment and control for confounding factors. By definition, a confounder is associated with both the exposure and the outcome, thus has the potential to influence the association between the exposure and the outcome. Confounding by various factors can be controlled for in the design phase of the study or in the analytical phase. In the realm of lead research, there are a wide range of potential confounders, the foremost of which is SES. Socioeconomic status is measured rather crudely in most studies with such indices as the Hollingshead Four-Factor Index of Social Position that incorporates education and income of both parents. However, even these so-called blunt measures often account for a great deal of the variance in neurodevelopmental outcomes. Given the crude nature of these measures, to control for confounding by SES as well as rearing environment of the child, many recent lead studies have incorporated more direct assessments such as the HOME scale, parental intelligence, parental attitude assessments, and measures of parental substance abuse and psychopathology. Given the relatively high correlation between indices of lead exposure and social environmental factors, the consistency among studies in finding effects following adjustment for these confounding factors is remarkable. It is important to consider the enormous experimental animal evidence not compromised by the possibility of confounding in examining lead effects on health (Bellinger, 2004; Davis et al., 1990; U.S. Environmental Protection Agency, 1986a, 1990).

Another problem in the analyses of data on lead and child development is the lack of critical consideration of which potential confounder in a particular model "owns" the variance in neurodevelopmental performance. Thus, for example, in the case of social class it is assumed that if an effect of lead is reduced to nonsignificance following adjustment for some measure of socioeconomic standing, the assumption is that all of the variance belongs to the confounder. However, in some instances this could be seen as an excessively conservative interpretation and raises the specter of Type II error. Social class could be seen as either a confounder or a proxy for exposure. Lower social class in urban children is closely linked to residence in older housing in poor condition that, in turn, is associated with higher levels of environmental lead (Clark et al., 1985). If studies adjust for social class in the usual manner, the effects of the toxicant will be underestimated (Bellinger, 2004). One extreme example of overcontrol of this nature can be found in the New Zealand studies where investigators regularly "controlled" for residence in older "weatherboard" housing (e.g., Fergusson et al., 1988a,b). However, it is worth noting that even in the models including this variable lead remained a significant predictor of intellectual and academic under-attainment in the Christchurch Health Study.

Most of the important confounding factors in lead studies have been identified and efforts have been made to control them in studies conducted since the 1990 Supplement. Invocation of the poorly measured confounder as an explanation for positive findings is not substantiated in the database as a whole when evaluating the impact of lead on the health of U.S. children (Needleman, 1995). Of course, it is often the case that following adjustment for factors such as social class, parental neurocognitive function, and child rearing environment using covariates such as parental education, income, and occupation, parental IQ, and HOME scores, the lead coefficients are substantially reduced in size and statistical significance (Dietrich et al., 1991). This has sometimes led investigators to be quite cautious in interpreting their study as positive (Wasserman et al., 1997). This is a reasonable way of appraising any single study, and such extreme caution would certainly be warranted if forced to rely on a single study to confirm the lead effects hypothesis. Fortunately, a large database of high quality studies on which to base inferences regarding the relationship between lead exposure and neurodevelopment exists. In addition, lead has been extensively studied in animal models at doses that closely approximate the human situation. Experimental animal studies are not compromised by the possibility of confounding by such factors as social class and correlated environmental factors. The enormous

experimental animal literature that proves that lead at low levels causes neurobehavioral deficits and provides insights into mechanisms is to be considered when drawing causal inferences (Bellinger, 2004; Davis et al., 1990; U.S. Environmental Protection Agency, 1986a, 1990).

In addition to being a confounder, social class and related variables have been shown to be effect modifiers in many studies of lead and child development (Bellinger, 2000; Tong et al., 2000). Effect modification occurs when the magnitude of an association between an exposure (lead) and an outcome (neurobehavior) varies across strata of some other factor (Last, 2001). The disadvantages that accompany poor education and underemployment have been found to exacerbate the effects of lead when carefully examined (Bellinger et al., 1989). Indeed, evaluating potential effect modifiers should be considered an important part of an overall data analytic plan.

6.3.3 Summary of the Epidemiologic Evidence for the Neurotoxic Effects of Lead in Children

Effects of lead on neurobehavior have been detected with remarkable consistency across numerous studies of various designs, populations studied, and developmental assessment protocols. The negative impact of lead on IQ and other neurobehavioral outcomes persist in most recent studies following adjustment for numerous confounding factors including social class, quality of caregiving, and parental intelligence.

Three meta-analyses and one international pooled analysis of seven prospective studies have confirmed that exposure to lead at low dose has an effect on the intellectual attainment of preschool and school age children. Recent analyses examining the association of lead with intellectual attainment and academic performance in children with low lead exposures have observed effects at blood lead concentrations below 10 μg/dL. The pooled analysis by Lanphear et al. (2005) observed a decline of 6.2 points (95% CI: 3.8, 8.6) in full scale IQ for an increase in concurrent blood lead levels from 1 to 10 μg/dL.

The effects of lead on behavior and mood of children has been an area of recent research. These studies have demonstrated that the impact of lead may extend into increased risk for antisocial and delinquent behavior. This may be a consequence of attentional problems and academic underachievement among children who have suffered higher exposures to lead during

their formative years. Several studies that have used methods of MRI and MRS to assess direct measures of brain damage also are suggesting evidence of harm due to lead exposure.

Attempts to eliminate or limit lead-associated neurodevelopmental morbidities with pharmacological or nutritional intervention strategies have been shown to be ineffective, further emphasizing the importance of taking environmental measures to reduce and possibly prevent exposure to lead in children.

6.3.4 Summary of Key Findings on the Neurotoxic Effects of Lead in Adults from the 1986 Lead AQCD

Lead intoxication in adults occurred primarily in occupational settings with historically high exposure levels. In more recent times, occupational lead exposure has been reduced to much lower levels and is often associated with no symptoms. The symptom constellation associated with high levels of lead exposure include impaired memory and attention span, irritability, headache, muscular tremors, and hallucinations (Cantarow and Trumper, 1944) that may progress to signs of frank encephalopathy (Smith et al., 1938). Symptoms of lead intoxication begin with blood lead >40 µg/dL (Baker et al., 1979) accompanied by poorer performance on cognitive and visuomotor tasks, reaction time, verbal learning, and reasoning ability that reflect involvement of both the central nervous system and the peripheral nervous system (Arnvig et al., 1980; Campara et al., 1984; Grandjean et al., 1978; Haenninen et al., 1978, 1979; Hogstedt et al., 1983; Mantere et al., 1982; Valciukas et al., 1978; Zimmermann-Tansella et al., 1983). Impaired occulomotor function, measured by saccade accuracy and velocity, depended upon the age group of the lead-exposed worker (Baloh et al., 1979; Glickman et al., 1984; Spivey et al., 1980).

With regard to peripheral nerve function as measured by nerve conduction studies, the 28 studies reviewed by the U.S. EPA in the 1986 Lead AQCD found no consistent single nerve involved but, overall, the exposed group had slower conduction velocity at blood lead concentrations as low as 30 µg/dL.

Studies reviewed in 1986 found that amyotrophic lateral sclerosis (ALS) was inconsistently associated with elevated lead levels in the nervous system. Chelation for 1 year did not did not alter elevated lead levels in the tissue of patients with motor neuron disease.

6.3.5 Neurotoxic Effects of Lead in Adults

6.3.5.1 Overview of Cognitive and Psychomotor Tests Associated with Adult Lead Exposure

Examination of lead effects on neurobehavioral performance in adults differs from that in children, since the neurobehavioral tests in adults focus on loss of abilities previously present rather than the lack of attainment of those abilities. Also, there is contribution of cognitive reserve acquired by years of education, self-education, on-the-job training, avocational, and non-avocational activities that increases the ability to compensate for the effects of lead exposure on learning new information. Medical conditions requiring medications, head trauma, and other neuropsychiatric conditions that impact nervous system performance have increased in prevalence in the adult population. These factors may increase the impact of lead exposure or be mistaken for the effects of lead and, therefore, must be handled in the analysis.

As alterations in mood may be associated with lead exposure, many neurobehavioral batteries use self-administered questionnaires to screen for mood. The Center for Epidemiologic Studies Depression Scale (CES-D) screens for depression. The Profile of Mood State (POMS) screens for six subscales, namely anger, confusion, depression, fatigue, anxiety/tension, and vigor. The six mood scales of the POMS were originally validated in a clinical psychiatric population; thus, the factor structure needed to be validated in an occupational population. Factor analysis of the POMS in lead smelter workers found only two relevant factors: (1) "general distress," composed of the subscales anger, confusion, depression, fatigue, and tension; and (2) "psychological adjustment," which contained vigor (Lindgren et al, 1999). This brings into question the use of the six scales as separate outcome variables in the study of lead exposure.

Neurobehavioral tests commonly used to demonstrate the effects of lead are listed below (for a more complete description, see Lezak, 1995). Mini-Mental-State Examination (MMSE), a screening tool for cognitive impairment, is a compilation of many cognitive domains including orientation to time and place, registration, and recall of three words, attention, language, and visual construction with a total possible score of 30 (Folstein et al, 1975). MMSE is sensitive to age and education. In 194 healthy subjects aged 40 to 89 years with 7-21 years of education, only 1% of the subjects obtained an MMSE score of 24/30 and none below (Bleecker et al., 1988). MMSE errors are sensitive to age effects including delayed recall, spelling "WORLD"

backwards and repetition of "no ifs, ands, or buts." With lead exposure, examination of errors is important to compare with age-related changes and to determine the biological plausibility of the effects of exposure especially when performing repeated measures of the test.

Neurobehavioral batteries should always include a benchmark test such as Vocabulary or a reading test such as the Wide Range Achievement Testing for Reading (WRAT) or the North American Reading Test (NART) that are considered to be resistant to neurotoxic exposure. Results from these tests should be adjusted for in the analysis. In blue-collar workers, this may be a better measure of educational achievement than years of education (Bleecker et al., 2002).

Neuropsychological batteries screening for the effects of lead usually include the following domains (Lezak, 1995): attention/concentration (Digit Span); conceptual and executive functioning (Stroop, Trails B); visuoperceptive/visuoconstructive (Block Design); visuomotoric (Reaction Time, Pegboard Test, Digit Symbol Substitution, Trails A); verbal memory (Rey Auditory Verbal Learning Test, Logical Memory, Paired Associated Learning); and nonverbal memory (Rey-Osterreith Complex Figure, Benton Visual Retention). When analyzing the association of lead exposure and test performance, adjusting for potential confounders is critical. Potential confounders are namely age, education (preferably a measure of verbal intelligence), depressive symptoms, alcohol use, and smoking. In some cases, age (Bleecker et al., 1997a) and education (Bleecker et al., 2002) may serve as effect modifiers. The association of lead and poorer neurobehavioral outcome has been found to be present only in older workers or those with less education.

6.3.5.2 Neurobehavioral Effects Associated with Environmental Lead Exposure

Exposure to chronic low levels of environmental lead and its association with effects on the nervous system were examined in several populations originally followed to study conditions associated with aging: the VA Normative Aging Study (NAS) (Payton et al., 1998; Weiskopf et al., 2004; Wright et al., 2003); the Study of Osteoporotic Fractures (Muldoon et al., 1996); and the Kungsholmen Project on aging and dementia (Nordberg et al., 2000). Studies reviewed in this section are summarized in Annex Table AX6-3.11.

The VA Normative Aging Study (NAS) is a multidisciplinary longitudinal investigation of the aging process established in 1963 and conducted at the VA Outpatient Clinic in Boston, MA. The NAS cohort cannot be considered to be exclusively representing the general

population, as bone lead measurements are higher than expected for only environmental exposure and, thus, suggest the possibility of other sources such as past occupational exposure, diet, and drinking water (Elmarsafawy et al., 2002, Vijayalakshmi et al., 1999).

The relationship of bone lead and blood lead to psychiatric symptoms in NAS (Rhodes et al., 2003) found mood symptoms for anxiety and depression potentially associated with bone lead levels. Education also was inversely related to bone lead; however, high school graduates had significantly higher general stress that may be related to SES and not lead exposure.

Neuropsychological testing in NAS found response speed sensitive to low levels of lead but it was not a consistent finding in all tests measuring the same domain upon examination of 141 healthy men with a mean age of 67 years, education 14 years. The mean blood lead level was 6 μg/dL, patella bone lead was 32 μg/g bone mineral, and tibia bone lead was 23 μg/g bone mineral (Payton et al., 1998). Vocabulary, a measure of verbal intelligence and predictor of neurobehavioral performance, was used as an outcome variable instead of being adjusted for as a potential confounder. Education was negatively correlated with bone lead and blood lead, suggesting other factors bedsides lead exposure may have contributed to neuropsychological performance. The handling of multiple comparisons was not addressed.

Another analysis of the NAS (Wright et al., 2003) examined 736 men, mean age 68 years with education level of 54% high school or less. The mean blood lead was 5 μg/dL, and mean patellar and tibia lead levels were 30 and 22 μg/g bone mineral, respectively. The subjects had a mean MMSE score of 27. Relation of MMSE scores <24 (n = 41) and blood lead by logistic regression estimated an odds ratio of 1.21 (95% CI: 1.07, 1.36). For patella lead and tibia lead, odds ratios of 1.21 (95% CI: 1.00, 1.03) and 1.02 (95% CI: 1.00, 1.04), respectively, were observed. Risk of MMSE <24 (6% of the present population versus 1% of previously described healthy aging study) when comparing the lowest and highest quartiles was 2.1 (95% CI: 1.1, 4.1) for patella lead, 2.2 (95% CI: 1.1, 3.8) for tibia lead, and 3.4 (95% CI: 1.6, 7.2) for blood lead. Interaction of age with patella lead and blood lead in predicting MMSE found steeper decreases in MMSE scores relative to age in the higher quartiles of patella lead and blood lead. Types of errors on the MMSE were not included. It was not addressed how medical conditions and medications that occurred over the duration of the study and could potentially affect cognitive performance were handled. If the community dwelling population in NAS (Wright et al., 2003) had older individuals with chronic medical conditions and less education

(213 subjects had an education less than high school) living in areas with higher past lead pollution, the confounding may be impossible to sort out.

Weisskopf et al. (2004) expanded the MMSE study in NAS by examining 466 men, mean age 70 years who had completed the MMSE twice with an interval of approximately 3.5 years. Mean blood lead was 4 μg/dL, and mean patella and tibia bone lead were 23 and 19 μg/g bone mineral, respectively. Baseline mean MMSE score was 27 and mean change in MMSE score over 3.5 years was 0.3 points. Even though MMSE change was significantly associated with bone lead, a change in MMSE score by a fraction of a point does not constitute a meaningful change of cognitive performance. To address the biological plausibility of change in the MMSE over 3.5 years, errors by functional domain need to be identified to rule out the possibility of random change with repeat performance.

Muldoon et al. (1996) studied participants in the Study of Osteoporotic Fractures for an association of nonoccupational lead exposure and cognitive function. The Study of Osteoporotic Fractures began in 1986 and included women over age 65 years living in four different communities – Baltimore, MD; Portland, OR; Minneapolis, MN; and the Monongahela Valley outside of Pittsburgh, PA. A sample of 325 women from rural sites with a mean age of 71 years (mean blood lead 4.5 μg/dL) and 205 women from urban sites with a mean age of 69 years (mean blood lead 5.4 μg/dL) were examined. The urban group was more educated and had higher use of cigarettes and alcohol. Performance examined by blood lead groups adjusting for age, education, smoking, and alcohol use found no significant differences in the urban group. However, in the rural group, individuals with blood lead >7 μg/dL had significantly poorer performance when compared to those with blood lead <4 μg/dL for Trails B, Digit Symbol, and Reaction Time. Response time across blood lead groups increased for the rural group and decreased or remained the same for the urban group. Mean MMSE for the whole population was 25, with poorer performance in the rural group—thus, suggesting an increased prevalence of clinical cognitive disorders of another etiology. Even though the neuropsychological battery was simple, 9 participants were unable to perform some of the tests including 3 on the MMSE. Such severe impairments were not found with higher occupational exposures, which raises the question as to whether other factors not measured accounted for these differences attributed to blood lead.

In the Kungsholmen Project on aging and dementia in Stockholm, Sweden, no relationship was found between blood lead and MMSE (Nordberg et al., 2000). The study population included 762 participants with a mean age of 88 years. The mean blood lead in this group was 3.7 μg/dL and the mean MMSE was 25. In contrast to the other populations examined, this study cohort was more homogenous, comprised entirely of elderly Swedes. Their likelihood of prior exposure to elevated lead levels was low.

Overall, these studies of environmental lead exposure in adults are difficult to interpret, as many competing risk factors for neurobehavioral performance in the elderly were not considered. Also, bone lead levels were higher than expected from environmental exposure suggesting unrecognized previous occupational exposure. The association of bone lead with neurobehavioral performance was unusual, in as much as it was not demonstrated in studies of occupational exposure (reviewed below). At this time, these studies do not demonstrate that the aging nervous system is at increased risk for poorer neurobehavioral performance related to environmental lead exposure as reported in children.

6.3.5.3 Neurological Symptoms Associated with Occupational Lead Exposure

Studies reviewed in this section are summarized in Annex Table AX6-3.12. Several occupational studies found blood lead levels of 29-43 μg/dL associated with POMS subscales (Hänninen et al., 1998; Maizlish et al., 1995; Niu et al., 2000). However, other studies with blood lead levels of 27-38 μg/dL found no relationship with POMS (Chia et al., 1997; Lucchini et al., 2000; Osterberg et al., 1997; Stollery et al., 1989). A screen for depression, CES-D, was administered to 803 lead-exposed Korean workers. CES-D was significant associated with tibia lead (mean 37 μg/g bone mineral), but not with blood lead (mean 32 μg/dL), after adjusting for covariates (Schwartz et al., 2001a).

Dimercaptosuccinic acid (DMSA)-chelatable lead reflects the mobilizable fraction of lead in the soft tissue. Korean lead-exposed workers (n = 95) with DMSA-chelatable lead (mean 289 μg) above the median of 261 μg were 6.2 times more likely to have tingling or numbness in their extremities, 3.3 times more likely to experience muscle pain, and 3.2 times more likely to feel irritable (Lee et al., 2000). The workers with higher chelatable lead were 7.8 times more likely to experience neuromuscular symptoms compared to workers with lower chelatable lead. Blood zinc protoporphyrin predicted weakness of ankle and wrist and fatigue while delta-

aminolevulinic acid (ALAD) in urine (mean 3 mg/L) predicted inability to sleep; however, blood lead (mean 45 μg/dL) was not significantly associated with any symptoms.

In some studies, difficulty concentrating, irritability, fatigue, muscle pain, and joint pain were more likely in workers with a mean blood lead of 43 μg/dL (Maizlish et al., 1995) and 27 μg/dL (Lucchini et al., 2000), whereas other studies with mean blood lead >30 μg/dL found no association with symptoms (Chia et al., 1997; Osterberg et al., 1997). Lucchini et al. (2000) provided an estimated threshold of blood lead 12 μg/dL for significant increase of neurological symptoms.

In summary, even though one study suggested a threshold for neurological symptoms at a blood lead of 12 μg/dL (Lucchini et al., 2000), other studies with blood lead >30 μg/dL found no association with lead-related symptoms. The study by Lee et al. (2000) observed that higher levels of DMSA-chelatable lead was associated with irritability, tingling or numbness in their extremities, muscle pain, and neuromuscular symptoms.

6.3.5.4 Neurobehavioral Effects Associated with Occupational Lead Exposure

Studies reviewed in this section are summarized in Annex Table AX6-3.13. Discriminate analysis of neurobehavioral performance found the group of tests that best differentiates lead-exposed workers (mean blood lead 49 μg/dL) from nonexposed workers were Simple Reaction Time (SRT), Digit Symbol (WAIS), and Trail Making Test (Part A) (Boey et al., 1988). Using a similar battery with 44 lead-exposed workers, mean blood lead 29 μg/dL, performance was significantly associated with blood lead for SRT, digit symbol and pursuit aiming (Niu et al., 2000).

Seventy workers grouped by blood lead (<20, 21-40, and 41-80 μg/dL) were examined on three occasions each separated by 4 months. Performance on reaction time was stable except in the high lead group where decision time was slowed more than movement time along with concentration difficulties that remained consistently across testing sessions. Memory testing did not improve with repetition in the high lead group (Stollery et al., 1991). Decision gaps as opposed to movement gaps were selectively affected by lead exposure in this population (Stollery, 1996).

A review of occupational lead exposure in 1995 (Balbus-Kornfeld et al., 1995) concluded that the association of cumulative lead exposure or body burden of lead and neurobehavioral

performance in adults was inadequately covered in the literature. Studies have addressed these deficiencies with the use of a working lifetime integrated blood index and bone lead concentrations. Even though exposure assessment has improved, there is variability based upon differences in past exposure versus present exposure, duration of exposure, frequency of monitoring for blood lead, lead exposure from other occupational sources and nonoccupational activities. Measurement of bone lead addresses some of these problems but the relationship of bone lead concentration and lead levels in the brain or peripheral nervous system is inconsistent.

Subsequent studies used measures of cumulative lead exposure, namely lifetime integrated blood index, weighted average blood lead, and bone lead. More consistent associations occurred with the lifetime integrated blood index and weighted average blood lead for visuomotor/visuoperceptive tasks of Pegboard, Pursuit Aiming, Digit Symbol, Trails, and Block Design (Bleecker et al., 1997a; Chia et al., 1997; Hänninen et al., 1998; Lindgren et al., 1996; Schwartz et al., 2005) while others found no association with these lead exposure measures (Lucchini et al., 2000; Osterberg et al.,1997; Schwartz et al., 2001a). Age served as an effect modifier for the association of the lifetime integrated blood index with pegboard (Bleecker et al., 1997a).

One difficulty with cumulative lead dose is the inability to separate the effect of past high exposure from a lower proximate exposure. To address this issue, workers with similar past high exposure were grouped by those with proximate exposure above blood lead of 40 μg/dL and those with proximate exposure below blood lead of 40 μg/dL and were compared on performance of verbal memory (Lindgren et al., 2003). Use of regression analyses found pattern group contributed significantly to the explanation of variance in verbal memory after adjusting for current blood lead and lifetime integrated blood index measures. The relationship between past high exposure and verbal memory no longer existed in the group that maintained proximate blood lead below 40 μg/dL, suggesting the possibility of reversibility of the effects of lead in adults.

The first study to report the effects of cumulative lead exposure on the nervous system examined 467 Canadian lead smelter workers, with a mean of 18 years of employment (Lindgren et al., 1996). Their mean blood lead level was 28 μg/dL, the weighted average blood lead level was 40 μg/dL, and the lifetime integrated blood index was 765 μg·year/dL. Fourteen neuropsychological variables were examined by MANCOVA using exposure groups of high,

medium, and low. The analysis was adjusted for age, education, years employed, CES-D, and alcohol use. Exposure groups categorized using lifetime integrated blood index differed significantly on digit symbol, logical memory, Purdue dominant hand, and Trails A and B. No concentration-response relationship between blood lead and neuropsychological performance was found. From this smelter population, 256 workers currently employed had a median MMSE score of 29 (range 19-30). A concentration-response relationship between lifetime integrated blood index and MMSE was found only in the 78 workers with a WRAT-R reading grade level less than 6. The absence of a concentration-response relationship in workers with higher reading grade levels and the same lifetime integrated blood index dose was attributed to increased cognitive reserve (Bleecker et al., 2002). An in-depth examination of verbal learning and memory in this same population found no association with blood lead. However, increasing lifetime integrated blood index or weighted average blood lead was associated with poorer storage and retrieval of previously learned material. Alterations in the ability to organize materials in long-term memory interfered with retrieval efficiency (Bleecker et al., 2005a). The one test sensitive to blood lead in this smelter population was simple reaction time that had a curvilinear relationship with slowing beginning at a blood lead of approximately 30 μg/dL (Bleecker et al., 1997b).

Fifty-four lead battery workers were stratified by those whose blood lead never exceeded 50 μg/dL (n = 26) and those who had higher exposure in the past (n = 28) to examine the neuropsychological effects of current low level blood lead versus those of higher blood lead in the past (Hänninen et al., 1998). Partial correlations controlling for age, sex, and education in the low group found block design, digit symbol, digit span, similarities, Santa Ana 1, and memory for design associated with recent measures of exposure and embedded figures with maximum blood lead (mean maximum blood lead 40 μg/dL). Embedded figures, digit symbol, block design, and associative learning were associated with the lifetime integrated blood index (mean 823 μg·year/dL) and maximum blood lead (mean 69 μg/dL) in the high blood lead group. There was essentially no association with bone lead in either group. A concentration-response relationship existed for digit symbol, embedded figures, and memory for design. Overall past high exposure with blood lead levels >50 μg/dL had the greatest effect on tests requiring the encoding of complex visually presented stimuli. The authors concluded that the effect of lead on brain function was better reflected by history of blood lead than content of lead in bone.

However, some studies that included measures of cumulative lead and current lead exposures found the strongest association with current blood lead. Schwartz et al. (2001a) examined the associations of blood lead, DMSA-chelatable lead, and tibia lead with neurobehavioral tests in 803 Korean lead-exposed workers from a variety of industries and 135 controls. In lead-exposed workers, the mean blood lead level was 32 μg/dL, DMSA-chelatable lead level was 186 μg, and bone lead levels was 37 μg/g bone mineral, compared to controls with a mean blood lead level of 5 μg/dL and bone lead level of 6 μg/g bone mineral. Compared to controls, lead-exposed workers performed significantly worse on SRT, Digit Span, Benton Visual Retention, Colored Progressive Matrices, Digit Symbol, and Purdue Pegboard after controlling for age, gender, and education. The association of DMSA-chelatable lead with test performance became nonsignificant after the addition of blood lead in the model. Bone lead was not associated with neurobehavioral performance. Blood lead was the best predictor for significant decrements in neurobehavioral performance on Trails B, Purdue Pegboard (4 measures) and Pursuit Aiming (2 measures). The effect of a 5 μg/dL increase in blood lead was equivalent to an increase of 1.05 years in age. Use of LOWESS functions suggested a threshold at blood lead 18 μg/dL after which there is a decline of performance in Purdue Pegboard (assembly) and Trails B.

From the above cohort of Korean lead workers, 212 consecutively enrolled workers were examined for protein kinase C (PKC) activity and the relations between blood lead and neurobehavioral performance (Hwang et al., 2002). Blood lead range from 5 to 69 μg/dL was associated significantly with decrements in Trails B, SRT, and Purdue Pegboard (3 measures). PKC activity, as measured by back-phosphorylation of erythrocyte membrane proteins, was not associated with neurobehavioral test scores. Addition of the interaction term of blood lead with PKC activity dichotomized at the median found significant effect modification with the association of higher blood lead and poorer neurobehavioral performance occurring only among workers with lower PKC activity that corresponds to higher in vivo PKC activity. The authors suggested that PKC activity might identify a subpopulation at increased risk of neurobehavioral effects of lead.

Occupational lead exposure and longitudinal decline in neurobehavioral performance was examined in 576 current and former Korean lead workers who completed testing at three visits at approximately yearly intervals (Schwartz et al., 2005). At baseline, the mean blood lead was

31 µg/dL and the mean tibia lead was 38 µg/g bone mineral. Blood lead from baseline correlated with those from visit 2 and 3 and baseline tibial lead correlated with that measured at visit 2. Cross-sectional associations of blood lead or short-term change occurred with Trails A and B, Digit Symbol, Purdue Pegboard (4 measures), and Pursuit Aiming after adjusting for potential confounders. However, longitudinal blood lead was only associated with poorer performance on Purdue Pegboard (4 measures). Historical tibial bone lead was associated with digit symbol and Purdue Pegboard (dominant hand). Magnitude of lead associations was expressed as the number of years of increased age at baseline that was equivalent to an increase of lead from the 25th to 75th percentile. The effect of cross-sectional blood lead at baseline was equivalent to 3.8 years of age, 0.9 years of age for historical tibial lead, and 4.8 years of age for longitudinal blood lead.

In summary, performances on visuomotor and verbal memory tasks are consistently associated with occupational lead exposure. In several studies, cumulative blood lead index was found to be a strong predictor of neurobehavioral performance. Lead concentrations in bone were a weaker predictor of lead effects on brain function.

6.3.5.5 Neurophysiological Function and Occupational Lead Exposure

A meta-analysis including 32 nerve conduction studies with occupational lead exposure found blood lead to be a weak predictor of peripheral nerve impairment (Davis and Svendsgaard, 1990). Nerve conduction velocities were reduced in lead-exposed subjects, with the greatest sensitivity observed in the median motor nerve. Decreasing effect sizes were observed with increasing duration of exposure. Meta-analyses of neurobehavioral effects in adults are presented in Annex Table AX6-3.14.

Studies reviewed in this section are summarized in Annex Table AX6-3.15. Nerve conduction studies of workers in a lead battery factory (Kovala et al., 1997) found sensory amplitudes of the median and sural nerves had a negative correlation with long-term exposure (lifetime integrated blood index and duration of exposure). Chia et al. (1996b) also found the strongest concentration-response relationship between median sensory conduction velocity and lifetime integrated blood index. He et al. (1988) found sensory conduction abnormalities related to blood lead levels.

Yokoyama et al. (1998) measured the distribution of conduction velocities in large myelinated fibers of the sensory median nerve twice at a year interval in 17 gunmetal workers.

In workers with a 1-year change in chelatable-lead (mobilized lead) greater than 440 μg/24 h, conduction velocities of faster fibers were decreased significantly. Measure of body burden (readily mobilized lead from soft tissue) was a stronger predictor of peripheral nerve impairment than blood lead.

A group of studies examined vibration threshold in the extremities (Chuang et al., 2000; Kovala et al., 1997; Schwartz et al., 2001a, 2005). In 60 workers exposed to lead, Kovala et al. (1997) found vibration threshold at the ankle related to the lifetime integrated blood index and duration of exposure while the finger vibration threshold was associated with current blood lead exposure. Overall historical blood lead measures were more closely associated with peripheral nerve function than bone lead in this population. By contrast, Schwartz et al. (2001a) also examined vibration thresholds and bone lead in 803 Korean workers and 135 controls and found that tibia lead (mean 37 μg/g bone mineral) but not blood lead (mean 32 μg/dL) was significantly associated with poorer vibration threshold in the dominant great toe but not the finger. In a follow-up study of 576 lead workers who completed three visits at yearly intervals, vibration threshold in the toe was associated with current blood lead (mean 31 μg/dL), longitudinal blood lead, and tibia lead (38 μg/g) after adjusting for covariates (Schwartz et al., 2005). Chuang et al. (2000) reported on vibration perception in the foot in 206 lead battery workers. There was a significant association with blood lead (mean 28 μg/dL) and weighted average blood lead (mean 32 μg/dL) with vibration perception in the foot after adjustment for covariates including the use of vibrating hand tools. A hockey stick regression analysis of foot vibration threshold versus mean blood lead concentration for the past 5 years found an inflection point around 30 μg/dL with a positive linear relation above this point, suggesting a potential threshold.

Bleecker et al. (2005b) examined peripheral nerve function in 80 smelter workers using Current Perception Threshold (CPT), a neuro-selective test that measures integrity of the large and small myelinated nerve fibers and unmyelinated nerve fibers. CPT was not associated with blood lead (mean 26 μg/dL) or bone lead (mean 40 μg/g bone mineral). CPT for large myelinated nerve fibers had a curvilinear relationship with weighted average blood lead (mean 42 μg/dL), with a threshold observed at 28 μg/dL. Results from further regression analyses suggested that even with cumulative lead exposure, intensity is more important than duration of exposure to lead with regard to the peripheral nervous system. At the highest criterion blood lead level, both large and small myelinated nerve fibers were impaired. The presence of

activated motor units, equated to ergonomic stressors by job title, enhanced the effect of lead on the peripheral nervous system.

In summary, occupational lead exposure studies consistently found peripheral sensory nerve impairment as opposed to the classic motor neuropathy described historically with high lead exposure. A possible threshold for this effect on the sensory nerves was observed at a blood lead of 28 μg/dL.

6.3.5.6 Evoked Potentials and Occupational Lead Exposure

Visual evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs) measure speed of conduction in the visual and auditory pathway. BAEPs have discrete waveforms with wave I arising from the auditory nerve; its latency reflects peripheral transmission time. Wave III is predominantly generated from the caudal pons and wave V from the inferior colliculus. The use of interpeak latencies removes abnormalities in the auditory nerve latency from changes in brainstem transmission in the auditory pathway. Studies reviewed in this section are summarized in Annex Table AX6-3.16.

Abbate et al. (1995) performed VEPs on 300 lead-exposed men (aged 30 to 40 years) in good health with no other neurotoxic exposure. Range of blood lead levels was 17 to 60 μg/dL. Individuals were stratified into 4 groups with mean blood lead levels of 23 μg/dL (n = 39), 30 μg/dL (n = 113), 47 μg/dL (n = 89), and 56 μg/dL (n = 59). P100 latency measured for VEPs were significantly prolonged across the blood lead groups. Linear regression found the association of blood lead and P100 were significant in each group, but the relationship was not proportional. Prolonged VEP began at a blood lead levels of 17-20 μg/dL. With age limited to one decade, contribution from age was not a concern. Even though there was no comparison group, careful screening ruled out other medical and eye conditions, and other potential exposures.

BAEPs recorded in 49 lead-exposed workers and age and sex matched controls (Discalzi et al., 1992) had mean blood lead levels of 55 μg/dL and a mean weighted average blood lead level of 54 μg/dL. Interpeak latencies, I-V, I-III, and III-V were all prolonged in the lead-exposed workers. In those workers with weighted average blood lead >50 μg/dL, I-V latency was longer. Discalzi et al. (1993) reported identical results in a subsequent publication of 22 battery storage workers with a mean blood lead of 47 μg/dL and a mean weighted average

blood lead of 48 μg/dL. Holstein et al. (1986) examined 20 adults accidentally exposed to lead through food until 1 year prior to the study. On the day of examination, the mean blood lead level was 31 μg/dL, while the mean weighted average blood lead was 43 μg/dL. Latencies I, III, and I-III interpeak intervals were longer in the exposed group with a concentration-response relationship observed for the weighted average blood lead and I-III interpeak interval.

BAEPs were performed in 359 currently-employed smelter workers with a mean of 17 years of employment. The mean blood lead levels was 28 μg/dL (SD 8.4), mean working-lifetime weighted average blood lead was μg/dL 39 (SD 11.9), and working-lifetime integrated blood lead index was 719 μg·year/dL (SD 421.0) (Bleecker et al., 2003). After adjusting for the contribution of age, blood lead and weighted average blood lead were significantly associated with Wave I, while lifetime integrated blood index was significantly associated with Wave III and I-III interpeak interval. Four groups similar in age were created with increasing abnormalities based upon clinical cut-off scores for wave I latency and I-V interpeak interval. Blood lead, weighted average blood lead, and lifetime integrated blood index were all significantly higher in the group with prolonged Wave I and I-V interpeak interval compared to the group with normal BAEPs.

In summary, one detailed study found blood lead associated with prolonged VEPs with a threshold effect at 17-20 μg/dL. The four studies examining BAEPs and lead exposure consistently found prolonged interpeak latencies in the brainstem auditory pathway more strongly associated with cumulative or average blood lead exposure.

6.3.5.7 Postural Stability, Autonomic Testing, and Electroencephalogram (EEG) and Occupational Lead Exposure

Postural sway measures balance or steadiness on a force platform. It is a complex task that requires the integration of visual, vestibular, and peripheral sensory inputs, as well as motor output. No standard protocol is used across studies. Studies reviewed in this section are summarized in Annex Table AX6-3.17.

Postural sway was evaluated in 49 chemical workers exposed to lead stearate, with a mean blood lead of 18 μg/dL, a mean weighted average blood lead of 24 μg/dL and a mean cumulative blood lead of 391 μg·year/dL (Yokoyama et al., 1997). Twenty-three controls were also examined. After adjustment for covariates, a concentration-response relationship was observed

for blood lead and sway in the anterior-posterior direction and for weighted average blood lead with right to left sway. The authors concluded that change in the vestibulocerebellum was affected by blood lead while the anterior cerebellar lobe was affected by average lead exposure.

Chia et al. (1994) measured postural sway parameters in 60 lead storage battery workers (mean blood lead 36 μg/dL) and 60 controls (mean blood lead 6 μg/dL). Computerized postural sway measurements showed that lead workers had poorer postural stability that increased with eyes closed but no concentration-response association was observed with blood lead. A second publication examined cumulative blood lead over 10 years and found that lifetime integrated blood index for the 2 years prior to testing was associated with all postural sway parameters with eyes closed (Chia et al., 1996c).

Postural control measured in 63 lead battery workers (mean past blood lead 38 μg/dL) indicated significantly increased mean body oscillations with eyes closed and head tilted forward (Ratzon et al., 2000). Total lead exposure was significantly associated with increased body oscillations with head tilted forward after adjusting for education, coffee consumption, hours of sleep, and estimate of health. In order to maintain balance, lead-exposed workers required increased oscillations when visual and vestibular inputs were altered.

The effects of lead on the cardiac autonomic nervous system, expressed as the decrease of R-R interval variation on an electrocardiogram, was examined in 172 male lead-exposed workers (mean blood lead 36 μg/dL) (Teruya et al., 1991). A significant blood lead concentration-related decrease of R-R interval variation during deep breathing was present in 132 workers with stable blood lead over the past year. An approximate threshold effect was found at blood lead $\geq$20 μg/dL. Similar findings were reported by Niu et al. (2000) in 44 lead exposed workers who had a mean blood lead of 29 μg/dL.

One hundred twenty-eight workers in the ceramic painting industry (mean blood lead 13 μg/dL) were monitored for measures of sympathetic nerve function by variations in R-R interval on electrocardiography and changes in finger blood flow with postural changes using Doppler flowmetry (Ishida et al., 1996). No significant association was found between blood lead levels and the results of the neurophysiological tests, except for change in finger blood flow. Increased blood lead was associated with decreased changes in finger blood flow.

Sixty workers in a lead battery factory examined with quantitative electroencephalographs found alpha and beta frequencies were more abundant in workers with higher long term lead

exposure (Kovala et al., 1997). Biomarkers of long-term lead exposure included tibia bone lead (mean 26 μg/g), calcaneal bone lead (mean 88 μg/g), lifetime integrated blood index (mean 546 μg·year/dL), and weighted average blood lead (mean 32 μg/dL). The finding of slow alpha activity positively correlated with lead exposure may reflect increased episodes of "microdrowsiness" in workers with higher lead exposure. In the study by Niu et al. (2000), quantitative electroencephalographs in 44 lead-exposed workers (mean blood lead 29 μg/dL) indicated significantly increased beta activity and diminished amplitudes abnormalities in 81% of exposed workers.

In summary, postural sway is associated with lead exposure at blood lead levels <40 μg/dL, and is believed to be caused by the effect of lead on the cerebellum. A standard protocol was not employed across the studies. Parasympathetic and sympathetic integrity is compromised in lead-exposed workers beginning at blood lead >20 μg/dL. Quantitative electroencephalographs found increased beta activity associated with lead exposure.

6.3.5.8 Other Neurological Outcomes Associated with Lead in Adults

Studies reviewed in this section are summarized in Annex Table AX6-3.18. The 1986 Lead AQCD concluded that the evidence for an association of lead and ALS or motor neuron disease was inconsistent. The subsequent publications remain mixed but more studies are reporting an association. Using 109 cases of ALS and 256 controls matched for age, gender, and region of residence, Kamel et al. (2002) examined the relation of lead and ALS using blood lead and bone lead levels. Ranges of exposure were <1 to 14 μg/dL for blood lead, −4 to 107 μg/g for patella lead, and −7 to 61 μg/g for tibia lead. History of occupational lead exposure increased the risk of ALS (adjusted odds ratio of 1.9 [95% CI: 1.1, 3.3]). Elevations in both blood lead and patella and tibia bone lead were found in ALS cases, though the precision of these measurements was questioned. In summary, this study found lead exposure from historical questionnaire data and biological markers to be associated with ALS. The same data was used to determine the associations of ALS with polymorphism in ALAD and VDR and the influence of genotype in the previously discussed associations of ALS with lead (Kamel et al., 2003). The ALAD2 allele was associated with a 2-fold increased risk of ALS after adjustment for age, gender, region, education, and physical activity. Additionally adjusting for blood lead

strengthened the association of ALAD2 and ALS risk. This was not found for bone lead or occupational history of lead exposure. VDR was not associated with lead or ALS risk.

A study from the Mayo Clinic examined risk factors for sporadic ALS in 45 male ALS patient-patient control pairs (Armon et al., 1991). When lifetime exposure to lead exceeded 200 hours, the relative risk for ALS was 5.5 (95% CI: 1.44, 21.0). Overall, men with ALS had worked more at blue-collar jobs with significantly more time welding or soldering than controls ($p < 0.01$). The association between lead exposure and development of ALS was supported as these authors had the same findings in a previous pilot study of another patient population (Roelofs-Iverson et al., 1984).

Another study of risk factors for ALS in 103 patients found increased odds ratio for manual occupation (2.6 [95% CI: 1.1, 6.3]) and occupational exposure to lead (5.7 [95% CI: 1.6, 30]) (Chancellor et al., 1993). A Swedish study of 92 cases of motor neuron disease (includes ALS, progressive bulbar palsy, and progressive muscular atrophy) found a Mantel-Haenszel odds ratio for welding equal to 3.7 (95% CI: 1.1, 13.0) (Gunnarsson et al., 1992).

Guidetti et al. (1996) performed a retrospective incidence, prevalence, and mortality survey in northern Italy. The area studied had documented lead pollution for years. Based upon 79 cases, incidence and prevalence rates of ALS were comparable to the surrounding area. A subsequent publication by this group found that mean blood lead levels in cases of sporadic ALS and controls were not significantly different (mean blood lead of 13 µg/dL versus 11 µg/dL) (Vinceti et al., 1997). Blood lead was associated with disability due to ALS but no support was found for involvement of lead in the etiology of sporadic ALS.

Louis et al. (2003) examined the relationship between blood lead and essential tremor (ET) in 100 cases with ET (mean blood lead 3 µg/dL) and 143 controls (mean blood lead 2 µg/dL). Ten cases and 7 controls had bone lead levels measured that were significantly correlated with blood lead suggesting that higher blood lead may have occurred in the past. Logistic regression adjusting for age and current cigarette smoking found an association between blood lead and ET. An odds ratio of 1.19 (95% CI: 1.03, 1.37) was estimated. Blood lead was higher in the 39 ET cases with no family history. Both current and lifetime prevalence of occupational lead exposure was the same in ET cases and controls. In a second publication (Louis et al., 2005), 63 ET cases (mean blood lead 4 µg/dL) and 101 controls (mean blood lead 3 µg/dL) who were similar in age, education, gender, and ethnicity were examined for interaction

of blood lead and ALAD gene polymorphisms and increased odds of ET. Of the 63 ET cases, 18 (29%) had an ALAD2 allele compared to 17 (17%) of the 101 controls (odds ratio of 1.98 [95% CI: 0.93, 4.21]). When log blood lead was examined by presence of ALAD2 allele in ET, log blood lead was highest in ET cases with the ALAD2 allele, intermediate in ET cases without an ALAD2 allele, and lowest in controls (test for trend, $\beta = 0.10$; $p = 0.001$). When the ALAD2 allele was present, blood lead was significantly associated with odds of ET (80.29 [95% CI: 3.08, 2,096.36]). This increased odds of ET with an ALAD2 allele was 30 times greater than in individuals with only an ALAD1 alleles. In the highest log blood lead tertile, ALAD2 allele was present in 22% of ET cases and 5% of controls. It was proposed that increased blood lead along with the ALAD2 allele could affect the cerebellum and, thereby, increase the risk of tremor.

Graves et al. (1991) performed a meta-analysis on 11 case-control studies of Alzheimer's disease for occupational exposure to solvents and lead. Four studies had data for lead exposure with a pooled analysis of relative risks for occupational lead of 0.71 (95% CI: 0.36, 1.41). The exposure frequencies were 16 of 261 (6%) for the cases and 28 of 337 (8%) for the controls. These nonsignificant results were further confirmed by measuring lead concentration in the brain of cases with diffuse neurofibrillary tangles with calcification (DNTC), Alzheimer's disease, and non-demented controls. The lead concentration was significantly higher in DNTC compared to Alzheimer's disease and non-demented controls (Haraguchi et al., 2001).

In summary, more studies are reporting an association with past exposure to lead, usually in the occupational setting, and the motor neuron disease ALS. There appears to be a 2-fold increased risk for ALS when the ALAD2 allele is present. The odds of ET in individuals with the ALAD2 allele were 30 times greater compared to those with only ALAD1 alleles.

6.3.5.9 Occupational Exposure to Organolead and Inorganic Lead

Compared to inorganic lead, organolead exposure has a greater impact on the brain and, therefore, is discussed separately. Direct comparison of trimethyl lead (a metabolite of organolead), tetraethyl lead, and inorganic lead on the in vitro assembly of microtubules from the mammalian brain found no effects with inorganic lead but trimethyl lead produced dramatic impairment of neurotubular structures and functions (Roderer and Doenges, 1983). Another study examining organic and inorganic lead found differential effects on neurite growth in

neurons in culture, suggesting that the mechanism of action for organic and inorganic lead was not the same (Audesirk et al., 1989). Studies reviewed in this section are summarized in Annex Table AX6-3.19.

Two hundred and twenty-two current employees that manufactured tetraethyl lead had cumulative lead exposure associated with poorer performance in many cognitive domains but most often in manual dexterity and verbal memory/learning (Schwartz et al., 1993). Simple visual reaction time and blood lead had a curvilinear relation with an increase in simple visual reaction time occurring above a blood lead of 30 μg/dL (Balbus et al., 1997, 1998).

In former organolead workers (n = 543), peak tibial lead was a stronger predictor of poorer cognitive function than current tibial lead (Stewart et al., 1999). Examination of the peripheral nervous system in this population found no strong association between lead biomarkers and measures of sensory and motor function (Tassler et al., 2001). Five hundred and thirty-five of these former organolead workers were re-examined over a 4-year period (Schwartz et al., 2000d, 2001b). Peak tibia lead predicted decline in tests of verbal memory and learning, visual memory, executive ability, and manual dexterity. Effect size for an increase of 15.7 μg/g bone mineral of peak tibia lead was equivalent to 5 more years of age at baseline. This relationship of neurobehavioral tests with bone lead levels was influenced by the apolipoprotein E (*ApoE)* genotype (Stewart et al., 2002). The slope of the relation between tibia lead and neurobehavioral outcome was more negative in those individuals with at least one ε4 allele than individuals without this allele. It is suggested that the presence of one *Apo*-ε-4 allele increases the risk of persistent central nervous system effects of lead.

Overall when these neurobehavioral outcomes related to organolead exposure are compared to the literature reviewed with inorganic lead exposure, the absence of effects on the peripheral nerves and the global nature of central nervous system impairment suggests the impact on the brain is greater with organolead exposure.

6.3.6 Summary of the Epidemiologic Evidence for the Neurotoxic Effects of Lead in Adults

There is no consistent evidence that environmental lead exposure is associated with impaired cognitive performance in the elderly if competing risk factors are considered. In adults, the effect of lead on the nervous system may not be detected through neurobehavioral testing due

to cognitive reserve, the ability to compensate for brain impairment. Cognitive reserve is related to pre-morbid cognitive abilities, education, and occupational attainment, and is able to modify the clinical expression of central nervous system insult from lead exposure. Therefore, when chronic lead exposure is the same in two groups of individuals that differ by educational achievement levels, the concentration-response relationship will only be seen in the group with low educational achievement, as cognitive reserve allows the high educational achievement group to compensate for the central nervous system expression of the effects due to lead.

Chronic occupational lead exposure affects the sensory nerve fibers in the extremities with a possible threshold at a weighted average blood lead level of 28 μg/dL. Intensity of lead exposure appears to be more critical than duration of exposure for this outcome. Slowing in the brainstem auditory pathway in the caudal pons was consistently associated with chronic occupational lead exposure.

Past occupational exposure to lead increased the risk of developing ALS and motor neuron disease in 4 studies. This risk was increased 2-fold by the presence of the ALAD2 allele. Essential tremor in two well-done studies was associated with low blood lead levels (mean 3 μg/dL). The odds of developing ET with the ALAD2 allele increased 30-fold compared to those individuals with only an ALAD1 allele.

Numerous studies of occupational lead exposure also found chronic and current blood lead associated with visuomotor and memory impairment with a threshold effect at blood lead 18 μg/dL. As with ET, postural sway abnormalities associated with blood lead <40 μg/dL is believed to result from the effects of lead on different parts of the cerebellum.

6.4 RENAL EFFECTS OF LEAD

6.4.1 Summary of Key Findings on the Renal Effects of Lead from the 1986 Lead AQCD

Chronic lead nephropathy is a disease characterized by tubulointerstitial nephritis, which can ultimately result in small, fibrotic kidneys. It occurs in individuals who sustain chronic high-level lead exposure. In these individuals, lead exposure is the primary cause of renal failure. The pathophysiologic characteristics of lead nephropathy and the populations at increased risk for this diagnosis were the foci of the human research portion of Section 12.5, entitled “Effects

of Lead on the Kidney," in the 1986 Lead AQCD. The 1986 document clearly identified several high-risk groups for this diagnosis, including children in the Queensland, Australia lead poisoning epidemic, moonshine alcohol drinkers, and lead workers in poorly controlled settings. The section concluded that data in the latter group indicated an increased risk for lead nephropathy associated with blood lead levels ranging from 40 to >100 μg/dL, with adverse renal effects possibly occurring at levels as low as 30 μg/dL.

The 1986 Lead AQCD noted that research at that time was not sufficient to address some of the most critical questions relating to the impact of lead exposure on the kidney. The last paragraph of the renal section begins with "Among the questions remaining to be answered more definitively about the effects of lead on the kidneys is the lowest blood lead level at which renal effects occurs." The last sentence reads "Conversely, the most difficult question of all may well be to determine the contribution of low levels of lead exposure to renal disease of non-lead etiologies." Advances in the research conducted since that document was written allow a much more informed discussion of exactly those critical issues. As discussed below, recent research indicates that lead nephropathy is merely the tip of the iceberg in terms of the contribution that lead makes to renal dysfunction overall. Research increasingly indicates that lead, at much lower doses than those causing lead nephropathy, acts as a cofactor with other more established renal risks to increase the risk for renal dysfunction and the rate of subsequent decline. The populations at risk for renal dysfunction (diabetics and hypertensives) are increasing worldwide, particularly in countries where obesity is epidemic. Lead exposure is declining in many industrialized countries, although less so among high-risk minority populations. The extent of the public health impact of lead on the kidney depends on the balance of these two factors.

6.4.2 Renal Outcome Definitions

The renal literature can be confusing since several of the clinical renal measures are inversely related. Therefore, the pertinent outcomes are briefly reviewed below. The glomerular filtration rate (GFR) is considered to be the best measure of renal function. GFR is assessed by urinary clearance of exogenous (e.g., ^{125}I-iothalamate) or endogenous (e.g., blood urea nitrogen [BUN] and serum creatinine) compounds. Creatinine is used most commonly. Therefore, increases in BUN or serum creatinine or decreases in renal clearance of creatinine or other markers are all consistent with decreased renal function. Serum creatinine and its reciprocal

have been the most frequently used measures of renal function in the lead-kidney literature. However, creatinine is not an ideal GFR marker, because it is influenced by factors such as muscle mass, diet, gender, age, and tubular secretion. Measurement or calculation of creatinine clearance takes some of these variables into account. Measured creatinine clearance utilizes timed urine collections, traditionally over a 24-h period, making compliance difficult. Therefore, equations to estimate creatinine clearance have gained popularity. The Cockcroft-Gault equation (Cockcroft and Gault, 1976) has been used most commonly. Recently, several equations to estimate actual GFR were studied in the Modification of Diet in Renal Disease (MDRD) Study (Levey et al., 1999). The abbreviated MDRD equation (GFR in mL/min/1.73m^2 = 186 $\times$ creatinine$^{-1.154}$ $\times$ age$^{-0.203}$ $\times$ (0.742 if female) $\times$ (1.212 if African American); Stevens and Levey [2005a]) estimates GFR more accurately than the Cockcroft-Gault equation in patients with renal insufficiency (Levey et al., 2003). Despite their promise, however, the MDRD equations are relatively new and their use in the literature on the renal effects of lead exposure has been limited to date.

Cystatin C is another recent addition to the tools used to assess GFR (Stevens and Levey, 2005b). This is a 13,000 Dalton, non-glycosylated basic protein, which is generated by all nucleated cells and filtered, reabsorbed, and catabolized, but not secreted, in the kidney. Very little appears in the urine. The majority of studies done to date indicate that serum cystatin C is a better marker for GFR than serum creatinine (Stevens and Levey, 2005b).

Most of the renal outcome measures discussed above were developed for use in the clinical setting. Unfortunately, they are insensitive for early renal damage, as evidenced by the fact that serum creatinine remains normal after kidney donation. Therefore, in the last two decades, the utility of renal early biological effect (EBE) markers as indicators of preclinical renal damage has been of interest. These can be categorized as markers of function (i.e., low molecular weight proteins that should be reabsorbed in the proximal tubules such as β_2-microglobulin and retinol-binding protein [RBP]); biochemical alteration (i.e., urinary eicosanoids such as prostaglandin E_2, prostaglandin $F_{2\ alpha}$, 6-keto-prostaglandin $F_{1\ alpha}$, and thromboxane B_2); and cytotoxicity (e.g., N-acetyl-β-D-glucosaminidase [NAG]) (Cardenas et al., 1993). Elevated levels may indicate an increased risk for subsequent renal dysfunction. However, with the exception of microalbuminuria in diabetes and β_2-microglobulin in cadmium exposure, most are research tools only and their prognostic value remains controversial.

European and Asian nephrotoxicant researchers have utilized them more frequently than have renal researchers in the United States. Prospective studies of most of these markers in nephrotoxicant-exposed populations are quite limited to date.

6.4.3 Lead Exposure Measure Definitions

Although these definitions are reviewed in detail elsewhere in this Lead AQCD, a brief discussion is included here due to the number of key studies in this section that measured bone or chelatable lead dose. Inorganic lead is a cumulative toxicant that is stored in bone. Blood lead is a relatively short-term measure (half-life of 30 days [Hu et al., 1998]) that reflects exposure from current exogenous sources and the release of lead from internal lead stores. Bone is a source of lead as well as a repository (Hu et al., 1998). As such, bone lead measures provide information on the potential for ongoing internal exposure as well as cumulative exposure. Lead in trabecular bone (commonly measured in the patella or calcaneus) is more bioavailable than lead in cortical bone (measured in the mid-tibia) and has a shorter half-life (Gerhardsson, et al., 1993; Hu et al., 1998). An additional lead measure, chelatable lead, is thought to represent a bioavailable pool of lead from blood, soft tissue, and bone. Either calcium disodium ethylenediaminetetraacetic acid (EDTA) or dimercaptosuccinic acid (DMSA; succimer) may be used for this purpose although DMSA is newer and, thus, has been used less frequently to date.

6.4.4 Lead Nephrotoxicity in Adults

6.4.4.1 General Population Studies

Over the past two decades, several studies have examined the effect of lead exposure on renal function in environmentally exposed general populations. This is a new category of lead-renal research with no high quality examples (by current standards) having been available for review in the 1986 Lead AQCD. The studies discussed below provide critical evidence that the adverse effects of lead on the kidney occur at much lower doses than previously appreciated. General population studies of the renal effects of lead are further summarized in Annex Table AX6-4.1.

6.4.4.1.1 Cadmibel Study

In the first large environmental study that adjusted for multiple renal risk factors, Staessen et al. (1992) evaluated 965 men and 1,016 women in the Belgian Cadmibel study. Lead dose was indexed by blood lead and zinc protoporphyrin. Renal outcome measures included serum creatinine and β_2-microglobulin and 24-h measured and calculated (Cockcroft and Gault, 1976) creatinine clearances. Mean blood lead was 11.4 μg/dL (range 2.3-72.5) and 7.5 μg/dL (range 1.7-60.3) in men and women, respectively. After adjustment, log transformed blood lead and zinc protoporphyrin, in separate models, were negatively associated with measured creatinine clearance (effect estimates are presented in Table 6-4.1). A 10-fold increase in blood lead was associated with a decrease in creatinine clearance of 10 and 13 mL/min in men and women, respectively. Both lead measures were also negatively associated with estimated creatinine clearance. This landmark study raised concern that the lead dose threshold for adverse renal effects in the general population was much lower than previously appreciated based on occupational data.

6.4.4.1.2 Normative Aging Study

Four studies assessing the renal impact of lead exposure in the Normative Aging Study have been published to date. Participants in this study were originally recruited in the 1960s in the Greater Boston area. Inclusion criteria included male gender, age between 21 and 80 years, and absence of chronic medical conditions. Payton et al. (1994) analyzed data from a periodic follow-up evaluation performed between 1988 and 1991 in 744 participants. Lead dose was assessed with blood lead; renal outcome measures included serum creatinine and 24-h measured and calculated (Cockcroft and Gault, 1976) creatinine clearances. Mean blood lead concentration and measured creatinine clearance were 8.1 μg/dL (SD 3.9) and 88.2 mL/min (SD 22.0), respectively. After adjustment, ln blood lead was negatively associated with ln measured creatinine clearance (effect estimates are presented in Table 6-4.1). Borderline statistically significant associations ($p < 0.1$) between blood lead and serum creatinine and estimated creatinine clearance were also observed.

Kim et al. (1996) studied 459 men whose blood lead levels from past periodic examinations, conducted every 3-5 years during 1979-1994, were measured from stored samples. Participants were randomly selected to be representative of the entire Normative Aging Study

Table 6-4.1. Summary of Key Studies on the Renal Effects of Environmental Lead Exposure

Reference Study location Study population Sample size	Mean exposure and outcome measures	Analysis methods Covariates adjusted for in analysis	Major significant findings
Muntner et al. (2003) NHANES III, 1988-1994 n = 15,211 4,813 hypertensives	Blood lead 4.21 µg/dL (hypertensives) 3.3 µg/dL (normotensives) Renal outcomes = elevated serum creatinine, chronic kidney disease (GFR <60 mL/min/1.73 m^2)	Multiple logistic regression Age, race, gender, diabetes, systolic blood pressure, smoking status, history of cardiovascular disease, body mass index, alcohol consumption, household income, marital status, and health insurance	Higher odds ratios of both increased serum creatinine and chronic kidney disease by quartile of blood lead in hypertensives but not normotensives Odds ratios for elevated serum creatinine in hypertensives Blood lead (range, µg/dL) / % / Odds ratio (95% CI) Quartile 1 (0.7–2.4) / 7.2 / 1.00 Quartile 2 (2.5–3.8) / 12.1 / 1.47 (1.03, 2.10) Quartile 3 (3.9–5.9) / 12.4 / 1.80 (1.34, 2.42) Quartile 4 (6.0–56.0) / 16.3 / 2.41 (1.46, 3.97) $p < 0.001$ for chi-squared test for trend Twofold higher blood lead associated with odds ratio of 1.43 (95% CI: 1.20, 1.71)
Payton et al. (1994) Boston, MA Normative Aging Study, 1988-1941 n = 744	Blood lead 8.1 µg/dL Measured creatinine clearance 88.2 mL/min	Multiple linear regression Age, body mass index, analgesic and diuretic use, alcohol consumption, smoking status, systolic/ diastolic blood pressure	Log blood lead negatively associated with log measured creatinine clearance −0.04 (95% CI: −0.079, −0.001) 10 µg/dL higher blood lead associated with a 10.4 mL/min lower creatinine clearance
Kim et al. (1996) Boston, MA Normative Aging Study, 1979-1994 n = 459	Blood lead at baseline 9.9 µg/dL Serum creatinine at baseline 1.2 mg/dL	Cross-sectional and longitudinal analyses Random-effects modeling Baseline age, time since initial visit and between visits, body mass index, smoking status, alcohol ingestion, education level, hypertension (defined as blood pressure ≥160 or 95 mm Hg or antihypertensive medication use), and baseline serum creatinine	In cross-sectional analyses of associations between log transformed blood lead and concurrent serum creatinine, the largest β was in the 141 participants whose peak blood lead ≤10 µg/dL: 0.06 (95% CI: 0.023, 0.097) Positive association between log transformed blood lead and change in serum creatinine over subsequent follow-up period in participants whose peak blood lead was ≤25 µg/dL 0.027 (95% CI: 0.0, 0.054)

Table 6-4.1 (cont'd). Summary of Key Studies on the Renal Effects of Environmental Lead Exposure

Reference Study location Study population Sample size	Mean exposure and outcome measures	Analysis methods Covariates adjusted for in analysis	Major significant findings
Wu et al. (2003) Boston, MA Normative Aging Study, 1991-1995 n = 709	Blood lead 6.2 µg/dL Patella lead 32.1 µg/g bone Calculated creatinine clearance 71.3 mL/min	Multiple linear regression Age, body mass index, hypertension, smoking status, alcohol ingestion, analgesic medication use	Significant association between patella lead and creatinine clearance $\beta = -0.069$ (SE not provided)
Tsaih et al. (2004) Boston, MA Normative Aging Study 1991-~2001 n = 448	Blood lead at baseline 6.5 µg/dL Tibia lead at baseline 21.5 µg/g bone mineral Serum Creatinine at Baseline 1.3 mg/dL	Longitudinal analysis, mean of 6 years between evaluations Age, body mass index, diabetes, hypertension, smoking status, alcohol consumption, analgesic use, baseline serum creatinine and its square	Lead dose not associated with change in creatinine in all Significant interaction of blood and tibia lead with diabetes in predicting annual change in serum creatinine For natural ln baseline blood lead $\beta = 0.076$ (95% CI: 0.031, 0.121) compared to $\beta = 0.006$ (95% CI: −0.004, 0.016) for non-diabetics For natural ln baseline tibia lead $\beta = 0.082$ (95% CI: 0.029, 0.135) compared to $\beta = 0.005$ (95% CI: −0.005, 0.015) for non-diabetics
Staessen et al. (1992) Belgium Cadmibel Study n = 1,981; 965 males	Blood lead 11.4 µg/dL (males) 7.5 µg/dL (females) Measured creatinine clearance 99 mL/min (males) 80 mL/min (females)	Multiple linear regression Age, age squared, body mass index, log transformed gamma-glutamyl transpeptidase, and diuretic use	Log transformed blood lead negatively associated with measured creatinine clearance −9.5 (95% CI: −18.1, −0.9) males −12.6 (95% CI: −20.3, −5.0) females Tenfold increase in blood lead associated with a decrease in creatinine clearance of 10 and 13 mL/min in men and women, respectively

population in terms of age and follow-up. Renal status was assessed with serum creatinine. Data from 4-5 evaluations were available for the majority of participants. Relations were evaluated cross-sectionally (associations between blood lead and concurrent serum creatinine) as well as longitudinally (associations between blood lead and change in serum creatinine over the subsequent follow-up period). Mean age, blood lead level, and serum creatinine, at baseline, were 56.9 years (SD 8.3), 9.9 μg/dL (SD 6.1), and 1.2 mg/dL (SD 0.2), respectively. With random-effects modeling, a significant positive association between ln-transformed blood lead and concurrent serum creatinine was observed. This association was stronger when models were confined to participants with lower peak blood lead levels, i.e., the β coefficient was largest in the 141 participants whose highest blood lead level was ≤10 μg/dL. In longitudinal analysis, ln-transformed blood lead was associated ($p = 0.05$) with change in serum creatinine over the subsequent follow-up period in the 428 participants whose highest blood lead level was ≤25 μg/dL. Similar to the cross-sectional analysis, the β coefficient in the participants whose highest blood lead level was ≤10 μg/dL was larger; however, in the longitudinal analysis, the standard error also increased such that the p-value was not significant.

Cortical and trabecular bone lead measurements were obtained in evaluations performed between 1991 and 1995 in 709 participants in the Normative Aging Study (Wu et al., 2003). Lead dose was assessed with blood, tibia, and patella lead concentrations. Renal outcome measures included serum creatinine and estimated creatinine clearance. Mean blood, tibia and patella lead levels were 6.2 μg/dL (SD 4.1), 22.0 μg/g bone mineral (SD 13.4), and 32.1 μg/g bone mineral (SD 19.5), respectively. After adjustment, analyses in the 670 participants from whom these data were available, revealed a significant inverse association between patella lead and creatinine clearance. A borderline significant ($p = 0.08$) inverse association between tibia lead and creatinine clearance was also observed. None of the lead measures were significantly associated with serum creatinine.

Tsaih et al. (2004) reported associations between baseline lead dose and change in serum creatinine in 448 men. Lead dose was assessed with blood, tibia, and patella lead. Serum creatinine was measured at baseline and at follow-up, an average of 6 years later. Six percent and 26% of subjects had diabetes and hypertension, at baseline, respectively. Mean blood lead levels and serum creatinine decreased significantly over the follow-up period in the group. Lead dose was not associated with change in creatinine in all participants. However, the authors found

a significant interaction between lead dose (blood and tibia lead) and diabetes on change in serum creatinine. Interaction was also observed between tibia lead and hypertension, although it is possible that many of the 26 diabetics were also included in the hypertensive group and were influential there as well.

6.4.4.1.3 NHANES III

Muntner et al. (2003) analyzed associations between blood lead and renal outcomes in 15,211 adult subjects enrolled in the NHANES III study, conducted from 1988 through 1994. Dichotomous renal outcome measures analyzed included elevated serum creatinine and chronic kidney disease (GFR < 60mL/min/1.73 m^2). Due to interaction between blood lead and hypertension, the population was stratified. Mean blood lead was 4.21 μg/dL in the 4,813 hypertensives and 3.30 μg/dL in normotensives. The prevalence of elevated serum creatinine in hypertensives and nonhypertensives was 11.5% and 1.8%, respectively; prevalence of chronic kidney disease was similar. The odds ratios for both renal outcomes increased by quartile of blood lead among the hypertensive subjects but not among those without hypertension. Among those with hypertension, after adjustment for age, race and gender, the odds ratios for elevated creatinine in quartiles 2, 3, and 4 compared to the lowest quartile of blood lead, were 1.56 (95% CI: 1.04, 2.35), 1.68 (95% CI: 1.24, 2.26), and 2.07 (95% CI: 1.26, 3.40), respectively. As shown in Table 6-4.1, the odds ratios were the same following additional adjustment. The authors noted that the "associations were strong, dose-dependent and consistent before and after comprehensive adjustment." They also noted that in nonhypertensives, higher blood lead was associated with a higher prevalence of chronic kidney disease in diabetics. This study is notable for the sample size, for the reported associations being observed at the lowest mean blood lead level in any environmental study to date, for the comprehensive adjustment for other renal risk factors, and for the study population being representative of the U.S. population.

6.4.4.1.4 Summary of Lead Nephrotoxicity in the General Population

Studies of environmentally exposed general populations constitute one of the two most important types of research on the adverse renal effects of lead during the past two decades. Study designs are generally strong; some have the added strength of analyzing longitudinal data. Populations are large, assessment of lead dose is comprehensive, including the use of bone lead

as a measure of cumulative lead body burden in some studies, and statistical approaches are advanced, utilizing a range of exposure and outcome measures, while adjusting for numerous renal risk factors. Given these strengths, the fact that these studies have reached consistent conclusions provides strong evidence indicating that lead is a contributor to renal dysfunction in susceptible populations at much lower levels that those identified in the 1986 Lead AQCD. Chronic kidney disease has been observed at the lowest lead dose levels studied (category II from 2.5 to 3.8 μg/dL in Muntner et al. [2003]). An association between cumulative lead dose (mean tibia lead of 21.5 μg/g bone mineral) and longitudinal decline in renal function has been observed as well, although data on any threshold for this effect were not reported (Tsiah et al., 2004). Susceptible populations include those with other risk factors for renal disease, including hypertension and diabetes. Populations who are also at increased risk for obesity, diabetes, and hypertension represent groups potentially most impacted by lead exposure.

6.4.4.2 Occupational Studies

The vast majority of studies in the lead-renal literature were conducted in the occupational setting. This was especially true prior to the 1986 Lead AQCD but is still currently the case. Occupational studies of the renal effects of lead are presented in Annex Table AX6-4.2. Recent studies in the general population, discussed above, and in the patient population, discussed in the next section, provide consistent evidence supporting a role for lead in renal dysfunction at lower lead concentrations of interest. However, one phenomenon that has been observed more frequently in occupational rather than environmental studies of lead exposure and kidney function deserves specific comment.

Several studies have reported statistically significant negative associations between higher lead dose and worse renal function, specifically positive associations between higher lead dose and lower BUN, serum creatinine and/or higher creatinine clearance. Roels et al. (1994) observed higher mean creatinine clearance in 76 lead workers compared to 68 controls from the same smelter who were not occupationally exposed to lead (mean of 121.3 versus 115.5 mL/min/1.73 m^2 in workers and controls, respectively [$p < 0.05$]). More importantly, in the combined group, tibia lead was positively correlated with measured creatinine clearance. However, no other significant associations between lead dose and the renal outcomes (which also included serum creatinine, urea nitrogen, and β_2-microglobulin, along with urinary NAG, RBP

and β_2-microglobulin as well as other early biological effect markers) were observed. Lead workers had evidence of high past exposure and controls also had high blood lead levels by current standards (mean blood and tibia lead levels were 43.0 and 14.1 µg/dL and 66 and 21 µg/g bone mineral, in workers and controls, respectively).

Weaver et al. (2003a) performed a cross-sectional analysis of first evaluation data from a longitudinal study of 803 lead workers in South Korea, including 94 former lead workers. Lead exposure was assessed with job duration; blood, tibia, and DMSA-chelatable lead; and three hematologic measures as surrogates for lead dose. Clinical renal function was assessed with blood urea nitrogen (BUN), serum creatinine, measured creatinine clearance, and calculated creatinine clearance (Cockcroft and Gault, 1976). Urinary NAG and RBP were also measured. Mean job duration, and blood, tibia, and DMSA-chelatable lead levels were 8.2 years (SD 6.5), 32.0 µg/dL (SD 15.0), 37.2 µg/g bone mineral (SD 40.4), and 767.8 µg/g creatinine (SD 862.1), respectively. Higher lead measures were associated with worse renal function in nine of the 42 associations, however, an additional five were in the opposite direction (higher lead measures associated with lower serum creatinine and higher creatinine clearances). These opposite direction (inverse) associations were observed only for the clinical outcomes whereas the associations between higher lead dose and worse renal function were predominantly with the EBE markers. In three of 16 models (analyses) assessing effect modification by age on associations between lead job duration and the three lead dose biomarkers with the four clinical renal outcomes, positive associations between higher lead measures and worse renal function in participants in the oldest age tertile were significantly different from associations in those in the youngest age tertile, which were in the opposite (inverse) direction; this pattern was observed at borderline significance ($p < 0.1$) in three other models. However, this pattern was not observed in the EBE marker models. Similar inverse associations were observed in this population in the third evaluation, performed a mean of 2.2 years after collection of the data discussed above, but only with DMSA-chelatable lead and not patella, blood, or tibia lead (Weaver et al., 2005b). Hsiao et al. (2001) also reported positive associations between higher blood lead and lower concurrent serum creatinine in an analysis of 8 years of annual medical surveillance data in 30 lead battery workers (this study is of note since it is one of the few longitudinal, occupational studies to date; additional findings are described in Annex Table AX6-4.2).

These inverse associations, evidenced by higher lead measures and lower BUN and serum creatinine and/or higher creatinine clearance, may represent lead-induced hyperfiltration, a phenomenon initially observed in patients with diabetes but also implicated in other settings, including hypertension and obesity (Nenov et al., 2000). In this process, initial supranormal renal function is paradoxically associated with increased risk for subsequent renal dysfunction. Hu (1991) has also reported increased mean creatinine clearance in 22 adults who were lead poisoned as children compared to matched controls. Longitudinal data for lead-exposed rodents (discussed in Section 5.7) are critical in relating this process to lead. However, in that work, despite similar initial hyperfiltration, subsequent renal dysfunction was much more severe in the high-dose lead-exposed rodents compared to the low-dose animals. This suggests that hyperfiltration may be one, but not the only, mechanism for the adverse renal effects of lead. Whether hyperfiltration contributes to pathology in humans is unclear; longitudinal studies are needed.

Regardless, the issue for this document is that significant findings could be obscured if opposite direction associations are present in different segments of the study population and interaction models to address this are not performed. This is a valid concern, since the factors involved in these inverse associations in lead exposed populations are not well defined at present. Work by Weaver and colleagues have used age as the effect modifier; however, other factors, such as lead job duration, may be more important modifiers.

Figure 6-4.1 provides an example of the different associations observed depending on whether effect modification is examined. In the work of Weaver et al. (2003a), in several models, no associations were observed when the entire population was studied; however, when interaction models using age as the effect modifier were evaluated, significant associations in opposite directions were observed.

6.4.4.3 Patient Population Studies

Studies in various patient populations have also contributed to the body of knowledge concerning adverse renal impacts of lead exposure. Such studies of renal effects of lead in patient populations are presented in Annex Table AX6-4.3. Populations studied include those with chronic renal insufficiency (CRI), end-stage renal disease (ESRD), gout, and hypertension. Patients were selected for study due to the fact that these diseases are thought to be increased by

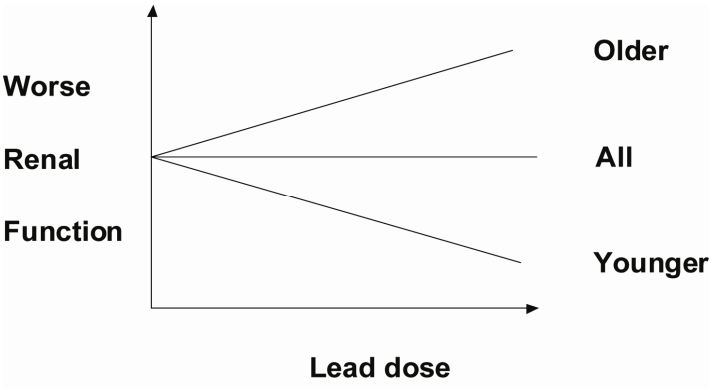


Figure 6-4.1. Effect on renal function evaluation using age as the effect modifier.

Source: Weaver et al. (2003a).

high-level lead exposure, particularly when two or more coexist in the same patient. Early work in this area was discussed in the 1986 Lead AQCD, but some research is discussed again below in order to allow conclusions to be drawn on the data to date. Early research focused on patients with potential lead nephropathy; and lead body burdens of interest, assessed with EDTA chelation, were above 600 to 650 µg/72 h. More recent work has involved patients with CRI but not ESRD and lead body burdens below that range. Of note, the terminology for degree of renal dysfunction was more variable in the older literature. Therefore, for clarity in the discussion below, patients with impaired renal function who are not on dialysis are noted to have CRI, rather than using terms such as "failure" that were used in some of the original reports.

Two issues have been a recurring concern in this work, particularly in work with patients on dialysis. The first concern is whether lead body burden is higher in all patients with renal insufficiency or failure due to decreased lead excretion (reverse causality). The second concern is whether EDTA-chelatable lead levels when measured over a 72-h period in patients with CRI can be equated to those in participants with normal renal function measured over 24 h. It is possible that, due to decreased excretion of EDTA in renal insufficiency, more lead per dose is ultimately chelated. These concerns have been addressed in various ways as noted in the research discussed below. Lastly, this work also illustrates the limitations of blood lead levels which often do not reflect the differences in lead body burden noted between populations.

6.4.4.3.1 Lead Body Burden in Chronic Renal Disease

Batuman et al. (1983) studied 27 hypertensives with CRI (defined as serum creatinine >1.5 mg/dL) and 21 without associated renal impairment. Blood lead levels were similar in the two groups. However, mean EDTA-chelatable lead levels were significantly higher in hypertensives with CRI than those without (860 and 340 μg/72 h, respectively). Further, chelatable lead levels in patients with CRI from causes not thought to be related to lead nephropathy and who had no history of lead exposure were similar to patients with hypertension but no CRI. This provides some evidence against reverse causality.

Sanchez-Fructuoso et al. (1996) performed a similar study in a much larger number of patients in Spain, none of whom had a known history of lead exposure. These authors reported that EDTA-chelatable lead levels >600 μg/72 h were present in none of 30 controls, 16 (15.4%) of 104 patients with essential (primary) hypertension and normal renal function, 74 (56.1%) of 132 patients with CRI of unknown etiology along with hypertension (64 of the 132 also had gout), but none of the 30 patients with CRI of known (non-lead related) etiology. Mean blood and EDTA-chelatable lead levels in the patients with CRI of known cause were not statistically different from controls with normal renal function. These researchers also reported significant correlations between bone lead levels (assessed by biopsy) and EDTA-chelatable lead level in 12 patients whose chelatable lead levels were >600 μg/72 h, which provides support for the validity of chelatable lead levels in CRI.

In contrast, Osterloh et al. (1989) reported no significant difference in EDTA-chelatable lead levels between 40 male subjects with hypertensive nephropathy (hypertension preceded renal insufficiency; serum creatinine 1.8-4 mg/dL) and 24 controls with renal dysfunction from other causes. Lead dose and serum creatinine were not correlated. Chelatable lead levels in this population were much lower than those reported by Wedeen et al. (1983) and Sanchez-Fructuoso et al. (1996). The authors noted that only 17% of their study participants had a history of possible lead exposure based on questionnaire. In contrast, Batuman et al. (1983) found that 89% of patients with hypertension and CRI had a possible history of lead exposure. The inconsistent results in these studies may reflect differences in the patients studied. Batuman et al. (1983) studied Veterans Administration patients, Sanchez-Fructuoso et al. (1996) studied patients from a low-medium income area in Madrid, Spain, and Osterloh et al. (1989) recruited patients from the database of a large health maintenance organization in California.

Van de Vyver et al. (1988) reported lead data from bone biopsies in 153 dialysis patients, 11 cadavers without known excessive lead exposure, 13 patients with renal insufficiency, gout, and/or hypertension and 22 lead workers. Bone lead levels in 5% of the dialysis population were in the range observed in lead workers, suggesting lead as a primary cause of their renal failure. Levels in the 10 patients with analgesic nephropathy were the lowest (all <7 μg/g). However, Winterberg et al. (1991) subsequently noted that the bone lead levels in patients with analgesic nephropathy and cadaver controls in Van de Vyver et al. (1988) were much higher than in control groups of other researchers. They reiterated the concern that lead did accumulate due to decreased renal excretion. In a longitudinal study, Price et al. (1992) reported similar half-lives of lead in bone in eight renal patients compared with age-matched controls who had XRF finger bone lead conducted twice 5 years apart. The small number and inclusion of outliers without formal statistical analysis limits conclusions that can be drawn from these data. The longitudinal studies of Lin and colleagues, discussed below, provide more definitive data in this regard.

6.4.4.3.2 Impact of Lead Body Burden on Decline in Renal Function in Patients with CRI

Lin and colleagues have addressed the issue of low-level lead as a cofactor with other renal risk factors in susceptible populations, including those with CRI and/or gout. They have approached this work in two ways: prospective follow-up of populations with CRI to determine if renal function decline is greater in those with higher lead body burdens and through randomized trials to determine if chelation therapy changes the rate of renal function decline. Importantly, their work is in an EDTA-chelatable lead range well below that considered abnormal as described in Section 6.4.4.3.1.

In their most recent publication, Yu et al. (2004) followed 121 patients over a 4-year period. Eligibility required well-controlled CRI. Importantly, serum creatinine between 1.5 and 3.9 mg/dL and EDTA-chelatable lead <600 μg/72 h were required at baseline. Patients with potentially unstable renal disease were excluded (i.e., due to systemic diseases such as diabetes). Sixty-three patients had "high-normal" EDTA-chelatable lead levels (≥80 but <600 μg/72 h); 58 had "low-normal" EDTA-chelatable lead levels (<80 μg lead/72 h). The groups were similar in most other baseline risk factors. Borderline statistically significant ($p < 0.1$) differences included mean older age in the high chelatable lead group and certain renal diagnoses. Fifteen patients in the "high-normal" chelatable lead group reached the primary endpoint (doubling of

serum creatinine over the 4-year study period or need for hemodialysis) compared to only two in the "low-normal" group ($p = 0.001$).

In a Cox multivariate regression analysis, chelatable lead was significantly associated with overall risk for the primary endpoint (hazard ratio for each 1 µg chelatable lead was 1.01 [95% CI: 1.00, 1.01; $p = 0.002$]). In this model, the only other variable reaching at least borderline significance ($p < 0.1$) was baseline serum creatinine. The associations between baseline chelatable lead or blood lead level and change in GFR (estimated by an MDRD equation [Levey et al., 1999]) were modeled separately using GEE. Based on these models, a 10 µg higher chelatable lead level or a 1 µg/dL higher blood lead level reduced the GFR by 1.3 and 4.0 mL/min, respectively, during the 4-year study period. Similar to the primary outcome analysis, of the many traditional renal risk factors adjusted for in these models, only diagnosis of chronic interstitial nephritis was significantly associated, in this case with an increase in GFR. Of note, chronic interstitial nephritis was also a more frequent diagnosis in the group with the low-normal chelatable lead levels ($p = 0.09$).

6.4.4.3.3 Therapeutic EDTA Chelation in Patients

Chelation in lead exposure is controversial due to the potential for it to be used in lieu of exposure reduction. Chelation in lead nephropathy, in particular, is controversial, because cases of acute tubular necrosis were reported following early clinical use of EDTA that involved large doses in the treatment of hypercalcemia and lead poisoning. Adverse renal effects have not been observed in subsequent work using much lower doses (Sanchez-Fructuoso et al., 1996; Wedeen et al., 1983).

Work prior to the 1986 Lead AQCD suggested that chelation might be beneficial in lead nephropathy (Morgan, 1975; Wedeen et al., 1979). This issue has been addressed more recently by Lin and colleagues in patients with much lower lead doses. Lin et al. (1999) studied 43 patients with serum creatinine and EDTA-chelatable lead levels between 1.5-4 mg/dL and 150 and 600 µg/72 h, respectively. Patients were followed for 12 months to determine their baseline rate of renal function decline. A group of 32 was then randomized; and 16 underwent a 2-month treatment period consisting of weekly chelation with 1 g EDTA; whereas the other 16 continued their regular care. Traditional renal risk factors, such as blood pressure control, were similar in the two groups. Prior to therapeutic chelation, the rate of progression of renal

insufficiency was not statistically different. However, actual improvement in renal function was noted in the treated group during chelation and subsequent renal function decline was slower in this group. The mean difference in the change in the reciprocal of serum creatinine post therapy was 0.000042 L/μmol per month (95% CI: 0.00001, 0.00007).

In subsequent work, Lin et al. (2003) published results of a randomized chelation trial in a larger group. This work included a 2-year prospective study of renal function decline prior to chelation in 202 patients with CRI and EDTA-chelatable lead <600 μg/72 h. Results of the Cox proportional-hazards model were similar to those reported in Yu et al. (2004). Associations between baseline EDTA-chelatable lead level and change in GFR were modeled using GEE. After adjustment, an increase of 10 μg in EDTA-chelatable lead was associated with a GFR decrease of 0.03 mL/min/1.73 m^2 of body-surface area during the observation period ($p < 0.001$). Of note, this effect, although statistically significant, is 40-fold lower than that reported in Yu et al. (2004) over a follow-up period that is only 2-fold shorter. At 24 months, 64 patients whose EDTA-chelatable lead levels were 80-600 μg/72 h were randomized; half to a 3-month treatment period consisting of weekly chelation with 1 g EDTA until their excreted lead levels fell below 60 μg/72 h and half to placebo infusion over 5 weeks. Renal risk factors were similar in the two groups. Mean blood lead levels were 6.1 μg/dL and 5.9 μg/dL in treated and control groups, respectively. In the subsequent 24 months, chelation in 19 (59%) participants was repeated due to increases in serum creatinine in association with rebound increases in EDTA-chelatable lead levels. Each received one additional chelation series (mean = 4.1 g EDTA) a mean of 13.7 months after the first chelation period. At the end of the study period, mean estimated GFR increased by 2.1 mL/min/1.73 m^2 of body-surface area in the chelated group compared to a decline of 6.0 mL/min/1.73 m^2 of body-surface area in the controls ($p < 0.01$) (see Figure 6-4.2). The 95% CI for the difference between the chelated and control groups was −11.0 to −5.1 mL/min/1.73 m^2 of body-surface area.

Lin and colleagues have also reported chelation results in patients with gout. Historically, gout was known to be a risk from high-level lead exposure such as in the Queensland, Australia epidemic and in moonshine alcohol drinkers (U.S. Environmental Protection Agency, 1986a). Higher EDTA-chelatable lead levels in patients with both gout and CRI compared to those with CRI or gout alone have also been reported in several studies at lower levels of exposure

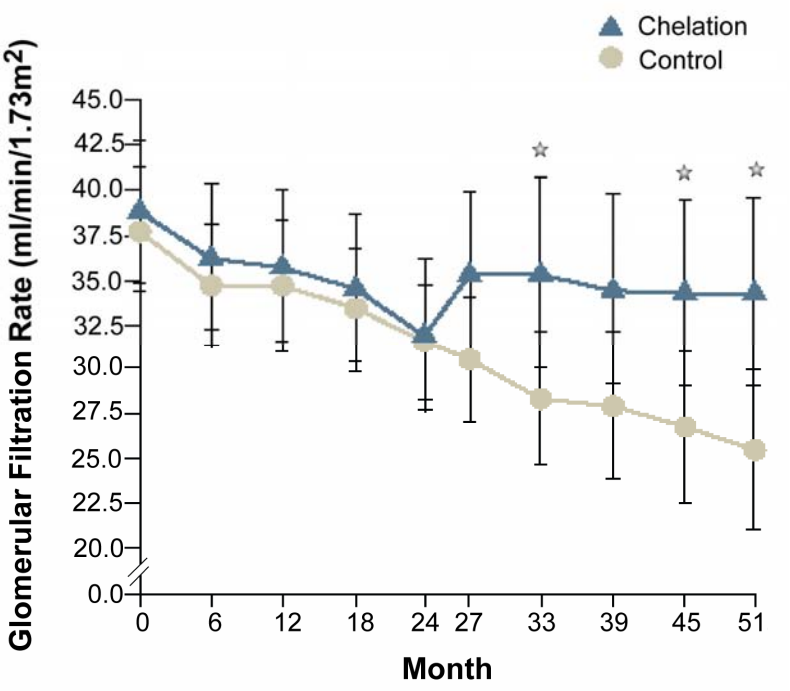


Figure 6-4.2. Estimated mean (±2 SE) glomerular filtration rate according to time in the chelation group (n = 31) and the control group (n = 30) during the observation and intervention periods. The patients in the chelation group received chelation therapy from month 24 to month 51. The asterisks indicate p < 0.05 by Student's t-test.

Source: Lin et al. (2003).

(Batuman et al.,1981; Sanchez-Fructuoso et al., 1996; Lin et al., 2001). Lin and colleagues have pursued this finding in chelation studies of patients with CRI with and without gout (2001) and in otherwise healthy patients with and without gout (2002). Both studies reported significant associations between EDTA-chelatable lead and uric acid measures before chelation and improvement in urate clearance and other uric acid measures after chelation (see Annex Table AX6-4.3 for data). In contrast, Miranda-Carus et al. (1997) did not find correlations between EDTA-chelatable lead body burdens above or below 600 µg/120 h and uric acid measures. Uric acid parameters were unchanged following chelation, although only six participants were studied and all had EDTA-chelatable lead above 600 µg/120 h. Therefore, lack of power as well as different lead body burdens may be explanatory factors for differences between this work and the Lin studies.

The key studies in patients followed prospectively with and without chelation constitute the other major advance in research on the adverse renal effects of lead over the past two decades. This work suggests that lead is nephrotoxic in susceptible populations at lower levels than currently appreciated. Blood lead levels (mean = 4.2 μg/dL [range 1.0–13.4]) and body lead burdens (mean = 99.1 μg/72 h [range 2.5–530]) were associated with decline in GFR over a 4-year follow-up period (Yu et al., 2004). Chelation was beneficial in a body lead burden range from 80 or 150 to 600 μg/72 h, depending on study (Lin et al., 2003; 1999). The published data do not allow a determination of whether a threshold exists. It is also possible that chelation has a direct beneficial effect on kidney function, regardless of lead exposure, since DMSA has been reported to prevent renal damage in a non-lead exposed rat model of nephrosclerosis (Gonick et al., 1996). If so, the benefits of chelation do not appear to occur via reversal of structural damage (Khalil-Manesh et al., 1992b); improved hemodynamics from reduction of reactive oxidant species may be a mechanism (Gonick et al., 1996).

Strengths of the work of Lin and colleagues include prospective study design, lead dose assessment including bioavailable body burden, statistical analysis that includes GEE for longitudinal data, and adjustment for more renal risk factors than any of the other key studies discussed in Section 6.4. Limitations include that fact that, to date, this type of research has been conducted in relatively small number of participants and in only one center. As noted above, the two reported lead body burden β coefficients in GEE models of decline in renal function vary widely. Therefore, small study sizes and differences in renal diagnoses between groups may be overly influential in the results. However, if confirmed in large populations, the potential public health benefit could be substantial. Therapeutic options would be available for high-risk patients, who, despite dramatic reductions in lead exposure in developed countries, are still adversely affected by lead. Lin et al. (2003) noted that, based on their data, chelation could delay the need for hemodialysis by 3 years. Therefore, this unique line of research is deserving of further study. Prospective studies consistent with the results of Yu et al. (2004) will likely be needed to justify randomized, controlled chelation trials.

6.4.4.4 Mortality Studies

As summarized in Steenland et al. (1992), mortality studies have consistently shown excess mortality from chronic kidney disease in lead workers. This increased risk has been most

apparent in workers exposed in earlier time periods, becoming nonsignificant in later calendar time periods in a number of studies. Steenland et al. (1992) reported similar results in a study of 1990 former lead smelter workers. This cohort was made up of predominantly white men who had worked in a lead-exposed department for at least 1 year between 1940 and 1965. Mean (SD) blood lead, measured in 1976 in 173 members of this cohort, was 56.3 µg/dL (12.9). There were 8 deaths from chronic kidney disease. Compared to the U.S. white male population, the standardized mortality ratio was 1.26 (95% CI: 0.54, 2.49). The standardized mortality ratio increased with duration of exposure from 0.79 in workers exposed 1-5 years to 2.79 in workers exposed >20 years, although the standardized mortality ratios did not reach significance (CI not reported). Lead exposure in U.S. industries has declined over the years, and this has been hypothesized as an explanation for the reduction in mortality from renal disease observed in this type of study. However, that fact that improved treatments for chronic renal disease have led to a decrease in mortality from end-stage renal disease (U.S. Renal Data System, 2004) may also be a factor. The mortality studies by Steenland et al. (1992) and others are further described in Annex Table AX6-4.4.

6.4.5 Lead Nephrotoxicity in Children

6.4.5.1 Studies in Adults Following Childhood Lead Poisoning

Henderson clearly established an increased risk for lead nephropathy in adult survivors of untreated childhood lead poisoning (Henderson, 1955). Lead nephropathy was responsible for substantial mortality in the Queensland, Australia population. However, as noted in the 1986 Lead AQCD, other studies of adults who survived childhood lead poisoning have not reported this degree of renal pathology. Studies published since 1986 have not observed the degree of renal pathology noted in the Queensland work either but have revealed some interesting findings. These studies, along with other studies of renal effects of lead in children, are presented in Annex Table AX6-4.5. Pertinent results are discussed below.

A study of comparing 21 adults, who had experienced childhood lead poisoning between 1930 and 1942, to age, sex, race, and neighborhood-matched controls found no significant differences in blood lead level, serum creatinine, or BUN (Hu, 1991). Mean measured creatinine clearance was unexpectedly higher in the previously lead-poisoned group compared to controls (112.8 versus 88.8 mL/min/1.73 m^2 [$p < 0.01$]). Mean in the lead-exposed group was also higher

than the predicted value of 94.2 mL/min/1.73 m^2 from the nomogram of Rowe et al. (1976). One survivor, who was identified but not included in the study, had been diagnosed with chronic interstitial nephritis on renal biopsy. Her blood lead was 30 μg/dL and her presentation was thus consistent with actual lead nephropathy. Strengths of this study included clear criteria for lead poisoning and assessment of clinical renal function that included both measured and estimated creatinine clearances. However, the study was limited by small size and the fact that the number enrolled was a very small subset of the initially identified cohort of 192. At least 43 (22.4%) of the 192 were confirmed to be deceased. That group had evidence of higher initial lead exposure, which raises concern regarding survivor bias in the study group. More importantly, the higher mean creatinine clearance in the lead exposed group provides further evidence for lead-related hyperfiltration. Again, as discussed in the occupational study section, this may hamper attempts to detect associations between lead dose and adverse renal effects.

Another study compared 62 participants who were diagnosed and chelated between 1966 and 1972 for initial blood lead levels >100 μg/dL to 19 age-matched siblings whose initial blood lead levels were <40 μg/dL (Moel and Sachs, 1992). Mean initial blood lead level was 150.3 μg/dL (SD 77.1) in the 62 survivors of lead poisoning; levels in the siblings could not be precisely quantified since values <40 μg/dL were not reported as exact values. Mean age at diagnosis was 2.2 years; age at follow-up was 22.2 years. Blood lead and renal function were serially monitored in the population. In 1983, mean blood lead in the poisoned group was statistically higher than in siblings (means of 14.5 and 11.6 μg/dL, respectively) but, by 1989, both groups had a mean lead of 7.4 μg/dL. Renal outcomes included serum creatinine, uric acid, and β_2-microglobulin, fractional excretion of β_2-microglobulin, urinary protein:creatinine ratio, and tubular reabsorption of phosphate. No statistically significant differences between previously lead-poisoned children and their siblings were observed. The prevalence of abnormal values between the two groups was not different. Initial blood lead level was not associated with serum creatinine, after adjustment for age, gender, and body mass index. However, since blood lead levels were not quantified in the siblings, their values were entered as 40 μg/dL in the continuous blood lead model. Lead was also entered as a dichotomous variable (poisoned versus siblings). Given the data available, the analysis was limited. No cumulative measure of lead was analyzed nor was the serially obtained data analyzed with longitudinal modeling. Four of 62 participants did experience an increase in serum creatinine such that their levels were

≥1.4 mg/dL by the end of the study period. These subjects may reflect lead-related renal toxicity, especially given the young age of the participants. However, it can be concluded that, despite lead exposures that are now considered extremely high, the degree of renal pathology was clearly not to the extent seen in Australia. The fact that these children were chelated when lead poisoning was diagnosed but the Queensland children were not may be an important distinction. Additional follow-up with longitudinal analysis would be of value in these children in order to evaluate their renal function as they develop other renal risk factors.

6.4.5.2 Lead Body Burden in Children with Chronic Renal Disease

Scharer et al. (1991) reported higher lead content in deciduous teeth in 22 German children, age 5-14 years, with varying degrees of renal insufficiency compared to a control group of 20 siblings or neighbors and a group of 16 children without known lead exposure. Mean dental lead content was 2.8, 1.7, and 1.4 μg/g, in the three groups, respectively. Lead levels in teeth were significantly higher in both the patient and sibling/neighbor control groups compared to the unexposed control group. Mean blood lead in the renal patients was only 2.9 μg/dL (range 1.1-10.1 μg/dL). Lead in teeth was not correlated with duration of renal impairment. However, reflective of the ongoing controversy at the time this article was published regarding whether decreased renal excretion causes increased lead storage, the authors attributed elevated lead levels to both exposure and accumulation from decreased renal excretion.

6.4.5.3 General Population Studies in Children

In the first study of the renal effects of lower level environmental lead exposure in children (as opposed to lead-poisoned children), Bernard et al. (1995) carried out a cross-sectional study of 195 children in the Czech Republic. One hundred forty-four children (63 boys and 81 girls) lived in 2 areas close to a lead smelter (designated as exposed groups one and two). A control group of 51 children lived in a rural area. Blood lead levels and urinary renal early biologic effect markers (RBP, β_2-microglobulin, NAG, albumin, and Clara cell protein) were obtained. Age ranged from 12 to15 years. In girls, mean blood lead concentrations in controls and exposure groups one and two were 8.4, 9.4, and 12.9 μg/dL, respectively. Corresponding values in boys were 8.7, 10.9, and 14.9 μg/dL, respectively. These levels were significantly

higher in both exposed groups compared to the control group. In contrast, blood cadmium levels were similar among all groups. After adjustment for age, sex, blood cadmium, and zinc protoporphyrin, log transformed blood lead was associated with log transformed RBP ($\beta = 0.302$, $p = 0.005$).

Verbeck et al. (1996) studied 151 Romanian children residing at various distances from a lead smelter. Associations between blood lead levels and renal outcome measures (urinary RBP, NAG, α_1-microglobulin, albumin, and alanine aminopeptidase) were analyzed. Mean age was 4.6 years (range of 3-6 years); gender was evenly divided. Mean blood lead was 34.2 µg/dL (SD 22.4), which is much higher than in Bernard et al. (1995). After adjustment for age and gender, a 10 µg/dL increase in blood lead was associated with a 13.5% (90% CI: 10.2, 17) increase in NAG excretion. No threshold was observed. Blood cadmium levels measured in a subset of the population were all <2 µg/L; however, this variable was not entered into the regression model.

Another study included 200 French children who resided close to smelters along with 200 age and gender matched controls recruited from areas believed to be unpolluted by heavy metals (De Burbure et al., 2003). Blood lead and cadmium were measured. Renal outcomes included urinary total protein, albumin, transferrin, β_2-microglobulin, RBP, brush border antigens, and NAG. Age ranged from 8.5 to 12.3 years. Geometric mean blood leads ranged from 2.7 µg/dL (SD 0.2) in female controls to 4.2 µg/dL (SD 0.2) in exposed males. The highest geometric mean blood cadmium was 0.52 µg/L. After adjustments for covariates, blood lead was not associated with any renal outcomes; however, blood cadmium was positively associated with NAG. This association was present in both control and exposed areas. Notably, the blood lead levels in this study were much lower than in the two studies discussed above.

Staessen et al. (2001) studied 200 17-year-old Belgian children. The two exposed groups were recruited from industrialized suburbs, whereas, the control group was recruited from a rural area. Mean blood lead levels were 1.5, 1.8, and 2.7 µg/dL in controls, and exposed groups one and two, respectively. The renal outcome measures analyzed were urinary β_2-microglobulin and serum cystatin-C. Although blood lead levels were low, after adjustment for sex and smoking status, blood lead was associated with both β_2-microglobulin and cystatin-C. Interestingly, blood cadmium was not associated with either outcome.

The current lack of sensitive markers of early renal damage that have been shown to predict subsequent renal function decline in longitudinal studies of lead exposed populations is problematic for research in this field. This is particularly true when studying children who do not have many of the other renal risk factors, such as hypertension and diabetes that older adults do. Coratelli et al. (1988) reported a decline in urinary NAG in association with a 1 month period of decreased occupational exposure in 20 adult lead battery factory workers followed over a 1 year period. Clinical renal function measures were not studied however. Sarasua et al. (2003) studied 526 adults and children, a mean of 4.5 years after an initial evaluation of renal function including measurement of urinary albumin, NAG, RBP, and alanine aminopeptidase. These participants were drawn from three populations exposed to volatile organic compounds and explosives via groundwater and controls. Follow-up was performed to determine if the EBE markers remained elevated and whether the presence of elevated EBE markers at baseline was associated with abnormalities in serum creatinine, serum cystatin C, 24-h creatinine clearance, and urine osmolality at follow-up. Among children who had elevated EBE markers at baseline, renal EBE markers remained elevated in 38%. However, none remained elevated in the 32 who had completed adolescence by the time of the follow-up. The authors noted the potential for puberty related biomarker changes. Further, abnormalities in the clinical measures were rare at follow-up. In contrast, elevated EBE markers at baseline in adults with chronic medical conditions of risk to the kidney, such as diabetes and to a lesser extent heart disease and hypertension, had persistent elevation of EBE markers and evidence of worse renal function at follow-up. Limitations of this study include limited data analysis, some loss to follow-up, and limited information on whether the original exposures for which these populations were studied may have influenced these results. The authors stated that no significant differences in renal outcomes between participants from exposed and control communities at follow-up were observed and noted that kidney function was not worse in exposed communities in the initial evaluations, which appeared to refer to the biomarkers as well. However, this report does not indicate whether exposure changed between the initial biomarker collection and the follow-up (i.e., decreased substantially or stopped altogether). Still the study illustrates the need for further prospective research to validate EBE markers in nephrotoxicant-exposed populations.

6.4.6 Mechanisms for Lead Nephrotoxicity

Individuals who have been heavily exposed to lead are at increased risk for both gout and renal disease (Shadick et al. 2000; Batuman 1993). Lead is thought to increase serum uric acid (urate) by decreasing its renal excretion (Emmerson, 1965; Ball and Sorensen, 1969; Emmerson and Ravenscroft, 1975). As discussed above, research in the last decade indicates that lead is nephrotoxic at lower levels than previously recognized. The same is true for uric acid (Johnson et al., 2003). Therefore, it is possible that one mechanism for lead-related nephrotoxicity, even at current lower levels of lead exposure, is via increasing serum uric acid.

In order to address this question, Weaver et al. (2005a) analyzed data from 803 current and former lead workers to determine whether lead dose was associated with uric acid and whether previously reported associations between lead dose and renal outcomes (Weaver et al., 2003) were altered after adjustment for uric acid. Outcomes included uric acid, blood urea nitrogen, serum creatinine, measured and calculated creatinine clearances, and urinary NAG and RBP. Mean uric acid, tibia lead, and blood lead levels were 4.8 mg/dL (SD 1.2), 37.2 μg/g bone mineral (SD 40.4), and 32.0 μg/dL (SD 15.0), respectively. None of the lead measures (tibia, blood, and DMSA-chelatable lead) were associated with uric acid, after adjustment for age, gender, body mass index, and alcohol use. However, when effect modification by age on these relations was examined, both blood and tibia lead were significantly associated in participants in the oldest age tertile ($\beta = 0.0111$ [95% CI: 0.003, 0.019] and $\beta = 0.0036$ [95% CI: 0.0001, 0.007]) for blood and tibia lead, respectively). These models were further adjusted for blood pressure and renal function. Hypertension and renal dysfunction are known to increase uric acid. However, they are also risks associated with lead exposure. Therefore, adjustment for these variables in models of associations between lead dose and uric acid likely results in overcontrol. On the other hand, since non-lead-related factors contribute to both renal dysfunction and elevated blood pressure, lack of adjustment likely results in residual confounding. Therefore, as expected, associations between lead dose and uric acid decreased after adjustment for systolic blood pressure and serum creatinine, although blood lead remained borderline significantly associated ($\beta = 0.0071$ [95% CI: −0.001, 0.015]). However, when the population was restricted to the oldest tertile of workers with serum creatinine greater than the median (0.86 mg/dL), likely the highest risk segment of the population, blood lead remained significantly associated with uric acid even after adjustment for systolic blood pressure and serum creatinine ($\beta = 0.0156$).

Next, in models of renal function in all workers, uric acid was significantly associated with all renal outcomes except NAG. Finally, in the oldest tertile of workers, after adjustment for uric acid, associations between lead dose and NAG were unchanged, but fewer of the previously significant ($p \leq 0.05$) associations noted between lead dose and the clinical renal outcomes in Weaver et al. (2003a) remained significant.

Data from the Normative Aging Study indicate that lead dose, at levels lower than those known to increase the risk for gout or in the study of Weaver et al. (2005a), is associated with increased uric acid (Shadick et al., 2000). Mean blood, patella, and tibia lead levels were 5.9 μg/dL, 30.2 μg/g bone mineral, and 20.8 μg/g bone mineral, respectively, in 777 participants. A significant association between patella lead and uric acid ($\beta = 0.007$ [[95% CI: 0.001, 0.013]; $p = 0.02$) was found, after adjustment for age, BMI, diastolic blood pressure, alcohol ingestion, and serum creatinine. Borderline significant associations between tibia ($p = 0.06$) and blood lead ($p = 0.1$) and uric acid were also observed. Notably these associations were significant even after adjustment for blood pressure and renal function, providing further evidence that low-level lead increases uric acid.

These data suggest that older workers comprise a susceptible population for increased uric acid due to occupational lead exposure. Uric acid may be one mechanism for lead-related nephrotoxicity. However, this is not the only mechanism, since in Weaver et al. (2005a), the association between blood lead and serum creatinine remained significant even after adjustment for uric acid. These mechanistic relations have more than just theoretical importance. Clinically relevant therapies may be possible since, as noted above, EDTA chelation has been reported to improve both renal function and urate clearance in patients with renal insufficiency and gout, even when EDTA-chelatable lead body burdens were low (Lin et al., 2001).

6.4.7 Susceptible Populations for Lead Nephrotoxicity

6.4.7.1 Chronic Medical Diseases

The general population studies by Tsaih et al. (2004) and Muntner et al. (2003) (discussed in section 6.4.4.1 General Population Studies above) indicate that patient populations with diabetes and hypertension are at increased risk for adverse renal effects of lead. The work of Lin and colleagues (several articles discussed in section 6.4.4.3 Patient Population Studies above) indicates that patients with CRI and gout are also at increased risk. In these settings, lead

appears to acts as a cofactor with other renal risk factors to cause early onset of renal insufficiency and/or a steeper rate of renal function decline. It is likely that the presence of larger high risk populations within general populations is an important factor in the lower lead dose thresholds noted for the adverse effects of lead on the kidney in environmental compared to occupational research.

6.4.7.2 Age

The work of Weaver and colleagues (discussed in Section 6.4.4.2.3 Korean Lead Workers above) suggests that older age is a risk factor. This is consistent with research in general populations (Lindeman et al., 1985) and is biologically plausible, since most renal risk factors increase with age. Gonick and Behari (2002) have summarized the data regarding the potential contribution of lead exposure to essential hypertension; similar issues may be involved with the renal dysfunction observed in aging.

6.4.7.3 Genetic Polymorphisms

6.4.7.3.1 δ-Aminolevulinic Acid Dehydratase (ALAD)

Research in the last two decades suggests that several genetic polymorphisms affect lead toxicokinetics (i.e., modify the relation between lead exposure and dose). Of those that are potentially relevant to the kidney, data on the gene that encodes for δ-aminolevulinic acid dehydratase (ALAD) are the most important in this regard. The ALAD enzyme is a principal lead binding protein; the isozymes in those with the ALAD2 allele are more electronegative and bind a greater proportion of blood lead than does the protein in individuals with the ALAD11 genotype (Bergdahl et al., 1997). Research to date indicates that individuals with the ALAD2 allele generally have higher blood lead levels than those with the ALAD11 genotype, although this may not be the case at lower levels of lead exposure (i.e., mean blood lead levels <10 μg/dL) (Kelada et al., 2001). Participants with the ALAD2 allele have been found to have lower bone lead levels in some studies (Hu et al., 2001; Kamel et al., 2003); other toxicokinetic differences have also been reported (Fleming et al., 1998; Hu et al., 2001; Schwartz et al., 1997; Smith et al., 1995). Overall, these data suggest that tighter binding of lead by the isozymes of the ALAD2 allele decreases lead sequestration in bone.

In contrast, data to determine whether the ALAD polymorphism impacts the renal toxicity of lead are still quite limited. The only environmentally exposed population in which this has been addressed is the Normative Aging Study. Wu et al. (2003) (discussed in detail in section 6.4.4.1.2 above) analyzed data to determine whether the ALAD genetic polymorphism modified associations between lead dose and uric acid, serum creatinine, and estimated creatinine clearance, 114 (16%) of the study group were either homozygous or heterozygous for the variant ALAD2 allele. None of the three outcomes were significantly different by genotype. However, effect modification by genotype on the association between tibia lead and serum creatinine was observed; the β coefficient (and slope) was greater in the group with the variant allele ($\beta = 0.002$ [SE not provided]; $p = 0.03$). Effect modification of borderline significance ($p < 0.1$) on relations between of patella and tibia lead with uric acid was observed; this was significant in participants whose patella lead levels were above 15 μg/g bone mineral ($\beta = 0.016$ [SE not provided]; $p = 0.04$). Similar to the serum creatinine model, patella lead was associated with higher uric acid in those with the variant allele. Genotype did not modify lead associations in models of estimated creatinine clearance.

The impact of the ALAD polymorphism on renal outcomes has been studied in four occupationally-exposed populations to date. The two that assessed both associations and effect modification by genotype are discussed here. Weaver et al. (2003b) analyzed data from 798 lead workers. Lead and renal function measures, as well as mean lead levels, were described in Weaver et al. (2003a) in Section 6.4.4.2 above. A total of 79 (9.9%) participants were heterozygous for the ALAD2 allele (none was homozygous). After adjustment, participants with the ALAD2 allele had lower mean serum creatinine and higher calculated creatinine clearance. Effect modification by ALAD on associations between blood lead and/or DMSA-chelatable lead and three of six renal outcomes was observed. Among those with the ALAD12 genotype, higher lead measures were associated with lower BUN and serum creatinine and higher calculated creatinine clearance. Among older workers (age ≥ median of 40.6 years), ALAD genotype modified associations between lead dose and uric acid levels. Higher lead dose was significantly associated with higher uric acid in workers with the ALAD11 genotype; associations were in the opposite direction in participants with the variant ALAD12 genotype (Weaver et al., 2005c).

Ye and colleagues (2003) assessed effect modification by ALAD on associations between blood lead with urinary NAG and albumin in a study of 216 lead workers. Geometric mean

blood lead was 37.8 µg/dL in 14 workers with the ALAD12 genotype and 32.4 µg/dL in workers with the ALAD11 genotype. After adjustment for age, NAG was borderline statistically higher in those with the variant allele whose blood lead levels were ≥40 µg/dL. In all lead workers, after adjustment for age, gender, smoking, and alcohol ingestion, a statistically significant positive association between blood lead and creatinine adjusted NAG was observed in the workers with the ALAD12 genotype but not in lead workers with the ALAD11 genotype (the groups were analyzed separately rather than in an interaction model).

Thus, two of the three studies reported steeper slopes for one or more associations between lead dose and adverse renal function in participants with the ALAD2 allele compared to those with the ALAD11 genotype which suggests that the variant ALAD gene confers additional risk for adverse renal outcomes in lead exposed populations. If the associations of Weaver et al., (2003b) represent lead-induced hyperfiltration their results could be consistent with increased risk from the variant allele as well. Ultimately, analysis of longitudinal data in the Korean lead worker population will be required to understand these complex relations.

6.4.7.3.2 BsmI Polymorphism of the Vitamin D Receptor (VDR) Gene

In contrast to ALAD, relatively few data on the *Bsm*I polymorphism of the gene that encodes for the vitamin D receptor (VDR) are available in lead exposed populations. Polymorphisms of the VDR gene are of interest in these populations due to the role of vitamin D and its receptor in regulating both intestinal calcium absorption and bone mineralization. These pathways impact lead absorption from the gastrointestinal tract and may impact lead storage and/or release from bone (Onalaja and Claudio, 2000). Analysis of data from the first evaluation of the Korean lead worker cohort found that participants with the B allele had significantly higher blood, DMSA-chelatable, and tibia lead levels than those with the bb genotype (Schwartz et al., 2000a); significantly higher patella lead in workers with the B allele was reported in data from the third evaluation (Theppeang et al., 2004). A study of 216 lead workers similarly reported higher blood lead levels in workers with the B allele (n = 20), after adjustment for age, gender, smoking, alcohol ingestion, and calcium ingestion, education, ALAD genotype, and ambient lead exposure (Ye et al., 2003). In a study of 504 former organolead manufacturing workers, with an average of almost two decades since last occupational exposure, VDR genotype was not associated with tibia lead concentrations (Schwartz et al., 2000c). However, the slope

of the positive association between age and tibia lead concentration was steeper in participants with the B allele compared to those with the bb genotype and tibia lead declined with years since last exposure in participants with the bb genotype, but increased in those with the B allele. In contrast, Chuang and colleagues (2004) found no difference in current or cumulative blood lead by *Bsm*I polymorphism in 544 lead workers.

Work in two of the populations described above has also provided information on the impact of the *Bsm*I VDR polymorphism. Of the 798 participants in Weaver et al. (2003b), 89 (11.2%) had genotype Bb or BB. No significant differences were seen in renal outcomes by VDR genotype nor was consistent effect modification observed. However, those authors assessed effect modification by this polymorphism on associations between patella lead and renal outcomes in current and former Korean lead workers in data from the third evaluation where patella lead was measured. Results were compared to those with three other lead biomarkers. The same six renal outcomes as in Weaver et al. (2003a) were measured. Mean blood, patella, tibia, and DMSA-chelatable lead were 30.9 μg/dL (SD 16.7), 75.1 μg lead/g bone mineral (SD 101.1), 33.6 μg lead/g bone mineral (SD 43.4), and 0.63 μg lead/mg creatinine (SD 0.75), respectively, in 647 lead workers (Weaver et al. [2005b]). Little evidence of effect modification by genotype on associations between patella lead and renal outcomes was observed. However, the VDR polymorphism did modify associations between the other lead biomarkers and serum creatinine and calculated creatinine clearance. Higher lead dose was associated with worse renal function in participants with the variant B allele. Models in two groups, dichotomized by median age, showed this effect was present in the younger half of the population. The authors were able to exclude different participant subsets as an explanation for the difference in VDR findings between the two evaluations. Longitudinal changes in renal function between evaluations may account for these findings and are currently being evaluated in longitudinal data analysis.

Ye and colleagues (2003) reported higher systolic blood pressure, after adjustment for age, in those with the variant allele whose blood lead levels were ≥40 μg/dL. In all lead workers, after adjustment for age, gender, smoking, and body mass index, a statistically significant positive association between blood lead and systolic blood pressure was observed in the 20 lead workers with the variant B allele, but not in lead workers with the bb genotype. Again, the fact that the genotype groups were analyzed separately, rather than in an interaction

model, decreased the study's power to detect a difference. This could be an explanatory factor for the lack of effect modification by VDR genotype on associations between blood lead and urinary albumin and NAG observed.

In conclusion, an increasing body of literature indicates that both of these polymorphisms affect lead toxicokinetics. However, data to determine if these polymorphisms impact renal function are still quite limited. Existing data are suggestive of an increased renal risk in lead exposed populations with the variant alleles of both polymorphisms.

6.4.8 Confounding of the Renal Effects of Lead by Other Potential Risk Factors

Studies selected for discussion in Section 6.4 above have generally controlled for at least the most basic risk factors known to affect renal function such as age, gender, and body mass index (or weight and height separately). Some have controlled for many other potentially important risk factors. In addition, exposure to other nephrotoxicants must be considered. Notably, although these are listed under confounders, some may be effect modifiers as well.

6.4.8.1 Cadmium

Similar to lead, cadmium is an ubiquitous nephrotoxicant that accumulates in the body. Environmental exposure in the United States occurs primarily through food and smoking (Agency for Toxic Substances and Disease Registry, 1993). Cadmium in food is a result of soil pollution from a variety of human activities such as phosphate fertilizer use, industrial releases from smelting, and fuel combustion. An analysis of NHANES III data, collected in a representative sample of the U.S. population from 1988-1994, indicates that mean urinary cadmium is 0.48 μg/g creatinine and 97.7% of the population has a level ≤2 μg/g creatinine (Paschal et al., 2000). Also similar to lead, cadmium causes proximal tubule pathology and is a risk factor for CRI.

The existing data indicate that cadmium, at exposure levels common in the U.S., confounds associations between lead exposure and at least one renal outcome, NAG. Roels et al. (1994) reported higher mean NAG in their lead-exposed group; however, NAG was correlated with urinary cadmium but not blood or tibia lead, despite the fact that mean urinary cadmium was only 1.04 and 0.53 μg/g creatinine in workers and controls, respectively. Cardenas et al.

(1993) reported a similar finding. Bernard et al. (1995) found an association between urinary cadmium and the NAG-B isoenzyme (released with breakdown of proximal tubular cells) in 49 cadmium workers and 20 age-matched controls. In multiple linear regression, urinary cadmium, but not lead, was associated with NAG-B, after adjustment for age. The association was significant even in the 44 participants with levels <2 μg/g creatinine. However, NAG-A (released by exocytosis) was correlated with urinary lead (the only lead measure), but not cadmium. Roels et al. (1995) reviewed data pertinent to the potential for cadmium confounding of associations between lead and NAG. In more recent work, Weaver et al. (2003a) measured urinary cadmium in a subset of 191 of the 803 workers in their study (mean urinary cadmium was 1.1 μg/g creatinine). Higher urinary cadmium levels were associated with higher NAG. Of the lead measures obtained, only tibia lead was significantly associated with NAG in the cadmium subset. When urinary cadmium and tibia lead were entered as covariates in the same model, both remained associated with NAG ($p < 0.05$). However, in comparing the effects, a 0.5 μg/g creatinine increase in cadmium had the same effect on NAG as a 66.9 μg/g bone mineral increase in tibia lead. When compared by ranges of exposure in this population, environmental level cadmium dose had a larger impact on NAG than did occupational lead dose.

Cadmium exposure may confound relations between lead exposure and other renal outcomes as well, although the data are too limited to draw firm conclusions. Positive associations between urinary cadmium, which is thought to be the best measure of cumulative cadmium exposure in the absence of cadmium-related renal damage, and low molecular weight (LMW) proteinuria are well established in the occupational setting. LMW proteinuria, most commonly assessed by β_2-microglobulin, is generally progressive at levels >1,500 μg/g creatinine in workers with substantial body burdens (one or more historical urinary cadmium >20 μg/g creatinine) but may also be progressive at lower levels (Roels et al., 1997; Bernard, 2004). More importantly, clinical renal function also declines as evidenced by decreasing GFR in cadmium exposed workers followed longitudinally after removal from exposure due to LMW proteinuria (Roels et al., 1989; 1997).

In contrast to the clear evidence that cadmium is a renal toxicant at occupational levels of exposure, the renal risk from lower level cadmium exposure remains uncertain. Most studies of environmental cadmium exposure are cross-sectional and have assessed EBE markers, rather than clinical renal outcomes (Alfven et al., 2002; Jarup et al., 2000; Noonan et al., 2002; Olsson

et al., 2002). The Cadmibel study, a general population study of exposed residents from both cadmium polluted and unpolluted areas (discussed in Section 6.4.4.1.1 above), found correlations between urinary cadmium and several urinary EBE markers (NAG, RBP, β_2-microglobulin, calcium, and amino acids) (Buchet et al., 1990). In those models, after adjustment for urinary cadmium and other covariates, blood lead was significant in models of β_2-microglobulin and amino acids but not NAG. However, in this same population, blood lead was inversely associated with creatinine clearance, whereas urinary and blood cadmium were not (Staessen et al., 1992). A 5 year follow-up was conducted to determine the significance of the EBE abnormalities (Hotz et al., 1999). In this study, models of renal function (two dichotomized outcomes: a 20% decline in creatinine clearance and a 20% increase in albumin excretion) in relation to quartiles of urinary cadmium and the EBE markers at baseline were analyzed by likelihood ratios. Baseline variables did not predict adverse renal outcomes. However, 25% of the original population was lost to follow-up; available data indicated that their baseline renal function was worse than those who participated in the follow-up study. This may have biased the study towards the null.

Two recent publications suggest that low-level cadmium exposure is associated with adverse clinical renal outcomes. Elevated urine cadmium levels were associated with prevalent microalbuminuria and decreased calculated creatinine clearance after adjustment for age, sex, race, smoking, and use of diuretics in an analysis of 16,094 participants in the NHANES III study (Young et al., 2004). Hellstrom et al. (2001) reported increased rates of renal dialysis and transplantation in residents of cadmium-polluted areas in Sweden. Compared to the "no-exposure group" (domicile >10 km from a battery plant), age-standardized rate ratios were 1.4 (95% CI: 0.8, 2.0) in the low-exposure group (domicile 2 to 10 km) and 1.9 (95% CI: 1.3, 2.5) in the moderate-exposure group (domicile <2 km). Exposure categorization was based on environmental monitoring in the study areas. Cadmium dose was not directly measured although occupationally exposed participants were considered in a separate group. Neither of these studies assessed lead exposure as a covariate, which would be important given the Cadmibel results (Staessen et al., 1992).

In conclusion, cadmium clearly confounds associations between lead dose and NAG. Given the similarities in both nephrotoxicants, cadmium may confound and/or modify associations between lead and other renal outcomes. However, data on the

concentration-response relation between environmental cadmium and the kidney are too limited to assess the potential for this at present. Future studies assessing both lead and cadmium are needed.

6.4.9 Summary of the Epidemiologic Evidence for the Renal Effects of Lead

In the last two decades, the quality of research on the renal impact of lead exposure has advanced dramatically. As a result, a much more accurate assessment of the adverse renal impact of lead exposure can now be made. Studies of environmentally-exposed general populations are one of the most important advances in this regard. The landmark Cadmibel study (Staessen et al., 1992) was the first to raise concern that the lead dose threshold for adverse renal effects in the general population was much lower than previously appreciated based on occupational data. Research in the Normative Aging Study population reached similar conclusions and suggested that both cumulative and circulating lead are associated with longitudinal decline in renal function. Diabetics were a particularly susceptible risk group in this regard. The NHANES III data analysis (Muntner et al., 2003) are notable for a sample size that is, by far, the largest of the environmental studies, comprehensive adjustment for other renal risk factors and the fact that population is representative of the U.S. population. Thus, the fact that renal dysfunction was observed in hypertensives at a mean blood lead of only 4.2 μg/dL and in the 1st quartile compared to the reference group (blood lead range from 2.5 to 3.8 μg/dL), provides strong evidence that the kidney is a target organ for adverse effects from lead at current U.S. environmental exposure levels.

Studies involving the longitudinal assessment of renal function decline in susceptible patient populations in relation to baseline chelatable lead body burden and therapeutic chelation constitute the other major advance in lead-renal research in the last two decades. Chelation was beneficial in an EDTA-chelatable lead level range from 80 or 150 to 600 μg/72 h, depending on the study (Lin et al., 1999, 2003). These studies suggested that lead body burden, at much lower levels than previously recognized, contributes to renal dysfunction in populations with CRI from a range of causes. This work also suggests that renal function in patients with CRI stabilizes and, in some cases, improves after therapeutic EDTA chelation of lead levels well below the level currently thought to require chelation.

A finding of note from the occupational studies is the observation of inverse associations (higher lead dose with lower BUN, serum creatinine, and/or higher creatinine clearance) in several studies. This may indicate lead-related hyperfiltration and have mechanistic implications. Regardless, significant associations could be obscured if opposite direction associations are present in different segments of the study population and interaction models to address this are not performed. This is a valid concern, since the settings in which these inverse associations are most likely are not well defined.

The renal impact in children from lead exposure at current environmental levels is difficult to assess, since the studies have involved measurement of EBE markers and their prognostic value is uncertain. Susceptible populations due to chronic medical diseases have clearly been established; risk from genetic polymorphisms may be important, but further study is required. Studies of potential mechanisms for the adverse renal effects of lead in humans, such as via uric acid have more than just theoretical importance, since EDTA chelation has been reported to improve both renal function and urate clearance in patients with renal insufficiency and gout (Lin et al., 2001). With an improved understanding of mechanisms, clinically relevant therapies may be possible.

6.5 CARDIOVASCULAR EFFECTS OF LEAD

6.5.1 Summary of Key Findings of the Cardiovascular Effects of Lead from the 1985 Lead AQCD and Addendum, and 1990 Supplement

The greater part of the evidence reviewed up to 1990 included analyses of the largest datasets available at the time, the National Health and Nutrition Evaluation Survey II (NHANES II), studying the U.S. population between 1976 and 1980, and the British Regional Heart Study (BRHS), studying men aged 40-59 years from 24 British towns. Analyses of the Welsh Heart Programme, a regional Welsh study, and the Caerphilly Collaborative Heart Disease Study, a cohort study of men aged 45-59 years living in one town in Wales, as well as smaller population and occupational exposure studies in the U.S., Canada, and Europe provided supporting evidence. These studies set enduring design and analysis standards by example for evaluating cardiovascular effects associated with blood lead levels in samples from diverse populations.

In general, the reviewed studies used multiple linear regression modeling of blood pressure and multiple logistic regression modeling of hypertension, cardiovascular mortality, and other cardiovascular disease, allowing adjustment of the blood lead effect on outcome by other factors known or suspected to be related to the exposure and outcome under study. The most commonly considered potential confounding factors were age, body mass index (BMI), alcohol use, and cigarette smoking.

These studies were almost exclusively cross-sectional studies, measuring cardiovascular outcome, blood lead, and control variables once, though one Canadian occupational study and one Danish birth-year cohort study used a longitudinal design. Studies sometimes presented analyses stratified by sex or age, by both sex and age, or by "race." Other analyses only reported results for one particular stratum. Separate analyses of datasets partitioned by stratified variables always reduce sample size available for statistical models, and, thereby, may reduce power to detect real effects.

Evaluated as a whole, the blood pressure studies supported a small but significant association between increasing blood lead concentrations and increasing blood pressure in study groups. The effect was more consistent across studies in middle-aged men than in other groups, ranging from a 1.5 to 3.0 mm Hg increase in systolic blood pressure for each doubling of blood lead from the mean blood lead level, and from a 1.0 to 2.0 mm Hg increase in diastolic blood pressure for each blood lead doubling, across a wide range of blood lead concentration down to 7 μg/dL. Most studies using multiple regression analyses stratified by sex were unable to find significant associations between blood pressure and blood lead in females, though one reanalysis of the NHANES II dataset did report a statistically significant relationship between diastolic blood pressure and lead in women aged 20 to 74 years. In studies reporting the use of different blood lead-blood pressure concentration-response relationships, log blood lead terms had lower probability values than linear blood lead terms, suggesting that increases in blood pressure with incremental fixed incremental increases in blood lead might be greater at lower blood lead concentrations than at higher concentrations.

Three studies of groups with occupational exposure reported mixed results. One study found significant excess mortality due to cardiovascular disease during the period 1946-1965 in a case-control study in the United Kingdom, but not 1966-1985. A study of U.S. battery and lead production workers from 1947-1980 found significant excess mortality due to "other

hypertensive disease" (codes 444-447 in the ICD 1955 classification system), but not due to hypertensive diseases outside those classifications. No excess mortality due to hypertension was found in a study of U.S. smelter workers between 1940 and 1965.

The BRHS study failed to reveal significant associations between blood lead and ischemic heart disease and stroke. However, electrocardiogram abnormalities associated with left ventricular hypertrophy were found related to blood lead in a subset of the NHANES II data, confirming an earlier study finding significant associations between ischemic changes and blood lead in lead workers.

Noninvasive measurement of bone lead concentration using XRF techniques was still maturing during the literature review period covered by the 1986 AQCD document and later addendum and supplement. No studies were reported using bone lead as a marker for lead exposure.

6.5.2 Effects of Lead on Blood Pressure and Hypertension

6.5.2.1 Introduction

Blood lead concentration remained the most widely used exposure index in blood pressure/hypertension epidemiologic studies from 1990 to present. Obtaining the sample is relatively noninvasive and quick, measurement techniques are well standardized and inexpensive with access to external quality assurance programs worldwide, and existing regulation and medical decision-making are based on blood lead levels. If exogenous lead exposure were the only determinant for blood lead concentration, it could be fair to state that a single blood lead measurement represented exposure to lead during the 30-90 day period preceding the measurement. However, blood lead concentration represents a combination of recent exposure to external sources and the influence of internal sources, principally bone lead. As detailed in Section 6.2, bone is a long-term storage depot for much of the lead absorbed by the body from external sources, and by weight can represent over 95% of the total body burden of lead in middle-aged persons, especially if external exposures are currently low. Bone lead has residence times of years to decades. Bones constantly absorb lead from and release lead to the circulatory system. Consequently, blood lead concentration is not only determined by current and recent past external exposure but is also influenced by existing bone lead concentration to a degree determined by current external exposure, accumulated past exposure stored in bones, and the

physiological state of the bones due to aging, disease, pregnancy, and lactation, among others. Studies using only blood lead concentration, as an exposure index cannot determine the relative contributions of current exogenous exposure and endogenous exposure to blood lead. Thus, they are unable to assess what part of measured blood lead effect on the circulatory system is due to possibly higher long duration past exposure and what part is due to the possibly immediate toxic effects of currently circulating lead. They are, instead, assessing a combined effect of past and present exposure in a proportion that will differ among subjects according to their past and present exposure, health history, and age.

Elevated blood pressure can be evaluated as a continuous measure (mm Hg) or as a dichotomized measure (hypertension). The definition of hypertension involves a categorical cut point of mm Hg above which one is hypertensive and below normotensive. Kannel (2000a,b) notes that this number has dropped over time for systolic/diastolic pressure and further notes a continuous graded influence of blood pressure even within what is regarded as the normotensive range. Some concern for an arbitrary definition as the cut point and one that has changed over time is a consideration. However defined, even if greater than the cut point at that time used clinically, the separation into these two groups offers a different perspective than blood pressure per se. Hypertension has a different clinical relevance than blood pressure changes themselves. The disease condition as an outcome and a change in mm Hg in relation to exposure both offer the opportunity for insight into the clinical relevance of the relationships. Biomarkers like bone lead and blood lead also add input into the acute/chronic nature.

The recently developed in vivo technique of XRF measurement of bone lead concentration has been used in a handful of studies to better assess the role of past exposure to lead on blood pressure and hypertension in essentially cross-sectional studies. Bone lead concentration provides a record of cumulative past exposure due to the long residence times of lead in bones, though the specific temporal pattern of past exposure cannot be readily determined from the measurement. Primarily cortical bones such as tibia have residence times measured in decades, whereas primarily trabecular bones such as calcaneus and patella have residence times measured in years to decades, reflecting different metabolic rates of the two bone types. As there is continual interchange of lead in bone and lead in blood, studies combining the measurement and modeling of both bone lead and blood lead have the best chance of dissecting out the roles of past and present lead exposure on blood pressure and hypertension.

The growing field of toxicogenetics now includes lead exposure epidemiology. The several studies combining subject evaluation of polymorphisms of genes thought to play a role in either the origin of cardiovascular disease, the toxicokinetics of lead or both are also reviewed. All epidemiologic studies of the cardiovascular effects of lead reviewed in this section as well as other additional studies are further summarized in Annex Table 6-5.1.

6.5.2.2 Blood Pressure and Hypertension Studies Using Blood Lead as Exposure Index

6.5.2.2.1 NHANES Studies

NHANES contributed the largest datasets analyzed in this review. As the surveys are also representative of the U.S. population, their results may be more readily applied to the general U.S. population than smaller cohort or occupational studies. The several papers using this dataset sometimes come to different conclusions, depending on the statistical techniques used in analysis, including logarithmic or linear specification of the lead variable, stratification of analyses according to sex or ethnic groups or use of interaction terms to define these groups, use of survey-design corrected models, choice of covariates in the models, and different age ranges analyzed.

NHANES II (1976-1980)

In one NHANES II-based study, males and females (number unreported but less than 9,000 combined) aged 20 to 74 years were studied with separate stepwise multiple regression models adjusted for sampling design (Schwartz, 1991). Mean blood lead levels were not reported. Covariates common to both male and female models were age and age^2, BMI, race, family history, cholesterol, zinc, tricep fold, and natural log lead. Models for men also included height and cigarette smoking. Natural log blood lead was significantly associated with diastolic blood pressure (systolic not reported) in males, with a 2.03 mm Hg diastolic (95% CI: 0.67, 3.39) increase for every doubling of blood lead, and for females a 1.14 mm Hg increase (95% CI: 0.13, 2.08). Interactions between blood lead and sex and between blood lead and race in a combined model were insignificant (not shown). The conclusion from these interaction terms is that the association between blood lead and diastolic blood pressure was not significantly different between men and women or between races. There was no mention of consideration of

model diagnostics, and the stepwise modeling may incorrectly include or exclude potentially confounding variables.

The other NHANES II-based study focused on black-white differences in blood pressure related to blood lead (Sorel et al., 1991). There were 473 blacks and 3,627 whites in the study, each nearly evenly divided by sex, aged 18 to 74 years. As is usual in U.S.-based studies, race/ethnicity was based on self-report. Survey design-adjusted multiple regression models were stratified on sex and included age, BMI, and linear blood lead as covariates. The effect of race and poverty index was assessed by including their terms in models with and without blood lead and determining change in race or poverty coefficients by comparing confidence intervals. Each 1 μg/dL increase in linear blood lead significantly predicted increased systolic blood pressure for both males (2.23 mm Hg [95% CI: 0.69, 3.61]), but not females (0.98 mm Hg [95% CI: −9.78, 3.06]) for each doubling of blood lead. The differences in black and white (race variable) blood pressure coefficients did not significantly change when lead was in or out of the model, either for subjects below the poverty index or above the poverty index. Race does not appear to significantly modify the relationship between blood lead and systolic blood pressure. The paper reported no model diagnostics. There were reporting inconsistencies in the female-stratified models, in which the coefficients and 95% CI did not correspond.

NHANES III (1988-1994)

A study using the NHANES III dataset from all adults 20 years of age and up examined the effect of natural log blood lead on systolic and diastolic blood pressure (Den Hond et al., 2002). Multiple regression analyses for each blood pressure measurement were stratified by sex and race, yielding four models for each blood pressure measurement. The mean blood levels were 3.6 μg/dL in white males (n = 4,685), 2.1 μg/dL in white females (n = 5,138), 4.2 μg/dL in black males (n = 1,761), and 2.3 μg/dL in black females (n = 2, 197). One group of covariates (age, age-squared, BMI, hematocrit, smoking, alcohol consumption, and an indicator variable for use of antihypertensive medications) were first entered as a block regardless of significance in each model, then another group of variables (coffee consumption, dietary calcium, dietary sodium/potassium ratio, total serum protein, total serum calcium, diabetes, and poverty index) was entered stepwise in the model without lead and the variable retained only if it was statistically significant ($p < 0.05$). Then log-transformed blood lead was forced into each model.

The model building procedure resulted in eight distinct models, each with their own unique mix of covariates. No model diagnostics were reported, nor was adjustment of results by survey sample weights and design. Only blacks had significant lead-systolic blood pressure associations; each doubling in blood lead was associated with a 0.90 mm Hg (95% CI: 0.04, 1.8) and 1.20 mm Hg (95% CI: 0.4, 2.0) increase in males and females respectively. The association of lead-diastolic blood pressure was also significant for black females (0.50 mm Hg [95% CI: 0.01, 1.1]). Interestingly, increasing blood lead was associated with significantly decreased diastolic blood pressure in white males (−0.6 mm Hg [95% CI: −0.9, −0.3]). The authors did not comment on their finding that the significant total serum calcium covariate in these two groups had opposite signs too (white male serum calcium $\beta = 6.50$ mm Hg/mmol/L, black female serum calcium $\beta = -5.58$ mm Hg/mmol/L). Though the authors offered no formal test of the difference between the two serum calcium coefficients, since both were significantly different than the null hypothesis coefficient of 0 and different in sign, it could be concluded that those coefficients were significantly different between the two groups. As the authors do not present the serum calcium coefficients before forcing lead into the models, it is not certain that blood lead in the model was associated with the significant sign difference of the calcium coefficients or if the calcium coefficients had opposite signs between the two groups without lead in the model. As each model had a different set of covariates, the presence or absence of one of the other covariates could have produced the same results. Nevertheless, this pattern of results may indicate significant confounding between serum calcium and blood lead associations with blood pressure. Though the study suggested differences between blacks and whites in response to lead, no statistical tests were performed of differences in lead coefficients based on race. In addition, the black-white effect differences associated with blood lead may be due to possible confounding in some or all of the models.

Limiting the study sample from NHANES III to women aged 40 to 59 years, another group of researchers addressed the relationship between blood lead and both blood pressure (n = 1,786) and hypertension (n = 2,165) (Nash et al., 2003). Blood pressure models excluded women who reported being under treatment for hypertension. Separate blood pressure multiple regression models were presented for diastolic and systolic blood pressure, each with and without stratification for dichotomous premenopausal/postmenopausal status. One block of covariates was entered without regard to statistical significance (age, race/ethnicity, BMI, and

serum creatinine). Another block of covariates (education, poverty income ratio, alcohol use, and cigarette smoking status) was entered second but only retained if variables were significantly associated with blood pressure. Finally, linear blood lead was forced in last. Logistic regression models for hypertension used the same covariate entry scheme with and without stratification on the menopause variable, but using a blood lead quartile exposure variable. Despite the stated procedure for covariate selection, all models used the same set of covariates: linear (or quartile) lead, age, race/ethnicity, alcohol use, cigarette smoking status, BMI, and serum creatinine. All models were adjusted for survey weights and design. Linear lead was significantly associated with systolic blood pressure only in the entire study sample; each 1 μg/dL increase in blood lead was associated with a 0.32 mm Hg (95% CI: 0.01, 0.63) increase in blood pressure. No associations were observed in the menopause-stratified analyses. Linear lead also was significantly associated with diastolic blood pressure in the entire study sample (0.25 mm Hg [95% CI: 0.07, 0.43]). Odd ratios of diastolic hypertension (>90 mm Hg) in logistic regression models was significantly related to blood lead with an odds ratio of 4.26 (95% CI: 1.36, 12.99) comparing the 1st quartile blood lead group (0.5-1.6 μg/dL) to the 4th quartile blood lead group (4.0-31.1 μg/dL) in all women not taking antihypertensive medications. Further stratification produced occasional significant odds ratios for either diastolic or systolic hypertension. There were some differences in table and text reporting of results and an inconsistency between the SE and the p-values.

Another study using the NHANES III database was notable for its formal testing of race and sex differences in lead effect by interactions terms (Vupputuri et al., 2003). The study used 5,360 white men (mean blood lead 4.4 μg/dL), 2,104 black men (mean blood lead 5.4 μg/dL), 5,188 white women (mean blood lead 3.0 μg/dL), and 2,300 black women (mean blood lead 3.4 μg/dL). Multiple linear and logistic regression models of blood pressure and hypertension (systolic ≥140 mm Hg, diastolic ≥90 mm Hg, and/or taking antihypertensive medication), respectively, were adjusted for age, high school education, BMI, alcohol, leisure-time physical activity, and dietary intake of sodium, potassium, and total energy. The models used linear lead, except for one set of hypertension models with a cut point for "high" lead exposure at ≥5 μg/dL. Subjects taking antihypertensive medication (n = 2,496) were not included in linear regression models of blood pressure. Neither age nor blood lead range were reported, nor was the technique of selecting and entering covariates in multiple regression models. Only coefficients for linear

lead effect for each model were reported. Significant interactions in multivariate models were found between lead and race and between lead and sex, though these analyses were not shown. Only black men and women had significant linear lead-blood pressure effects in adjusted systolic (0.25 mm Hg [95% CI: 0.06, 0.44] for black men and 0.47 mm Hg [95% CI: 0.14, 0.80] for black women with each 1 μg/dL increase in blood lead) and diastolic blood pressure (0.19 mm Hg [95% CI: 0.02, 0.36] for black men and 0.32 mm Hg [95% CI: 0.11, 0.54] for black women). Linear blood lead association with hypertension was significant only in women. The odds ratios were 1.09 (95% CI: 1.04, 1.13) for white women and 1.10 (95% CI: 1.06, 1.16) for black women for each 1 μg/dL increase in blood lead. The authors presented insufficient detail to evaluate this pattern of results. The use of diagnostic testing was not mentioned.

European Population Studies

The Health Survey for England 1995 examined a representative sample of the English population living in private households and provided up to 2,563 men and 2,763 women with a mean age of 47.6 years in a study of blood lead-blood pressure relationships (Bost et al., 1999). Precise blood lead range was not given but was at least from less than 1.5 μg/dL to greater than 8.5 μg/dL. The study used stepwise multiple regressions modeling of diastolic and systolic blood pressure stratified by sex, with and without adjustment for alcohol, and with and without subjects on antihypertensive medications. Candidate covariates, selected from a larger pool, included age, alcohol use (heavy drinkers versus all other drinkers and nondrinkers), SES (manual classes versus non-manual classes), location of residence in country (northern resident versus non-northern resident), smoking, and common log blood lead. As nonsignificant variables did not remain in the models, each model contained a unique mix of covariates. A doubling in blood lead in men was associated with an increase in diastolic blood pressure of 1.07 mm Hg (95% CI: 0.37, 1.78) when alcohol consumption was not in the model and 0.88 mm Hg (95% CI: 0.13, 1.63) when alcohol consumption was in the model. Women had a significant response to lead only for diastolic blood pressure in the model without adjustment for alcohol and with subjects using antihypertensive medication. There were no significant effects of lead on systolic blood pressure in any model. The authors provided no statistical justification for stratified modeling nor did they test for significant differences in lead coefficients as a result of the stratification.

U.S. Cohort Studies

The Boston-based Normative Aging Study, part of a longitudinal study of male veterans, examined the effects of blood lead on blood pressure in 798 men, aged 45-93 years old, with blood lead between 0.5 and 35.0 µg/dL (Proctor et al., 1996). Using multiple regression modeling with forced entry of natural log lead and other covariates (age, age^2, BMI, dietary calcium, exercise, smoking, alcohol, heart rate, and hematocrit), the authors found a significant increase of only diastolic blood pressure (0.83 mm Hg [95% CI: 0.08, 1.52]) for each doubling of blood lead. Though the relationship between blood lead and systolic blood pressure was positive, it was not significant. Nearly half the blood lead measures were derived from frozen red blood cells collected previously (up to several years earlier) and corrected for hematocrit determined at the time blood pressure was measured. Possible errors in correction of these samples and the non-contemporaneous nature of the resulting blood lead concentrations may have compromised the results.

Cheng et al. (2001), using the same Normative Aging Study data and stepwise multiple regression, found a near-zero association between systolic blood pressure and linear blood lead (−0.03 mm Hg for each µg/dL increase in blood lead) in 519 men aged 48 to 93. The subjects selected for this analysis were all free of hypertension (systolic>160 mm Hg or diastolic>95 mm Hg). Differences in subject selection procedures and modeling techniques may have accounted in the different results between Cheng et al. and Proctor et al. They also reported on incidence of hypertension developing between 1991 and 1997 using Cox proportional hazards models. Controlling for age, age^2, BMI, and family history of hypertension, linear blood lead was not significantly associated with risk of developing hypertension (systolic >140 mm Hg or diastolic >90 mm Hg) in normotensives at the start of the period (rate ratio of 0.98 [95% CI: 0.91, 1.06]) for each 1 µg/dL increase in blood lead.

Gerr et al. (2002) similarly reported near-zero linear blood lead effects on blood pressure on a combined group of 19-29 year old males and females (n = 502), half of whom had lived around active lead smelters as children, using forced entry of all covariates. Among the covariates forced into the model was tibia lead concentration, expected to be significantly correlated with blood lead. This may have reduced or confounded the effects of blood lead.

Korrick et al. (1999) examined linear and natural log blood lead effect on hypertension, defined as self-reported or physician diagnosis of hypertension or systolic or diastolic

≥140/90 mm Hg, in 284 middle-aged women from the Nurse Health Study based in Boston. The association of hypertension and blood lead was nonsignificant.

Rothenberg et al. (1999) tested a group of 1,527 women, aged 15 to 42 years, in their third trimester of pregnancy, with blood lead ranging from 0.5 to 40.4 μg/dL. They stratified testing into immigrant (n = 1,188) and nonimmigrant (n = 439) groups. They used forced entry of all covariates in multiple regression models, including natural log lead, age, BMI, coffee, iron supplement, and job stress, and found lead-related significant increases in systolic (1.18 mm Hg [95% CI: 0.45, 1.91] for each doubling of blood lead) and diastolic (1.02 mm Hg [95% CI: 0.37, 1.34]) blood pressure only in immigrants. The small size of the nonimmigrant group may have reduced power to detect significant effects. In a follow-up of 668 women returning for postpartum testing (Rothenberg, et al., 2002), using multiple regression models with forced entry of natural log blood lead, tibia and calcaneus lead, age, BMI, parity, smoking, immigrant status, and education, the authors found a significant decreases in systolic (−1.05 mm Hg [95% CI: −1.96, −0.14]) and diastolic (−1.16 mm Hg [95% CI: −1.98, −0.35]) blood pressure associated with doubling in blood lead in the postpartum women. This subgroup of women had no significant blood lead effects in the third trimester. Although the covariate pattern was different from the larger prenatal study (Rothenberg et al., 1999), thorough testing of possible confounding, especially with the bone lead measures, revealed no significant change in blood lead effects. This study finding is similar to that reported by Den Hond et al. (2002) for white males. No significant effect of blood lead on prenatal or postpartum hypertension (≥140/90 mm Hg) was found.

Morris et al. (1990) recruited a group of 105 women and 145 men, aged 18-80 years, from a clinic specializing in non-drug hypertension treatment. Blood lead ranged from 5-40.5 μg/dL. Multiple regression was performed with forced entry of natural log lead, age, BMI, dietary calcium, "other nutrients," serum ionized calcium, and erythrocyte protoporphyrin. Only men were found to have lead-related significant increases in systolic (3.17 mm Hg [95% CI: −2.13, 8.48] for each doubling of blood lead) and diastolic (1.32 mm Hg [95% CI: −2.12, 4.75]) blood pressure. Small study size limits conclusions based on nonsignificant findings in women. Dietary calcium is associated with reduced blood lead in many studies and could be considered a confounder with blood lead. Erythrocyte protoporphyrin is a biomarker of lead exposure and correlates with blood lead over at least part of the blood range in study subjects. There was the

inclusion of at least two collinear variables, a high proportion of covariates to subjects, and possible subject selection bias.

European Cohort Studies

The Glostrup Population Study (Copenhagen) studied 1,009 men and women (all born in 1936) longitudinally from 1976 to 1987 (Møller and Kristensen, 1992). Blood lead ranged from 2 to 62 µg/dL, depending on the year and sex stratum studied, with mean concentration dropping by ~40% over the study period. They used multiple regression with forced entry of natural log lead, BMI, tobacco use, and physical activity. Strongest associations between a doubling of blood lead and blood pressure were found early in the study period. In 1976, a doubling of blood lead was associated with 3.42 mm Hg (95% CI: 1.25, 5.58) increase in systolic blood pressure and 2.95 mm Hg (95% CI: 1.08, 4.83) increase in diastolic blood pressure in women. For men in 1981, a doubling of blood lead was associated with an increase of 1.89 mm Hg (95% CI: 0.00, 3.78) in systolic blood pressure and 1.14 mm Hg (95% CI: −0.37, 2.65) in diastolic blood pressure. No formal longitudinal analyses were performed, only analyses stratified by year and sex and analyses relating change in lead and other covariates to change in blood pressure from one study period to the next. As the relative risk of mortality was associated with increasing blood lead over the study period (see below), the general reduction in lead-associated blood pressure increase over the study period may have been masked by lead-associated mortality.

The Europe New Risk Factor Project in Rome collected data from 1,319 males aged 55-75 years with blood lead between 4.0 and 44.2 µg/dL (Menditto et al., 1994). They reported significantly increased systolic (4.71 mm Hg [95% CI: 2.81, 6.61]) and diastolic (1.25 mm Hg [95% CI: 0.33, 2.16]) blood pressure associated with a doubling of blood lead.

The Cadmibel studies from Belgium specifically selected part of their study group from those living near nonferrous smelters. Staessen et al. (1993) reported on 827 men and 821 women, aged 20 to 88 years, with blood lead ranging from 2.7 to 84.9 µg/dL for men and 1.3 to 42.4 µg/dL for women. They forced natural log blood lead into stepwise multiple regression models stratified by sex. Covariates available for selection were age, age^2, BMI, pulse rate, log gamma-glutamlytranspeptidase, serum total calcium, log serum creatinine, urinary potassium, smoking, alcohol, contraceptive use, and menopause. Near-zero nonsignificant relationships were found between blood lead and blood pressure for systolic blood pressure for

women and diastolic blood pressure for men and women. They reported a significant decrease in men's systolic blood pressure with increasing blood lead (−1.1 mm Hg for a doubling of blood lead), similar to the relationship found by Den Hond et al. (2002) for white men and by Rothenberg et al. (2002) for postpartum women. Stepwise regression results in different covariate patterns for each stratum and capitalizes on chance significance due to repeated testing.

A follow-up of the Cadmibel study, the PheeCad study, evaluated 359 men and 369 women, aged 20 to 82 years (Staessen et al., 1996). Fifty-nine percent of the men had occupational exposure. They were measured two times, at baseline and at follow-up about 5 years later. Women's mean blood lead at baseline and follow-up was 6.6 µg/dL (range 3.3-24.50 and 4.8 µg/dL (range 1.7-11.8). Men's mean blood lead at baseline and follow-up was 11.4 µg/dL (range 5.6-28.8) and 7.7 µg/dL (range 3.7-20.1). Multiple regression models were stratified on sex and in women on menopausal status. Time-integrated blood pressure measurements were used. Each doubling of blood log lead was significantly associated with a 5.19 mm Hg (95% CI: 1.05, 9.34) increase in diastolic blood pressure in 187 pre- and perimenopausal women. None of the other strata showed significant blood lead-related effects. Using 24-h ambulatory blood pressure readings during the follow-up showed significant associations between natural log blood lead and diastolic blood pressure in the group of all 345 women (2.42 mm Hg [95% CI: 0.00, 4.84]). There were no significant lead effects on systolic blood pressure in women or all blood pressure in men. Change in blood pressure and change in covariates between baseline and follow-up were used to assess the effect of change of blood lead in longitudinal analyses, similar to Møller and Kristensen (1992) above.
No significant effects of change in blood lead on change in blood pressure were found. Due to stratification and resulting small groups, there may have been reduced power to detect significant effects of lead.

U.S. Occupational Studies

Glenn et al. (2003) was one of the few studies to use a prospective design and was the only study using statistical techniques designed for repeated measures. They studied 496 male workers from New Jersey with former organolead exposure. Using generalized estimating equations with baseline linear blood lead, age, BMI, antihypertensive medication, smoking, education, measurement technician, and number of years to follow-up measurement of blood

pressure (range 10 months-3.5 years), they found that every 1 μg/dL increase in baseline blood lead was associated with 1.13 mm Hg/year (95% CI: 0.25, 2.02) increase in blood pressure over the observation period.

Schwartz et al. (2000b) reported significant blood lead associations with 543 male former organolead workers. Stepwise backward multiple regression showed an increase of 2.3 mm Hg in systolic blood pressure for each doubling in blood lead. The association with diastolic blood pressure was not significant.

Sharp et al. (1990) studied 132 black bus drivers (blood lead range 3.1-20.9 μg/dL) and 117 nonblack bus drivers (blood lead range 2.0-14.7 μg/dL) in San Francisco, aged 30 to 60 years. They used natural log blood lead in multiple regression models and found for each doubling of blood lead an increase of 5.22 mm Hg (95% CI: 0.60, 9.84) in systolic blood pressure among blacks, 3.27 mm Hg (95% CI: 0.10, 6.44) in diastolic blood pressure among blacks, and −3.96 mm Hg (95% CI: −8.32, 0.42) in systolic blood pressure among nonblacks.

Sokas et al. (1997) reported a possible race interaction ($p = 0.09$) on systolic blood pressure with linear blood lead in 264 construction workers aged 18-79 years. Each 1 μg/dL increase in blood lead increased systolic blood pressure in blacks by 0.86 mm Hg more than in whites. Neither the black or white lead coefficients were significant.

European Occupational Studies

Maheswaran et al. (1993) reported on 809 male factory workers with blood lead between less than 21 to more than 50 μg/dL from Birmingham, England. Unfortunately, the inclusion of factors that were related to blood lead, including additional direct measure of lead exposure in addition to linear blood lead, years working in factory, and inclusion of zinc protoporphyrin, may have biased the blood lead effect and resulted in nonsignificant lead effects on blood pressure.

Telišman et al. (2004) also reported nonsignificant effects of natural log blood lead on blood pressure in 115 male industrial workers with blood lead between 9.9 and 69.9 μg/dL, but included erythrocyte protoporphyrin in models, a variable correlated with blood lead over much of the observed blood lead range. Coefficients were not given, as lead did not enter into stepwise regression models.

Asian Occupational Studies

Male and female factory workers (n = 798) from Chonan, Korea (blood lead between 17.8 and 64.8 µg/dL) were studied principally for the effects of genotype of ALAD and vitamin D receptor on cardiovascular response to lead (Lee et al., 2001). These aspects are covered more thoroughly below. As part of their work, the authors developed multiple regression models examining the effect of linear blood lead on blood pressure with forced entry of age and age^2, BMI, sex, antihypertensive medication, lifetime alcohol, and ALAD and vitamin D genotypes. A marginally significant effect of blood lead on systolic blood pressure (diastolic blood pressure not modeled) was noted, with a 10 µg/dL increase in blood lead associated with a 0.7 mm Hg (95% CI: −0.04, 1.4) increase in blood pressure.

Nomiyama et al. (2002) used a combined group of 193 female crystal glass workers and nonexposed controls, aged 16 to 58 years, with blood lead between 3.8 and 99.4 µg/dL. The authors used a stepwise multiple regression with a novel technique to reduce collinearity among covariates. From a large group of covariates, they selected covariates eligible to enter the regression from a factor analysis. Although the stepwise entry of these variables resulted in different models for systolic and diastolic blood pressure, both models included linear blood lead, age, urine protein, and plasma triglycerides. The diastolic model additionally included family hypertension and low density lipoprotein. Each 10 µg/dL increase in blood lead was significantly associated with a 1.26 mm Hg (95% CI: 0.58, 1.94) increase in systolic blood pressure and a 1.05 mm Hg (95% CI: 0.52, 1.57) in diastolic blood pressure. In alternative models with ordered categories of blood lead, systolic blood pressure was 7.5 mm Hg (95% CI: 3.0, 12.0) and diastolic blood pressure was 6.3 mm Hg (95% CI: 3.4, 9.1) higher in workers with blood lead ≥60 µg/dL than in controls with <11.4 µg/dL. Models did not control for BMI.

Wu et al. (1996) examined the effect of ordered blood lead category on blood pressure of 112 male (aged 18-67 years) and 110 female (aged 18-71 years) lead battery factory workers in multiple regression models. Blood lead ranged from 8.3 to 95.4 µg/dL. Nonsignificant blood lead effects were found possibly due to the inclusion of two additional lead exposure measurements, ambient air lead and work history, likely leading to substantial collinearity with blood lead.

Meta-Analysis of Blood Lead-Blood Pressure Studies

The most recent meta-analysis of the blood lead-blood pressure literature analyzed 31 studies from a large pool of studies published up to 2001 (Nawrot et al., 2002). Two other meta-analyses were also published during this reporting period (Schwartz, 1995; Staessen et al., 1994), covering many of the earlier papers cited in Nawrot et al. (2002), and derived similar coefficients for the lead effect, so they will not be reviewed here. The meta-analysis authors selected studies with 50 or more subjects, with subjects 10 years of age and up, with blood pressure and blood lead measurement techniques presented in sufficient detail to estimate effect sizes, and with preference given to papers with models adjusting for age, BMI, and "additional factors of proven importance." Where possible, studies with stratified analyses based on sex and race were entered in the meta-analysis as separate subgroups. Studies were weighted by the number of subjects to arrive at estimates and CIs for lead effect on diastolic and systolic blood pressure. Nearly half the studies reported lead effects from linear lead terms, the remainder from log-transformed lead. To include both types of studies in the analyses, the authors reported effect sizes based on doubling the mean blood lead concentration. For models using logarithmic blood lead, this doubling has the same effect anywhere in the range of blood lead in the study. For models using linear blood lead, the doubling effect was referenced from the mean blood lead reported. Figures 6-5.1 and 6-5.2 depict the effect estimates for systolic and diastolic blood pressure, respectively, included in the meta-analysis from Nawrot et al. (2002). Ninety-five percent CIs overlapped for males and females and for blacks and whites, indicating no significant differences in lead effect by gender or race. In the group of studies as a whole, the combined meta-analysis coefficients for each doubling of blood lead were highly significant for both systolic (1.0 mm Hg [95% CI: 0.5, 1.4]) and diastolic (0.6 mm Hg [95% CI: 0.4, 0.8]) blood pressure. The meta-analysis supports the statistical association between increased blood lead and increased blood pressure over a wide range of populations in many studies. Two major systematic reviews of the lead-blood pressure literature were published during this review period (Hertz-Picciotto and Croft, 1993; Research Triangle Institute, 1999). The findings here, especially noting the significant effects from the meta-analysis (Nawrot et al., 2002), continue to support the significant association between blood lead and blood pressure/hypertension in diverse segments of the general population.

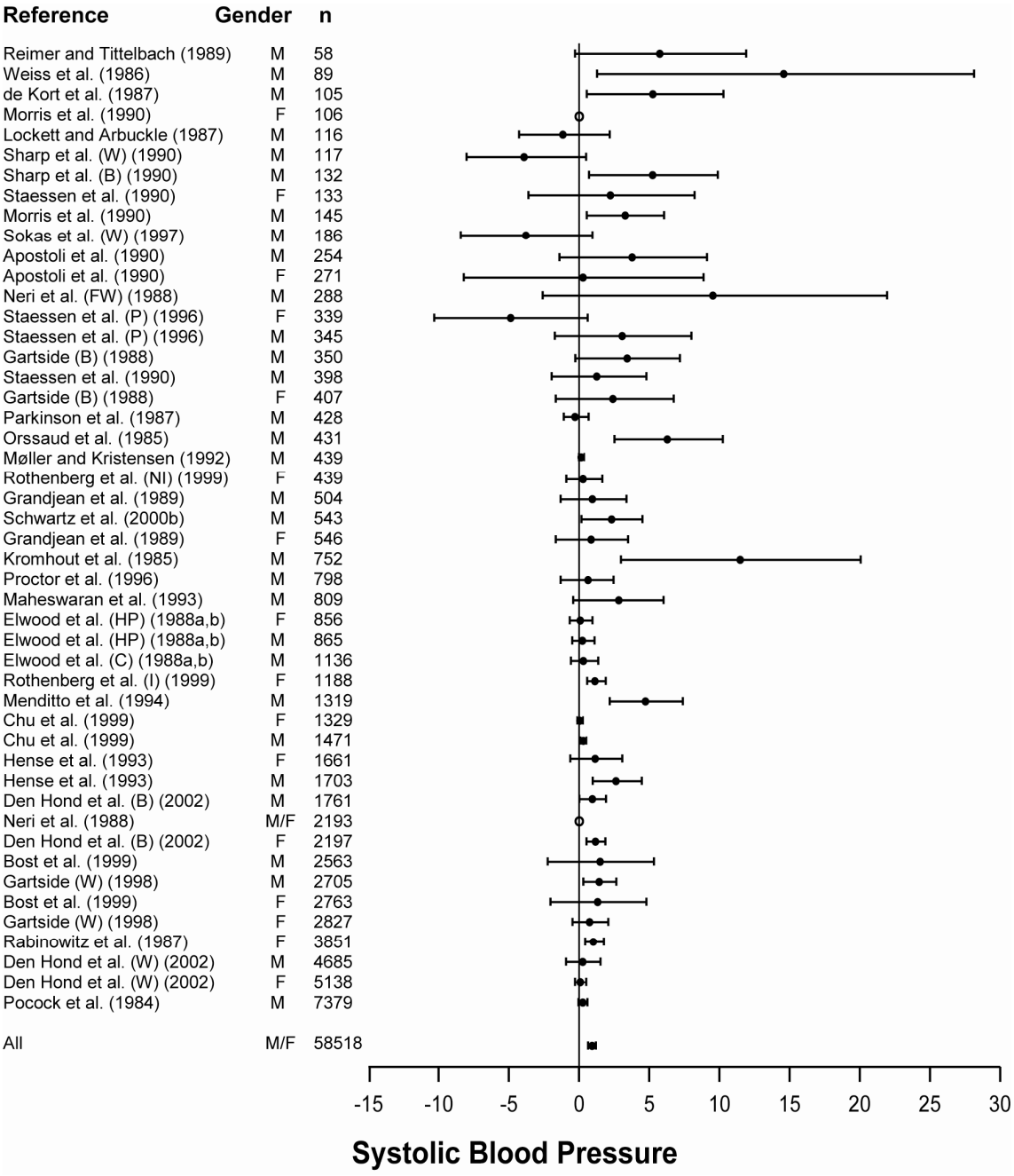


Figure 6-5.1. Change in the systolic pressure (effect estimate in mm Hg) associated with a doubling of the blood lead concentration. Studies arranged vertically by increasing study size.

Study key: C = Caerphilly Study, HP = Welsh Heart Program, P = PheeCad Study, W = whites, B = blacks, NI = nonimmigrants, I = immigrants, FW = foundry workers, CS = civil servants.

Source: Nawrot et al. (2002).

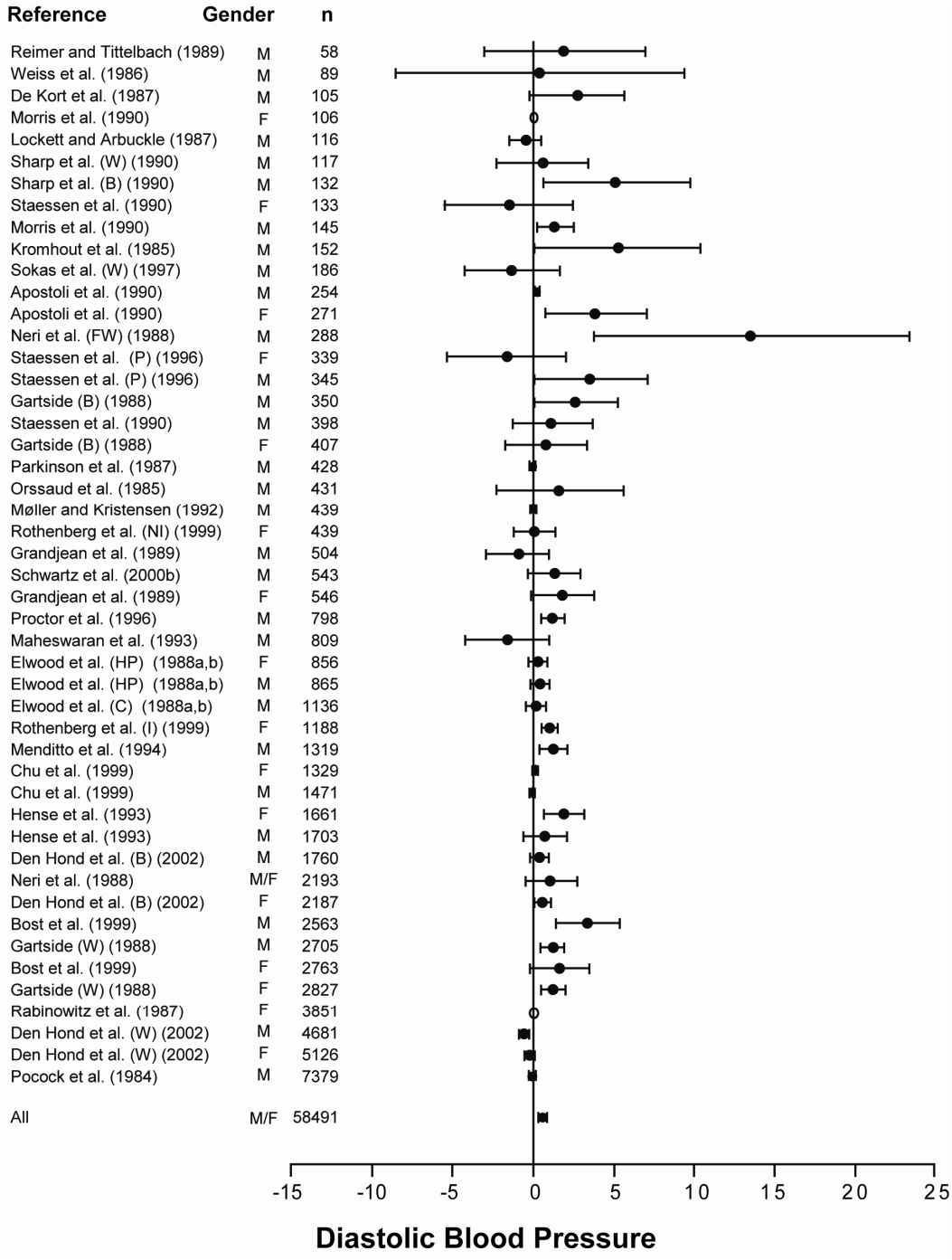


Figure 6-5.2. Change in the diastolic pressure (effect estimate in mm Hg) associated with a doubling of the blood lead concentration. Studies arranged vertically by increasing study size.

Study key: C = Caerphilly Study, HP = Welsh Heart Program, P = PheeCad Study, W = whites, B = blacks, NI = nonimmigrants, I = immigrants, FW = foundry workers, CS = civil servants.

Source: Nawrot et al. (2002).

Quantitative estimates for the effect of doubling the mean blood lead concentration on systolic and diastolic blood pressure from the various studies discussed here are summarized in Tables 6-5.1 and 6-5.2. Results from these individual studies also generally appear to agree with the results of the meta-analysis by Nawrot et al. that increased blood lead levels are significantly associated with increased systolic and diastolic blood pressure. Figures 6-5.1 and 6-5.2 graphically depict the results of many of the studies discussed. The effect estimates in the figures also reflect the effect of doubling blood lead on blood pressure. Most of the effects are based on concurrent blood lead. Effects for the entire study population are presented unless only effects in subsamples are reported. Other selection criteria used in a few instances were subjective.

A Bayesian meta-analysis was performed to examine the use of log-linear and linear blood lead in blood pressure regression models (Figure 6-5.3). A significant blood lead effect on systolic pressure was observed using both log-linear and linear blood lead. Heterogeneity also was significant for both log-linear lead ($p = 0.0002$) and linear lead ($p = 0.05$). The source of heterogeneity could be due to several factors, including different methods of statistical analysis, different study protocols, and subject selection differences. The log-linear and linear lead effects were 0.62 mm Hg (95% CI: 0.12, 1.11) and 0.98 mm Hg (95% CI: 0.51, 1.45), respectively, for systolic blood pressure. The difference between the effect estimates from using log-linear or linear lead was nonsignificant. This meta-analysis suggests there are significant differences between the studies, but overall there is a combined effect of blood lead on systolic blood pressure. The fact that several individual studies did not detect a significant effect may be due to small study size or other factors affecting effect measurement precision.

6.5.2.3 Blood Pressure and Hypertension Studies Using Bone Lead as Exposure Index

Korrick et al. (1999) used a case-control design to study the relationship between hypertension and three measures of lead exposure (blood lead, tibia [cortical bone] lead, and patella [trabecular bone] lead in women. The final study sample consisted of 89 hypertension cases and 195 controls, excluding those with history of hypertension, cardiovascular disease, renal disease, diabetes, or malignancy, use of antihypertensive medications, BMI $\geq$29, and incomplete data, aged from 47 to 74 years. Cases were selected through a randomization procedure that produced approximately equal numbers of cases for each of three blood pressure

Table 6-5.1. Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Linear Lead (Coefficients Represent Effect of Doubling Blood Lead Calculated from Mean Blood Lead or Mid-point of Range)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)[d] or (IQR)[e] [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
POPULATION OR COMMUNITY STUDIES										
Cheng et al. (2001) Boston, U.S. Normative Aging Study 1991-1997	Males (519) [mean age = 66.4]	5.9[a] (3.9)[d] [range not given]	Multiple linear regression forced entry of linear lead, age, age^2, BMI, family hypertension, smoking, alcohol, dietary calcium.	Not stated	Not applicable	Alcohol, smoking, age, dietary calcium	−0.2 (−2.0, 1.6) [0.92]	Not tested	Not tested	—
Hu et al. (1996)	—	—	Almost completely overlapping with Cheng et al. (2001).	—	—	—	—	—	—	—
Gerr et al. (2002) Eastern Washington, Western Idaho, U.S. 1994	Females and Males (502) [19-29]	2.2[a] (1.9)[d] [<1->7]	Linear multiple regression with forced entry of linear blood lead, tibia lead, age, BMI, sex, education, birth control pills, smoking, height, hemoglobin, serum albumin, childhood residence, income, alcohol.	Not stated	Not applicable	Age, tibia lead, smoking, alcohol, hemoglobin	0.0 (−1.1, 1.1) [0.57]	Not applicable	Age, tibia lead, smoking, alcohol, hemoglobin	−0.3 (−2.8, 1.6) [0.48]
Nash et al. (2003) U.S.-NHANES III 1988-1994	Females (1,786) [40-59]	2.9[a] (not stated)[d] [0.5-31.1]	Multiple linear regression (survey weighted), excluding treated hypertensives, with forced entry of linear lead, age, BMI, race/ethnicity, serum creatinine. Education, poverty, alcohol, smoking among variables for stepwise entry.	Not stated	Not applicable	Alcohol, smoking, age	0.9 (0.0, 1.8) [0.46]	Not applicable	Alcohol, smoking, age	0.7 (0.2, 1.2) [0.26]

Table 6-5.1 (cont'd). Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Linear Lead (Coefficients Represent Effect of Doubling Blood Lead Calculated from Mean Blood Lead or Mid-point of Range)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)d or (IQR)e [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
POPULATION OR COMMUNITY STUDIES (cont'd)										
Vupputuri et al. (2003) NHANES III, U.S.	Black female (2,300) [≥18-?]	3.4[a] (3.3)[d] [not stated]	Multiple linear regression (not survey corrected) with forced entry of all variables: linear lead, age, BMI, education, alcohol, physical activity, dietary Na, K, and calories.	Not stated	Not applicable	Age, alcohol	1.6 (0.5, 2.7) [0.82]	Not applicable	Age, alcohol	1.1 (0.4, 1.8) [0.36]
	Black male (2,104) [≥18-?]	5.4[a] (3.3)[d] [not stated]					1.3 (0.3, 2.4) [0.54]			1.0 (0.1, 2.0) [0.48]
	White female (5,188) [≥18-?]	3.0[a] (3.3)[d] [not stated]					0.3 (−0.4, 1.1) [0.38]			0.0 (−0.5, 0.4) [0.22]
	White male (5,360) ([≥18-?]	4.4[a] (3.3)[d] [not stated]					0.4 (−1.0, 1.8) [0.72]			0.0 (−0.5, 0.5) [0.27]
Sorel et al. (1991) NHANES II, U.S. 1976-1980	Female (2,056) [18-74]	13.2[a] (not stated) [not stated]	Multiple linear regression (survey corrected) with forced entry of linear lead, age, BMI.	Not stated	Not applicable	Age	Errors in original article	Not applicable	Age	Errors in original article
	Male (2,044) [18-74]	20.1[a] (not stated) [not stated]					1.7 (−0.6, 3.8) [0.56]			2.6 (0.8, 4.2) [0.87]

Table 6-5.1 (cont'd). Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Linear Lead (Coefficients Represent Effect of Doubling Blood Lead Calculated from Mean Blood Lead or Mid-point of Range)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)[d] or (IQR)[e] [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
POPULATION OR COMMUNITY STUDIES (cont'd)										
Hense et al. (1994) Augsberg, Denmark 1987-1988	Female (no alcohol) (701) [28-67]	Not stated (not stated) [<3->8]	Multiple linear regression with forced entry of linear lead, age, BMI, hematocrit, residence, smoking in women. In men, analyses were stratified by place of residence.	Not stated	Not applicable	Age, smoking, hematocrit	0.4 (−2.6, 3.4) [1.53]	Not applicable	Age, smoking, hematocrit	1.2 (−0.8, 3.1) [0.99]
	Female (<40 g/day) (877) [28-67]	Not stated (not stated) [<3->10]					0.7 (−1.5, 2.9) [1.12]			1.5 (0.1, 2.9) [0.71]
	Female (≥40 g/day) (83) [28-67]	Not stated (not stated) [<3->14]					11.0 (3.8, 18.3) [3.64]			7.3 (2.8, 11.8) [1.36]
	Male, urban (118) [28-67]	Not stated (not stated) [not stated]	No blood lead values shown; thus, there are no coefficients calculated and shown				—			—
	Male, rural (no alcohol) (147) [28-67]	Not stated (not stated) [<5->11]	Multiple linear regression with forced entry of linear lead, age, BMI, hematocrit, residence, smoking in women. In men, analyses were stratified by place of residence.	Not stated	Not applicable	Age, smoking, hematocrit	2.8 (−2.4, 8.0) [2.63]	Not applicable	Age, smoking, hematocrit	0.2 (−3.3, 3.8) [1.80]
	Male, rural (<40 g/day) (463) [28-67]	Not stated (not stated) [<6->12]					5.8 (1.9, 9.8) [2.01]			3.5 (0.8, 6.2) [1.37]
	Male, rural (≥40 g/day) (356) [28-67]	Not stated (not stated) [<7->15]					5.0 (0.6, 10.9) [2.87]			3.3 (0.3, 6.3) [1.53]

Table 6-5.1 (cont'd). Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Linear Lead (Coefficients Represent Effect of Doubling Blood Lead Calculated from Mean Blood Lead or Mid-point of Range)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)[d] or (IQR)[e] [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
OCCUPATIONAL STUDIES										
Glenn et al. (2003) New Jersey, U.S. 1994-1998	Males, former organolead workers	—	Only measured change in blood pressure over a period ranging from 10 months to 5 years. Design not commensurate with other studies in this table. See Glenn (2001), below.	—	—	—	—	—	—	—
Glenn et al. (2001) New Jersey, U.S. 1996-1997	Males, former organolead workers (213) [mean age = 58.0]	5.2[a] (3.1)[d] [not stated]	Subset of Schwartz (2000), see below.	—	—	—	—	—	—	—
Schwartz et al. (2000b) New Jersey, U.S. 1996-1997	Males, former organolead workers (543) [41.7-73.3]	4.6[a] (2.6)[d] [1-20]	Multiple backward elimination stepwise linear regression models. Pool of available covariates not specified.	Not stated	Age, BMI, smoking, antihypertensive medications	Age, smoking	2.3 (0.2, 4.4) [1.15]	Age, BMI, smoking, antihypertensive medications	Age, smoking	1.3 (−0.3, 2.9) [0.86]
Sokas et al. (1997) Maryland U.S. 1989-1990	Male, construction workers (264) [18-79]	8.0[a] (not given) [2-30]	Multiple linear regression, presumably with forced entry (not stated). Covariates available for entry not stated. Insufficient information given for separate black and white blood pressure effects on blood pressure.	Not stated	Linear lead, BMI, age, hematocrit, erythrocyte protoporphyrin, race, race by lead interaction	Age, hematocrit, erythrocyte protoporphyrin	Not given here, as coefficient was altered by presence of race-lead interaction	Linear lead, BMI, age, hematocrit, erythrocyte protoporphyrin, race, race by lead interaction	Age, hematocrit, erythrocyte protoporphyrin	Not given here, as coefficient was altered by the race-lead interaction

Table 6-5.1 (cont'd). Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Linear Lead (Coefficients Represent Effect of Doubling Blood Lead Calculated from Mean Blood Lead or Mid-point of Range)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)[d] or (IQR)[e] [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
OCCUPATIONAL STUDIES (cont'd)										
Maheswaran et al. (1993) Birmingham Europe Dates not given	Male factory workers (809) [mean age 43.3]	31.5[b] (5.5)[d] [<21->50]	Multiple linear regression, forced entry of age, BMI, alcohol, zinc protoporphyrin, years working, smoking, linear lead.	Not stated	Not applicable	Age, alcohol, zinc protoporphyrin, years working, smoking	2.2 (−0.9, 5.4) [1.60]	Not applicable	Age, alcohol, zinc protoporphyrin, years working, smoking	−1.3 (−3.5, 0.9) [1.12]
Lee et al. (2001) Chonan, Korea 1997-1999	Male and female lead-using factory workers (798) [17.8-64.8]	32.0[a] (15.0)[d] [4-86]	Multiple linear regression with forced entry of age, age^2, sex, BMI, antihypertensive medication, lifetime alcohol, ALAD and vitamin D receptor genotypes.	Not stated	Not applicable	Age, alcohol	2.2 (−0.1, 5.5) [1.18]	Not shown	Not shown	—
Lustberg et al. (2004) Chonan, Korea 1997-1999	Overlapping study with Lee (2001), above	—	Used deciles as lead variable.	—	—	—	—	—	—	—
Nomiyama et al. (2002) Beijing, China Dates not given	Female crystal toy makers and nonexposed sewing workers (193) [16-58]	37.6[a] (9.2)[d] [3.8-99.4]	Multiple linear regression with forward stepwise addition of variables ($p < 0.2$). Candidate variables were selected from a very large group and narrowed down to ten by factor analysis. The ten available for entry were not stated.	Not stated	Linear lead, age, urine protein, plasma triglyceride	Age	4.7 (2.0, 7.4) [1.35]	Linear lead, age, urine protein, plasma triglyceride, family hypertension, low density lipoprotein	Age	3.9 (1.9, 5.9) [1.04]
Wu et al. (1996) Central Taiwan Data collection dates not given	—	—	Ordered categories of lead used. Coefficients cannot be calculated.	—	—	—	—	—	—	—

Table 6-5.2. Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Logarithmic Lead (Coefficients Represent Effect of Doubling Blood Lead)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)[d] or (IQR)[e] [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
POPULATION OR COMMUNITY STUDIES										
Den Hond et al. (2002) NHANES III U.S. 1988-1994	Black males (1,761) [≥20]	4.2[c] (2.7, 6.5)[e] [<1.2->20.0]	Multiple linear regression (no adjustment for survey design): forced entry of log lead, age, age^2, BMI, hematocrit, smoking, alcohol, antihypertensive drugs. Forward stepwise entry ($p < 0.05$) among coffee, dietary calcium, dietary Na/Ca, serum total protein, serum total calcium, diabetes.	Not stated	Serum total protein	Alcohol, smoking, age	0.9 (0.04, 1.8) [0.43]	Coffee, dietary Na, diabetes, serum total protein,	Age, smoking, alcohol, dietary calcium	0.3 (−03, 1.0) [0.16]
	Black females (2,197) [≥20]	2.3[c] (1.4, 3.9)[e] [<0.8->9.0]			Dietary Na/Ca, serum total protein	Alcohol, smoking, age	1.2 (0.4, 2.0) [0.42]	Dietary Na/K, serum total protein, serum total calcium	Age, smoking, alcohol	0.5 (0.01, 1.1) [0.26]
	White males (4,685) [≥20]	3.6[c] (2.3, 5.3)[e] [<1.2->15.0]			Dietary calcium, dietary Na/Ca, serum total protein, serum total calcium	Alcohol, smoking, age, dietary calcium	0.3 (−0.2, 0.7) [0.23]	Dietary Na/Ca, serum total protein, serum total calcium, diabetes	Age, smoking, alcohol	−0.6 (−0.9, −0.3) [0.15]
	White females (5,138) [≥20]	2.1[c] (1.3, 3.4)[e] [<0.8->8.0]			Serum total protein, diabetes	Alcohol, smoking, age	0.1 (−0.4, 0.5) [0.32]	Dietary calcium, serum total protein, diabetes	Age, smoking, alcohol, dietary calcium	−0.2 (−0.5, 0.1) [0.14]
Morris et al. (1990) Oregon, U.S. 1984-1989	Females (106) [18-80]	6.9[a] (3.6)[d] [?-39]	Linear multiple regression with stepwise entry among ln lead, age, BMI, dietary calcium, "other nutrients," serum Ca^{2+}, erythrocyte protoporphyrin.	Not stated	Age, dietary calcium, BMI	Age, dietary calcium	Not stated	Age, dietary calcium, hemoglobin	Age, dietary calcium	Not stated
	Males (145) [18-80]	8.0[a] (4.4)[d] [5-40.5]			Age, ionized calcium	Age	3.2 (Not given)	Age, hemoglobin, smoking	Age, hemoglobin, smoking	1.3 (Not given)

Table 6-5.2 (cont'd). Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Logarithmic Lead (Coefficients Represent Effect of Doubling Blood Lead)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)[d] or (IQR)[e] [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
POPULATION OR COMMUNITY STUDIES (cont'd)										
Proctor et al. (1996) Normative Aging Study Boston, U.S. 1991-1993	Males (798) [45-93]	6.5a (4.0)d [0.5-35.0]	Multiple linear regression with forced entry of all variables: ln lead, age, age^2, BMI, dietary calcium, exercise, smoking, alcohol, heart rate, hematocrit.	Not stated	Not applicable	Alcohol, smoking, dietary calcium, age	0.6 (−0.8, 1.9) [0.69]	Not applicable	Alcohol, smoking, dietary calcium, age	0.8 (0.1, 1.5) [0.41]
Rothenberg et al. (1999) Los Angeles, U.S. 1995-1998	Pregnant women, immigrant (1,188) [>14-<44]	2.3b (1.3)d [0.5-40.4]	Multiple linear regression with forced entry of all variables: ln lead, age, BMI, coffee, iron supplement, job stress.	Residual analyses, outliers, heteroscedasticity	Not applicable	Age	1.2 (0.5, 1.9) [0.37]	Not applicable	Age	1.0 (0.4, 1.5) [0.28]
	Pregnant women, nonimmigrants (439) [>14-<44]	1.9b (+1.3, −0.8)[d] [not stated]				Age	0.3 (−1.1, 1.6) [0.67]		Age	0.1 (−1.3, 1.4) [0.67]
Rothenberg et al. (2002) Los Angeles, U.S. 1995-2001	Females third trimester (637) [15-43]	1.9b (+3.6, −1.0)[d] [not stated]	Multiple linear regression with forced entry of all variables: ln lead, age, BMI, education, immigrant status, smoking, alcohol, parity. Hypertensive subjects ≥140/90 mm Hg (third trimester or postpartum) were excluded.	Residual analyses, outliers, heteroscedasticity	Not applicable	Alcohol, smoking, age	0.0 (−0.9, 0.8) [0.43]	Not applicable	Alcohol, smoking, age	0.1 (−0.5, 0.8) [0.34]
	Females postpartum (637) [15-43]	2.3b (+4.2, −1.2)[d] [0.4-23.7)					−1.0 (−2.0, −0.1) [0.46]			−1.2 (−2.0, −0.3) [0.41]

Table 6-5.2 (cont'd). Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Logarithmic Lead (Coefficients Represent Effect of Doubling Blood Lead)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)[d] or (IQR)[e] [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
POPULATION OR COMMUNITY STUDIES (cont'd)										
Schwartz (1991) NHANES II U.S. 1976-1980	Females (<5,000) [20-74]	Not stated	Multiple linear regression with forced entry of ln lead, age, age^2, and BMI. Stepwise entry ($p < 0.05$) among race, cigarettes/day, tricep skinfold, family hypertension, exercise, ln serum Zn, dietary K and Na, serum cholesterol, height, and ln dietary vitamin C.	Not stated	No results presented	No results presented	No results presented	Race, zinc, family hypertension, tricep fold, cholesterol	Age	1.1 (0.2, 2.0) [0.48]
	Males (<5,000) [20-74]							Race, zinc, family hypertension, tricep fold, cholesterol, height, cigarettes	Age, cigarettes	2.0 (0.6, 3.4) [0.69]
Bost et al. (1999) Health Survey for England 1995	Females (2,763) [16-not given]	2.6[b] (not stated) [<1.5->8.5]	Multiple linear stepwise regression (forward or backward not stated), with possible entry of age, log BMI, log lead, alcohol, social class, place of residence, and smoking.	Not stated	Age, BMI, residency	Age	No results presented (nonsignificant)	Age, BMI, alcohol	Age, alcohol	No results presented ($p > 0.05$)
	Females (2,563) [16-not given]	3.7[b] (not stated) [<1.5->8.5]			Age, BMI, alcohol, social class	Age, alcohol	No results presented (nonsignificant)	Age, BMI, alcohol	Age, alcohol	0.9 (0.1, 1.6) [0.38]
Menditto et al. (1994) Rome, Europe New Risk Factor Project 1989-1990	Males (1,319) [55-75]	11.3[a] (not stated) [4.0-44.2]	Multiple linear regression with forward stepwise entry among ln lead, age, BMI, heart rate, lipids, triglycerides, glucose, smoking, alcohol, skinfold.	Not stated	BMI, heart rate, serum lipids, age, glucose, smoking, skinfold, triglycerides, skinfold	Smoking	3.9 no other measures given	BMI, heart rate, age, smoking, lipids, triglycerides	Smoking	1.2 no other measures given

Table 6-5.2 (cont'd). Systolic and Diastolic Blood Pressure and Blood Lead Modeled with Logarithmic Lead (Coefficients Represent Effect of Doubling Blood Lead)

Reference, Study Location, Period	Study Population, Sample Size (n), Age [years]	Blood Lead Mean[a], Geom. Mean[b], or Median[c] (SD)[d] or (IQR)[e] [range] µg/dL	Model Type and Variables Considered	Model Diagnostic	Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
					Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]	Unique Covariates	Lead-Associated Variables	Coefficient (95% CI) [SE]
OCCUPATIONAL STUDIES										
Sharp et al. (1990) San Francisco, U.S. 1986	Male bus drivers, black (132) [30.4-60.7]	6.5[b] (+2.7, −1.9)[d] [3.1-20.9]	Linear multiple regression analysis of unspecified type. All models presented here adjusted for ln lead, age, age^2, BMI, caffeine, smoking. Also examined effect of stratified caffeine modeling (not shown here as group sizes were less than 100), and effect of successive addition of covariates on lead coefficient, and including alcohol use (not shown).	Used influence diagnostics to identify two influential subjects. Analyses stratified by race showed maximum 10% change in lead coefficients without influential subjects. Data shown here includes all subjects.	Not applicable	Age, smoking	5.2 (0.6, 9.8) [2.3]	Not applicable	Age, smoking	3.3 (0.1, 6.4) [1.6]
	Male bus drivers, nonblack (117) [30.6-58.9]	6.2[b] (+2.7, −1.8)[d] [2.0-14.7]					−3.9 (−8.3, 0.4) [2.3]			0.5 (−2.3, 3.4) [1.4]
Telišman et al. (2004) Zagreb, Croatia 2000-?	Male industrial workers (115) [20-43]	36.7[b] (not given) [9.9-69.9]	Linear multiple regression with forward stepwise entry among ln or linear lead, years of exposure, age, smoking, alcohol, BMI, ALAD, erythrocyte protoporphyrin, blood Cd, serum Zn, serum Cu. Neither form of lead variable was reported as significant, but coefficients not shown. Even though forward stepwise was used and insignificant lead variables were not shown, other nonsignificant variables were shown in models.	Not stated			None given			None given

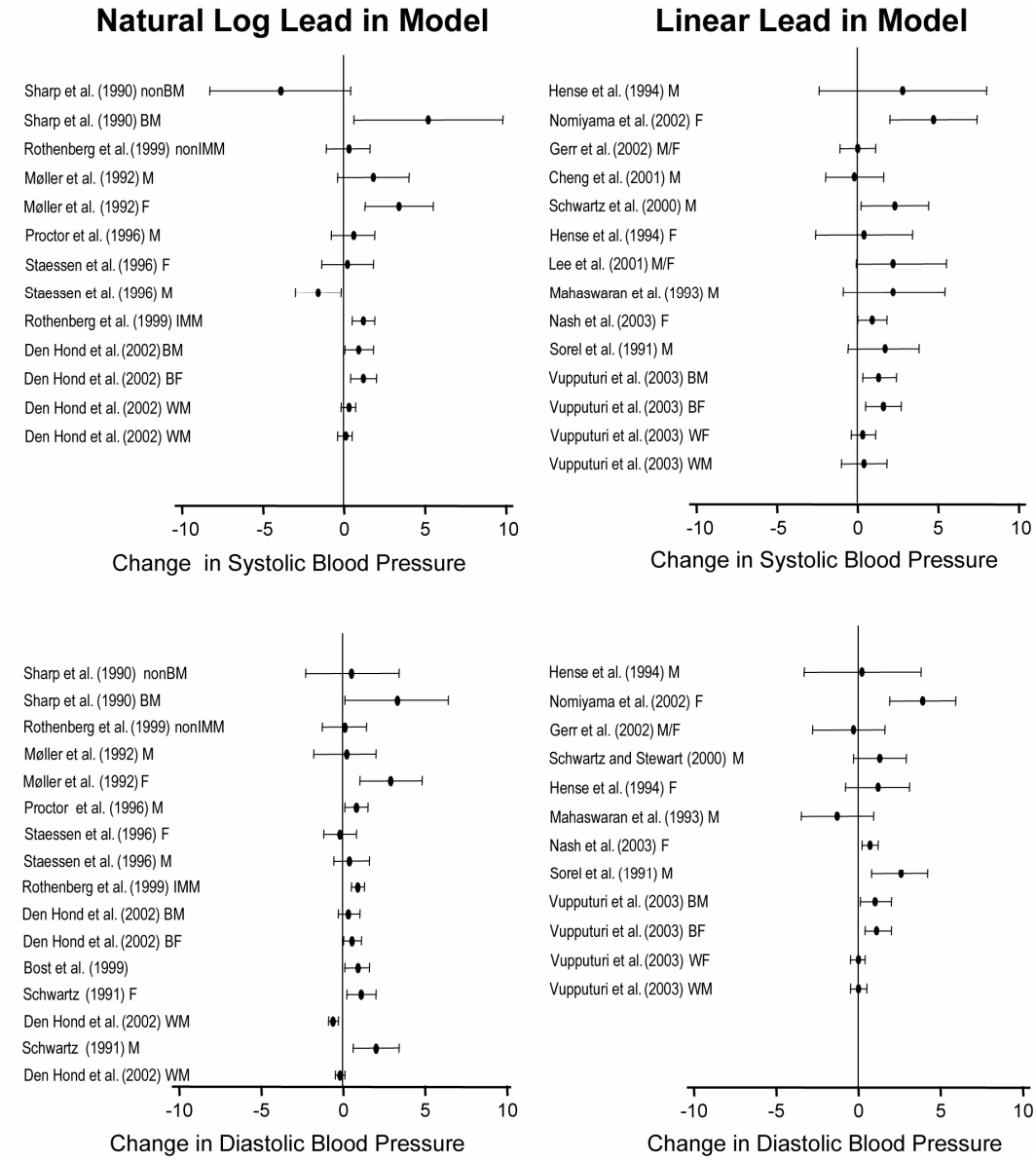


Figure 6-5.3. Effect of doubling mean blood lead on estimate of blood pressure change with 95% CIs. Studies arranged vertically by increasing study size. Where multiple models from the same study were presented, such as repeated measures over time or adding a confounding variable, only the effect estimate from the first model is shown. When the same study was multiply published with subsamples, only the effect estimate from largest study is shown.

Study key: B = blacks, W = whites, M = males, F = females, IMM = immigrants, non-IMM = nonimmigrants.

categories, hypertensive (≥140 mm Hg or 90 mm Hg), high normal (≥121/75 mm Hg up to hypertension limit), and low normal (<121/75 mm Hg). As many as four controls were matched to cases by 5 year age grouping. Though they did not match cases and controls on other potential confounding variables, they included these variables in their models. The dependent variable was constructed by placing blood pressure measurements into the three groups. The mean blood lead level was 3.1 μg/dL; the mean tibia and patella lead levels were 13.3 μg/g and 17.3 μg/g, respectively. An ordered logistic regression with proportional odds assumptions was used to asses linear blood lead, patella and tibia bone lead effects on odds of hypertension, controlling for age, BMI, dietary calcium, alcohol use, dietary sodium, smoking, and family hypertension. They presented results from four models with the same covariates determined a priori, but with each lead variable tested separately. Only patella lead concentration significantly ($p = 0.03$) predicted increased odds for hypertension, but the effect was small. Each 10 μg/g increase in patella lead was associated with an odds ratio of 1.28 (95% CI: 1.03, 1.60). Separate analyses testing interactions of alcohol use, age, and menopausal status showed no significant interaction with patella lead, though the small sample size had little power to detect significant interaction effects. Model diagnostics were given for justifying the use of proportional odds ordinal regression but none were given justifying use of a linear blood lead term in the models.

Rothenberg et al. (2002) investigated associations between both hypertension and blood pressure with blood lead, tibia lead, and calcaneus lead in 668 women, aged 15-44 years, in the third trimester of pregnancy and during a 3-month postpartum period using a cohort design and multiple logistic and multiple linear regression modeling. Subject exclusion criteria were blood lead > than 5 geometric SDs from the geometric mean, documented renal disease, cardiovascular disease, diabetes, use of stimulant drugs, and extreme postnatal obesity (BMI >40). Geometric mean prenatal and postnatal blood lead levels were 1.9 μg/dL and 2.3 μg/dL, respectively. Mean tibia and calcaneus lead levels were 8.0 μg/g and 10.7 μg/g, respectively. Variables in all models were selected a priori and retained in the models regardless of significance level. Control variables were education, smoking status, immigrant status, parity, age, and BMI in all models. Prenatal models also controlled for postpartum hypertension in lieu of family history of hypertension. None of the subjects used antihypertensive medications during the study. All three lead variables were simultaneously tested in all models. Third trimester blood lead

ranged from 0.4 to 30.0 μg/dL, postpartum blood lead ranged from 0.2 to 25.4 μg/dL. Calcaneus lead ranged from −30.6 to 49.9 μg/g and tibia lead ranged from −33.7 to 42.5 μg/g. Only calcaneus lead was significantly associated with an increase in hypertension (either ≥140 mm Hg systolic or ≥90 mm Hg diastolic) during pregnancy, with an odds ratio of 1.86 (95% CI: 1.04, 3.32) for each 10 μg/g increase of calcaneus lead. No association between calcaneus lead and hypotension was found postpartum. The authors found the same pattern of trabecular lead concentration association with blood pressure during but not after pregnancy in normotensive women. A 10 μg/g increase in calcaneus lead was associated with ~0.75 mm Hg (95% CI: 0.04, 1.46) increase in systolic and ~0.58 mm Hg (95% CI: 0.01, 1.16) increase in diastolic blood pressure in the third trimester. Only blood lead, tested simultaneously with tibia and calcaneus lead, was significantly associated with postpartum maternal blood pressure, but the relationship was negative, higher blood lead associated with lower postpartum blood pressure. For a doubling in blood lead, the systolic blood pressure increased −1.05 mm Hg (95% CI: −1.96, −0.14) and diastolic increased −1.16 mm Hg (95% CI: −1.98, −0.30). Though the authors thoroughly explored lead interaction with all other covariates in the models, they were unable to discover an effect modifier among them to explain the relationship. Postpartum physiological changes were discussed in relation to this last result. Thorough diagnostic testing was performed for all models. Only linear age terms were used in the models without exploration of age^2 terms. The authors did not use the repeated measures nature of the design in their analyses, instead they analyzed third trimester pregnancy data and postpartum data separately. They did not statistically test differences in coefficients from the same variables in the two parts of the study.

Two studies examined a subset of subjects participating in the Normative Aging Study. Hu et al. (1996) used a cross-sectional design of 590 men with median age in the mid-60s (range 48-92 years). Blood lead ranged from 1 to 28 μg/dL, tibia lead from <1 to 96 μg/g, and patella lead from 1 to 142 μg/g. Logistic regression models were initially constructed by adding age, race, BMI, family history of hypertension, smoking, alcohol use, and dietary sodium and calcium. Testing linear blood lead, tibia lead, and patella lead one by one against hypertension status (systolic >160 mm Hg, diastolic >96 mm Hg, or taking antihypertensive medication), they found no significant relationships with any of the lead variables, each entered separately. Only when they used backward elimination of nonsignificant variables did they find a significant odds ratio of 1.50 (95% CI: 1.09, 2.10) for each doubling of tibia lead from the mean (20.8 μg/g) for

hypertension. Later, Cheng et al. (2001) followed up the same group, constructing a multiple linear regression model for systolic blood pressure (diastolic blood pressure was not mentioned in model descriptions) in subjects not hypertensive at baseline measurement. They used a fixed set of control variables, including age and age terms, BMI, family history of hypertension, and alcohol and calcium intake, selected by univariate and bivariate testing of a larger set. After entering linear blood lead, tibia, and patella bone lead separately into the models, they reported a significant association only with tibia lead (1.60 mm Hg [95% CI: 0.00, 4.44] increase in systolic blood pressure for each doubling of tibia lead from the mean). Several years later (not specified in methods but no more than 6 years), the group of subjects that was originally not classified as having definite hypertension was retested for presence of definite hypertension ($\geq$160/95 mm Hg). Each lead measure was separately entered into a Cox's proportional hazards model of incident definite hypertension. Only patella lead showed a significant increase in the rate ratio in subjects with no history of definite hypertension, 1.14 (95% CI: 1.02, 1.28) for each 10 µg/g increase in patella lead. Similar results were obtained when the borderline hypertensive group (>140/90 mm Hg) was combined with the definite hypertension group in patella lead. A rate ratio of 1.23 [95% CI: 1.03, 1.48]) was estimated. Use of linear lead terms may have affected the ability of the studies to detect significant blood lead effects.

A pair of studies using the same group of male workers (age range 42-74 years) previously exposed to organic and inorganic lead at an industrial plant in the U.S. investigated the role of blood lead and bone lead on blood pressure. Blood lead ranged between 1 and 20 µg/dL and tibia lead ranged from −1.6 to 52 µg/g. The study by Schwartz et al. (2000b) controlled for age, BMI, current smoking, and current use of antihypertensive medication in backward elimination linear multiple regression models for blood lead, tibia lead, and DMSA-chelatable lead, forcing each lead term into separate models. Only blood lead was a significant predictor of blood pressure. In multiple logistic regression models, only blood lead in workers <58 years of age was significant in predicting hypertension (>160/96 mm Hg). Although this study used linear blood lead in one model, it used another model with both linear and squared-blood lead. Both lead terms were significant in the respective models. In a follow-up study (Glenn et al., 2003) with most of the same subjects of the first study, subsequent measurements of blood pressure occurred at intervals of 4-12 months for 10.2 months to 3.5 years. The study was notable not only for its prospective nature but in the use of statistical models adjusting for

repeated measurements. Models were constructed by adding to a base model containing age at start of study, race, BMI, and indicator variables for technician. Lead variables were always forced in the models, but it is not clear if they were each tested separately. Other potential confounder variables were added stepwise to the model if they met a probability criterion. Both increasing linear blood lead and tibia lead were significantly associated with increasing systolic blood pressure times the number of years of follow-up blood measurement, but not with change in diastolic blood pressure. Each 10 μg/g increase in tibia lead was associated with a 0.78 mm Hg, year (95% CI: 0.24, 1.31) increase in systolic blood pressure for workers followed for the longest time. No model diagnostics were reported.

Gerr et al. (2002) tested the effect of blood lead and tibia lead only in young adults (age 19-29 years), both males and females, on blood pressure. Half the subjects had grown up around an active lead smelter. Multiple linear regression models always used age, sex, height, BMI, current smoking status, frequency of alcohol consumption, current use of birth-control medication, hemoglobin level, serum albumin, and income, regardless of significance levels. Both blood lead (as a linear term) and bone lead (a four category ordinal variable from <1 μg/g to >10 μg/g) were tested together. Tibia lead concentration in the highest group was associated with a significant increase in both systolic (4.26 mm Hg) and diastolic (2.80 mm Hg) blood pressure when compared to the lowest tibia lead group. No model diagnostics were presented.

6.5.3 Other Cardiovascular Outcomes

6.5.3.1 Ischemic Heart Disease

A community-based case-referent study taken from the Stockholm Heart Epidemiology Program compared survivors of first-time myocardial infarction with matched referents based on sex, age, year of study enrollment, and hospital catchment area (Gustavsson et al., 2001). The authors assessed lead exposure by a three category ordinal scale based on lead levels in airborne dust. In the comparison of unexposed to >0-0.03 mg/m^3 (mean 0.01 mg/^{3}) and unexposed to >0.04 mg/m^3 (mean 0.10 mg/m^3), the relative risk was 0.88 (95% CI: 0.69, 1.12) and 1.03 (95% CI: 0.64, 1.65), respectively.

In a reanalysis of the NHANES II dataset, the influence of linear blood lead in the diagnosis of left ventricular hypertrophy (LVH) based on examination of electrocardiograms and body habitus data in less than 9,900 subjects (exact number not given) of age 25-74 years was

tested in a survey-adjusted stepwise logistic regression model (Schwartz, 1991). The final model adjusted LVH by age, race, and sex. The odds ratio for LVH was 1.33 (95% CI: 1.20, 1.47) for each 10 µg/dL increase in blood lead over an unreported blood lead range. The author reported no significant interactions between blood lead and race or between blood lead and sex, though the article noted that the number of cases of LVH was small. The linear lead effect had greater significance than the natural log lead effect, the reverse of the relationship between the two lead specifications usually seen when blood pressure is the outcome variable.

In another study of electrocardiograms in 775 men (mean age 68 years, range 48-93) from the Normative Aging Study, patella and tibia lead concentrations were significantly associated with increased heart rate-corrected QT and QRS intervals in men under 65 years but not over 65 years in multiple regression stepwise analysis (Cheng et al., 1998b). Only tibia lead concentration was significantly associated with an increased odds ratio of intraventricular conduction deficit (2.23 [95% CI: 1.28, 3.90]) for every 10 µg/g increase in tibia lead), but only in men under 65 years. In contrast, both tibia and patella lead concentration was significantly associated with atrioventricular conduction deficit (odds ratio of 1.22 [95% CI: 1.02, 1.47] and 1.14 [95% CI: 1.00, 1.29] for each 10 µg/g increase in tibia and patella lead, respectively), but only for men greater than or equal to 65 years. None of the lead measurements were significantly associated with arrhythmia. Linear blood lead terms were not significantly associated with any of the above outcomes. Though the authors reported examining both saturated models (models with all considered control and confounding variables, significant or not) and stepwise models, only stepwise models were presented or discussed with each lead term forced into separate models. Thus, each model had an individual mix of control/confounding variables, though age was common to all models. Despite using age as a control/confounding variable in all models, the article offered no statistical justification for the age-stratified analysis.

A group of male and female battery factory workers (n = 108) working for at least 10 years and who were hired from 1960 to 1983 had blood lead levels from 1970 to 1994 ranging from 5 to 93 µg/dL (Tepper et al., 2001). Using a fixed covariate multiple logistic regression model, including age, BMI, sex, and family history of hypertension, the authors found a nonsignificant odds ratios for risk of hypertension (>165/96 mm Hg or self-reported use of hypertension medications) comparing the first tertile (138-504 µg/dL·year) cumulative blood lead index with the third tertile (747-1447 µg/dL·year) index. Echocardiogram left ventricular

mass was not significantly related to cumulative blood lead index or time-weighted average blood lead.

The discrepancy in blood lead results between the two electrocardiogram studies by Schwartz (1991) and Cheng et al. (1998b) could well be explained by population differences. Though both used large datasets, the age range of the NHANES II subject pool was between 25 and 74 years and used both men and women, whereas the age range for the Normative Aging study was 48 to 93 years and used only men. Furthermore, the Cheng et al. study had 775 subjects whereas the Schwartz had a much larger, though unspecified number. The Tepper et al. (2001) study had the least number of subjects (n = 108), which may have resulted in not detecting significant effects on a different measure of LVH. Nonetheless, the two electrocardiogram studies each reported a significant lead effect, and the study with bone lead (Cheng et al., 1998b) is particularly interesting, not only for its older sample but because the bone lead exposure measure reflected accumulated past exposure, which blood lead only partly reflects. The two studies are in agreement that lead exposure, either past or present, is significantly associated with ischemic heart disease.

6.5.3.2 Stroke

No published articles relating lead specifically to stroke were uncovered, though some ICD diagnostic codes (the cerebrovascular codes) reported in other parts of this section included stroke.

6.5.3.3 Cardiovascular/Circulatory Mortality

A recent follow-up of the NHANES II cohort provided mortality data used to associate past blood lead concentration with increased circulatory mortality in the U.S. population (Lustberg and Silbergeld, 2002). Blood lead concentration as measured during 1976-1980 was divided into three categories (<10 μg/dL, 10-19 μg/dL, and 20-29 μg/dL) after eliminating 109 subjects with blood lead ≥30 μg/dL, leaving 4,190 subjects 30-74 years of age in the mortality sample followed to the end of 1992. During the follow-up period, 929 subjects died of all causes. ICD-9 codes 390-459 (circulatory) accounted for 424 deaths. Proportional hazards models using a priori selected potential confounding variables (age, sex, race, education, income, smoking, BMI, exercise, and location) were used to calculate risk ratios of cardiovascular

mortality for the two higher lead categories compared against a <10 µg/dL reference. The 20-29 µg/dL category showed a significant relative risk of 1.39 (95% CI: 1.01, 1.91) for cardiovascular mortality.

Another longitudinal study combined fatal and nonfatal coronary heart disease (ICD-8 codes 410-414) and cardiovascular disease (ICD-8 codes 410-414 and 430-435) categories from a Danish 1936 birth cohort (N = 1052) followed from 1976-1990 (Møller and Kristensen, 1992). During the study period, 54 cases of cardiovascular disease with 19 deaths were reported. Log-transformed blood lead was used in a Cox proportional hazards model, controlling for a priori selected variables of tobacco use, cholesterol, physical activity, sex, systolic blood pressure, and alcohol. Two other models were also examined, those leaving out alcohol or both alcohol and systolic blood pressure. None of the adjusted models showed significant risk hazard for combined fatal and nonfatal cardiovascular disease, though blood lead was significantly associated with outcome in all models except the one containing both alcohol and systolic blood pressure for "total mortality" risk hazard, which presumably counted noncardiovascular mortality as well (not detailed in article). This article is notable for its detailed discussion of using confounding variables, such as hemoglobin and alcohol use, in multivariate models of lead-cardiovascular associations. Small sample size and low death rate may have contributed to the nonsignificant results.

An occupational study, using 1,990 male workers who worked at least 1 day between 1940 and 1965 in an active lead smelter in the U.S. (mean length of employment at smelter 13.8 years; mean estimated length of lead exposure 9.9 years), failed to show an association with lead and standardized mortality ratios compared to the U.S. population reference group up to 1988 (Steenland et al., 1992). Neither mortality from ischemic heart disease (ICD-9 410-414), hypertension with heart disease (ICD-9 402 and 404), hypertension with no heart disease (ICD-9 401, 403, and 405), nor cerebrovascular disease (ICD-9 430-438) were significantly higher in the study group than in the U.S. population when examined in their totality or stratified by "high lead exposure" (>0.2 mg/m^3 lead in air, surveyed in 1975) or "duration of exposure." Imprecise estimation of lead exposure may have contributed to the nonsignificant results.

A study of 664 male workers in a Swedish lead smelter from 1942-1987 examined standardized mortality ratios for cardiovascular disease compared to the county population mortality figures from 1969-1989 (Gerhardsson et al., 1995a). Blood lead measurements were

available from the workers since 1969 (mean 62.1 µg/dL) and dropped steadily from that date to 1985 (mean 33.1 µg/dL). The consecutive blood lead measurements in the subjects allowed construction of a cumulative blood lead index. Standardized mortality ratios were significantly elevated in the group for all cardiovascular diseases (ICD-8 390-458) and for ischemic heart disease (ICD-8 410-414), 1.46 (95% CI: 1.05, 2.02) and 1.72 (95% CI: 1.20, 2.42), respectively. However, there were no indications of a concentration-response relationship when analyses were stratified by cumulative blood lead index, peak blood lead, or other exposure indices.

In a study of 1,261 male newspaper linotype operators working in 1961 and followed until 1984, 38% had died from all causes (Michaels et al., 1991). Compared to the New York City population reference group, there was a marginally significant increased standardized mortality ratio in the printers of 1.35 (95% CI: 0.98, 1.82) for cerebrovascular disease (ICD-8 430-438), which became highly significant in those with 30 or more years exposure (1.68 [95% CI: 1.18, 2.31]; 37 of the total 43 deaths due to cerebrovascular disease). Atherosclerotic heart disease (ICD-8 410-414) mortality in printers was significantly below that expected from the general population, with a standardized mortality ratio of 0.63 (95% CI: 0.59, 0.73).

Two studies were longitudinal in nature, following the same cohort for a period from 12 to 16 years (Lustberg and Silbergeld, 2002; Møller and Kristensen, 1992). They both used large community cohorts (NHANES II and a Danish birth cohort, respectively) and they both used multivariate proportional hazards models with blood lead as the principal predictor. Both studies found a significant increase in risk ratio with increased blood lead.

Another study examined occupationally-exposed subjects and used population reference groups to assess differences in mortality. Steenland et al. (1992) showed no significant increased mortality from ischemic heart disease (ICD-9 410-414), hypertension with heart disease (ICD-9 402 and 404), hypertension with no heart disease (ICD-9 401, 403, and 405), nor cerebrovascular disease (ICD-9 430-438) in the study group than in the U.S. population, even in the high lead exposure group.

6.5.3.4 Other Cardiovascular Effects

Peripheral arterial disease (PAD), flow-limiting atherosclerosis in lower limb muscular arteries, was studied using Phase 1 (1999-2000) of the NHANES IV, the most recent NHANES

dataset (Navas-Acien et al., 2004). PAD was categorized as a ratio of brachial artery (arm) systolic blood pressure to posterior tibial artery (ankle) systolic blood pressure < 0.90. One hundred thirty-nine subjects were classified as having PAD; there were 1,986 subjects without the disease. Blood lead was classified by quartile, with the 1st quartile containing subjects with blood lead <1.4 μg/dL and the 4th quartile containing subjects with blood lead >2.9 μg/dL. Age range was 40 to >70 years. Three sets of covariates were tested in separate models. The first set, common to all models, included age, sex, race, and education. The second set included the first set and added BMI, alcohol intake, hypertension, diabetes, hypercholesterolemia, and glomerular filtration rate. The third set added self-reported smoking status and serum cotinine. Compared to first quartile blood lead, 4th quartile blood lead subjects had significant odds ratios for PAD of 3.78 (95% CI: 1.08, 13.19) and 4.07 (95% CI: 1.21, 13.73) for the first two models. The odds ratio of 2.88 (0.87, 9.47) for the third model was not statistically significant. However, the increasing odds ratio trend from 1st through 4th quartile was significant for all 3 models ($p \geq 0.02$).

6.5.4 Potential Confounding of the Cardiovascular Effects of Lead

6.5.4.1 Confounding by Copollutants

High on the list of other metals that might be associated with cardiovascular disease is cadmium, through its known effects on kidney function. If blood lead and blood cadmium strongly covary in a sample by sharing a common source (e.g., when the study sample is drawn from a population living near a nonferrous smelter emitting both metals), including simultaneous blood lead and cadmium measurements in the same model would likely show a significant reduction in both coefficients when compared to either metal alone. If, however, blood cadmium and lead do not covary in the sample, their coefficients in the model together would be much the same as when tested separately. In a study of PAD (Navas-Acien et al., 2004) discussed in Section 6.5.3.4, investigators not only tested both lead and cadmium in separate models but also tested them simultaneously. The correlation coefficient between natural log lead and natural log cadmium was 0.32 ($p < 0.001$), highly significant, though leaving 90% of the variance between them unexplained. In addition, they tested possible interactions between lead and cadmium, and between the two metals and sex, race-ethnicity, smoking status, renal function, and C-reactive protein. Although none of the interactions were significant, when blood lead and blood cadmium

were in the same model together they both had significant trends of increasing odds ratios with increasing quartile of each metal, but the nonsignificant point estimate of the odds ratio for blood lead comparing 1st and 4th lead quartile tested alone dropped further when tested with cadmium (odds ratio of 2.88 versus 2.52). Cadmium between 1st and 4th quartile, on the other hand, showed a similar drop from cadmium tested alone to cadmium tested with lead (odds ratio of 2.82 versus 2.42), but both point estimates remained significant. Thus, though point estimates of both lead and cadmium were approximately the same whether tested alone or together, the larger variance associated with the lead coefficients rendered them nonsignificant. Part of the difference in variance between the two metals could be explained by noting that the reference group (lowest quartile) for lead contained a little over half the number of subjects (n = 472; 18 cases, 454 noncases) than the reference group for cadmium (n = 856; 27 cases, 829 noncases). The odds ratios for PAD with smoking status dropped from 4.13 (95% CI: 1.87, 9.12) to 3.38 (95% CI: 1.56, 7.35) when lead was added to the model, but both odds ratios remained highly significant and the difference was not statistically tested. The failure to find a significant interaction between the two metals and between smoking status and both metals suggests that none of the odds ratio changes discussed above were significant. The same pattern of results was found when using cotinine blood levels instead of self-reported smoking habit. Adding cadmium alone or cadmium and lead together resulted in nonsignificant odds ratios for both indices of smoking.

The Belgian Cadmibel studies also were ideally situated to test possible interactions between blood lead and cadmium, but the technique of stepwise addition of variables to the multiple regression models of blood pressure did not allow retention of both metal variables together in the same model (Staessen et al., 1996). From the lack of both cadmium and lead in any one model, it can be inferred that, if both variables had been forced into the model together, they both would have had nonsignificant coefficients.

6.5.4.2 Confounding by Smoking Status

Most studies reviewed in this section have controlled for tobacco use, where it often appears related to lower blood pressure. The majority of reviewed studies including smoking as a covariate never present the coefficients of smoking or related covariates. Only the Navas-

Acien et al. (2004) study discussed in the previous section systematically addressed the issues related to possible confounding or effect modification with tobacco use.

6.5.4.3 Confounding by Alcohol Consumption

Possible confounding by alcohol use, generally associated with increased blood pressure, was thoroughly discussed in the 1990 Supplement (Grandjean et al., 1989). Alcohol, especially in Europe, contained substantial lead during much of the 20th century. This can be seen in the MONICA Augsberg, Germany cohort study (Hense et al., 1994). The study group was stratified by sex and then, only in men, by rural-urban location. Within each strata, the blood lead range differed by alcohol use. In women, for example, the 10th and 90th percentile values of blood lead were approximately (as estimated from graphs) 3.5 and 8.5 µg/dL for self-reported abstainers, 4.5 and 10.5 µg/dL in those drinking from 1 to 39 g/day, and 6.0 to 14.0 µg/dL in those drinking 40 plus g/day. Despite the finding that only women in the highest alcohol-use group had a significant lead effect, it cannot be determined if the increase in lead coefficient is significant because the three coefficients associated with use of alcohol strata were not tested for differences among themselves; they were only tested for their significance from the null hypothesis of 0. Another study was based on subjects from the New Risk Factors Survey from the area around Rome, intended to determine confounding effects of a number of social and biochemical variables on the blood lead-blood pressure relationship (Menditto et al., 1994). Alcohol consumption, as well as BMI, heart rate, non-HDL cholesterol, and HDL cholesterol, triglycerides, cigarettes smoked/day, and skinfold thickness were all examined. A doubling of blood lead was associated with an increase of 4.71 mm Hg in systolic and 1.25 mm Hg in diastolic blood pressure. Alcohol as a true confounding variable is likely limited to studies in areas where alcohol contributes significantly to blood lead. In a study of 249 bus drivers in San Francisco, CA, natural log lead coefficients against blood pressure changed less than 10% when alcohol use was included as a covariate (Sharp et al., 1990). Blood lead according to alcohol use was not reported. Another study based on a U.S. population found a significant increase in blood lead of a mixed group of males and females according to alcohol use, ranging from mean blood lead of 7.3 µg/dL in nonusers to 9.2 µg/dL in those reporting more than 2 ounces/day over 3 days (Morris et al., 1990), with no report of significant effects of alcohol on blood pressure.

6.5.4.4 Confounding by Dietary Calcium Intake

The main thrust of the previously reported Morris et al. (1990) study was to examine the effects of dietary calcium on the effect of lead on blood pressure in 78 males and 64 females between 18 and 80 years, many of whom were hypertensive (undisclosed number), though those using medications for hypertension discontinued their use 1 month before testing started. Subjects were excluded if they had "secondary hypertension." The investigators measured serum calcium and assessed dietary calcium intake, among other variables. There were no changes in blood lead or blood pressure noted as a result of dietary calcium supplementation.

Proctor et al. (1996), using the Normative Aging Study, examined possible modification of the effect of natural log blood lead (blood lead range 0.5-35 μg/dL) on blood pressure in 798 men aged 45-93 years by dietary calcium intake assessed by food questionnaire. The study used multiple regression models with a fixed set of covariates, including age and age^2, BMI, adjusted dietary calcium, exercise, smoking, alcohol use, sitting heart rate, and hematocrit. Increased blood lead was significantly associated with diastolic blood pressure and systolic blood pressure. Only systolic blood pressure significantly decreased with increased dietary calcium (0.004 mm Hg decrease for every 1 mg/day increase of dietary calcium). The authors formed dichotomized calcium intake (cut point at 800 mg/day) and blood lead (cut point at 15 μg/dL) variables to test the interaction between blood lead and calcium on blood pressure. They did not find a significant interaction.

A study of a subset of the Cadmibel Study with 827 males and 821 females, age 20 to 88 years, selected from areas known to represent a wide range of cadmium exposure, specifically studied total serum calcium interactions with blood lead on blood pressure (Staessen et al., 1993). Stepwise regression models, selecting from log blood lead, age and age^2, BMI, pulse rate, log serum gamma-glutamyltranspeptidase, serum calcium, log serum creatinine, urinary potassium, smoking, alcohol intake, contraceptive pill use (females only), and a menopause indicator variable (females only), were stratified by sex for systolic and diastolic blood pressure. The stepwise procedure resulted in models each with a different mix of covariates. Increased serum calcium was significantly associated with increased systolic blood pressure in both males and females. Every increase of one log unit of blood lead was associated with nonsignificant changes in blood pressure in women but with a significant decrease in systolic blood pressure in men (systolic log blood lead $\beta = -5.2$). A separate set of models were constructed with an

interaction term between serum calcium and log blood lead (details not shown). In women only, both main effects of lead and calcium and the interaction effect were significant (no coefficients presented). At the 25th percentile of serum calcium (2.31 μmol/L), a doubling of blood lead was associated with a 1.0 mm Hg increase in systolic blood pressure. At the 75th percentile of serum calcium (2.42 μmol/L) a doubling of blood lead was associated with a 1.5 mm Hg increase in systolic blood pressure. Furthermore, serum calcium may itself be confounded with age in women, as women showed a sharp rise in serum calcium in their sixth decade of life, coincident with menopause, whereas the trend for serum calcium in men was steadily downward for each subsequent decade of age. The authors did not test an interaction term including calcium and age or calcium and menopausal status. Thus, the significant interaction effect between calcium and lead on blood pressure may be a result of differences due to menopause.

6.5.4.5 Summary of Potential Confounding of the Lead Effect on Cardiovascular Health

The effects of cadmium exposure, smoking, alcohol use, dietary and serum calcium levels have all been formally tested in a few studies, without significant effects as confounders of the lead effect. Failure to find a significant confounding effect with lead, however, does not argue to maintain these variables uncritically in models of blood pressure. If alcohol contains lead, increased alcohol use will lead to increased blood lead. In this case, both variables in the model will be collinear and this tends to distort estimated coefficients and standard errors of their effect on cardiovascular outcome. Tobacco use may influence lead levels much more in occupational studies than in community exposure studies, especially if smoking in the factory is allowed. Frequent hand to mouth behavior will increase lead exposure and, consequently, raise blood lead concentrations. Serum calcium may statistically modify the lead effect differentially by gender due to menopause in women. Menopause also affects lead turnover. If serum calcium, blood lead, and blood pressure are all statistically related, serum calcium should not be used in blood lead-blood pressure/hypertension studies.

6.5.5 Gene-Lead Interactions

Study authors characterized sodium-potassium adenosine triphosphatase α2 (ATP1A2) polymorphism in 220 workers formerly exposed to a mix of organic and inorganic lead in the U.S., noted above in other references (Glenn et al., 2001). The ATP1A2 (3′) one kilobase probe

produced two homozygous (4.3/4.3 and 10.5/10.5) and one heterozygous (4.3/10.5) genotypes and two homozygous (8.0/8.0 and 3.3/3.3) and one heterozygous (8.0/3.3) genotypes for the 2.5 kilobase ATP1A2 (5′) probe. Of the 209 subjects with data on both polymorphisms, 43.5% were doubly homozygous for 8.0/8.0 and 4.3/4.3, 34.4% were homozygous for 8.0/8.0 and heterozygous for 4.3/10.5, 11.5% were heterozygous for 8.0/3.3 and homozygous for 4.3/4.3, 5.3%. Also, 5.3% were doubly homozygous for 8.0/8.0-10.5/10.5, and 4.8% were doubly heterozygous for the two genotypes. Although only 13 African American workers participated, prevalence of the 10.5 kilobase allele in the ATP1A2 (3′) genotype was statistically higher for them than for other races. Prevalence of hypertension ($\geq$160/96 mm Hg or use of hypertension medication) was significantly higher in those with the 10.5/10.5 genotype than in others. Controlling for age, BMI, lifetime number of alcoholic drinks, the 10.5/10.5 genotype was associated with an odds ratio of 7.7 (95% CI: 1.9, 31.4) for hypertension when compared to the 4.3/4.3 homozygous genotype, but there were no effects of either blood lead, tibia lead, or their interaction with ATP1A2 (3′) genotype. A multiple linear regression model for linear blood lead and systolic blood pressure, controlling for age, use of hypertensive medication, current smoking, quartiles of lifetime alcohol consumption, and season, showed a significant main effect for 10.5/10.5 homozygous contrasted against combined 4.3/4.3 and 4.3/10.5 groups, associated with a 25.5 mm Hg reduction in blood pressure, primarily due to limited blood lead range of the homozygous group (maximum blood lead of the 10.5/10.5 group 9 μg/dL; maximum blood lead of the contrast group = 20 μg/dL). But the interaction between linear blood lead and the 10.5/10.5 condition resulted in a significant increase of the blood lead effect on blood pressure by 5.6 mm Hg for every 1 μg/dL blood lead compared to the blood lead effect in the other genotypes. The authors stated, but did not show analysis or coefficients, that the ATP1A3 (3′) polymorphism also significantly interacted with tibia lead and systolic blood pressure. There were no significant relationships using the ATP1A2 (5′) gene. Thus, the ATP1A2 (3′) polymorphism appears to directly influence both prevalence of hypertension and the effect of lead on blood pressure, though the small group (n = 9 with all measures) with the important 10.5/10.5 homozygous pattern would argue for enlarging this important study.

Another research group focused on polymorphisms of two genes suspected to be involved in lead toxicokinetics, the vitamin D receptor (VDR) and delta-aminolevulinic acid dehydratase (ALAD) (Lee et al., 2001). Polymorphism of both genes is well studied and prevalence appears

associated with race or ethnic background. Nearly 800 Korean workers aged 18-65 years (79.4% males) from lead-using businesses were classified according to ALAD polymorphism (1-1 [homozygous] versus 1-2 [heterozygous]) and VDR polymorphism (bb [predominant homozygous] versus Bb plus BB [infrequent polymorphisms]). The homozygous 1-1 ALAD polymorphism was found in 90.1% of the group and the homozygous bb polymorphism was found in 88.8% of the group. When compared to a smaller group of non-lead-exposed workers, blood lead concentration (mean exposed 32.0 µg/dL [range 4-86] mean nonexposed 5.3 µg/dL [range 2-10] and tibia lead concentration mean exposed 37.2 µg/g [range −7-338]; and mean nonexposed 5.8 µg/dL [range −11-27]) were much higher. The study used stepwise multiple regression models, selecting covariates remaining significant in the models from among a large set of potential control and confounding variables. They also allowed potential confounders to remain in the models if "there were substantive changes in the coefficients of predictor variables" with their addition. Systolic models controlled for age and age^2, sex, BMI, antihypertensive medication use, and cumulative lifetime alcohol use. Depending on the presence or absence of linear blood lead, tibia lead, and DMSA chelatable lead in the models, and the gene-age interactions tested, blood urea was added to the model. Diastolic models controlled for age, sex, BMI, cumulative alcohol consumption, and linear blood lead. Hypertension (systolic >160 mm Hg or diastolic >96 mm Hg) logistic multiple regression models controlled for age, sex, BMI, tibia lead, and current alcohol use. Among the exposed workers bb VDR genotypes had significantly lower DMSA-chelatable blood lead and lower diastolic and systolic blood pressure than the combined Bb and BB genotypes. The only significant interaction reported between predictor variables and gene polymorphism on blood pressure was with the VDR polymorphism bb allele, who had a less pronounced increase in systolic blood pressure with age than subjects with the B allele. There were only marginally significant associations of systolic blood pressure with tibia lead and linear blood lead. There were no significant associations in models of diastolic blood pressure with linear blood lead, DMSA-chelatable blood lead, or tibia lead. Tibia lead was significantly associated with hypertension (odds ratio of 1.05 [95% CI: 1.00, 1.12] for each 10 µg/dL increase in tibia lead). Workers with VDR B allele had significantly higher prevalence of hypertension (odds ratio = 2.1 [95% CI: 1.0, 4.4]) than workers with the bb genotype, but no other lead variable or interaction with VDR status was reported significant. Though VDR status was significantly related to blood

pressure and prevalence of hypertension, there were no significant effects of ALAD polymorphism on blood pressure or hypertension or of VDR interactions with any lead exposure variable.

Lustberg et al. (2004) studied these same Korean lead workers (n = 793) to examine the relationships between the G^{894}–T^{894} polymorphism in the gene regulating endothelial nitric oxide synthase (eNOS) and blood lead effects on blood pressure and hypertension. Nitric oxide metabolism has been suggested both as a mechanism for altered blood pressure and for moderating the effects of lead on blood pressure, though there is experimental support for and against both hypotheses. After classifying subjects as homogenous for the GG type (85%), heterogeneous for both types (TG) (14%), or homogenous for TT (1%), the TG and TT types were combined into a single group (TG/TT). Diastolic and systolic multiple regression models were constructed with a fixed set of covariates, including smoking, alcohol consumption, age, sex, BMI, and education. Logistic regression models used blood pressure criteria of either ≥140 mm Hg diastolic blood pressure, ≥90 mm Hg systolic blood pressure, or self-report of using antihypertensive medications. There was no effect of genotype on diastolic or systolic blood pressure or on hypertension prevalence in multiple regression models, nor any significant interaction of lead exposure indices with gene status.

6.5.6 Summary of the Epidemiologic Evidence for the Cardiovascular Effects of Lead

The combined blood lead studies using blood pressure/hypertension as an outcome continue to support the conclusions of the 1990 Supplement that there is a positive association between blood lead and increased blood pressure. The occasional finding of significant negative associations of blood lead with blood pressure (e.g., the Cadmibel study, one NHANES III study, the postpartum phase of the Los Angeles pregnancy study) have not been adequately explained and require further confirmation and study. The reported meta-analysis succinctly characterizes the blood pressure findings with blood lead: 1.0 mm Hg systolic pressure increase with each doubling of blood lead; 0.6 mm Hg diastolic pressure increase with each doubling of blood lead. Although females often show lower lead coefficients than males, and blacks higher lead coefficients than whites, where these differences have been formally tested, they are usually not statistically significant. The tendencies may well arise in the differential lead exposure in these

strata, lower in women than in men, higher in blacks than in whites. The same sex and race differential is found with blood pressure.

The most promising developments in this field since the 1990 Supplement have been the use of bone lead as a long-term cumulative lead exposure index and the introduction of genetic analysis into the studies as potential lead effect modifiers. With one exception, all studies using bone lead have found a consistently positive and significant effect on blood pressure and/or hypertension. The ability to estimate past exposure in cross-sectional studies is a significant advance. The results of the bone lead studies to date highlight the important role of accumulated lead exposure in the development of cardiovascular problems.

Though the study of genetic polymorphisms is still in its infancy in this field, it too holds great promise in accounting for individual variability in development of cardiovascular disease and individual response to lead exposure.

6.6 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF LEAD

6.6.1 Summary of Key Findings of the Reproductive and Developmental Effects of Lead from the 1986 Lead AQCD

Lead has been implicated as a risk factor for reproductive outcomes for over a century Rom, 1976; Oliver, 1911). As early as 1860, increased rates of stillbirths and spontaneous abortions were found in women with occupational exposure to lead (usually in the ceramics industry) and in women with husbands employed in the lead industry, compared to unexposed women (Rom, 1976). Other early investigations found increased rates of physically and mentally "retarded" offspring among these same groups. In 1910, these findings resulted in the first lead-related occupational regulation; the British Committee on Occupational Health recommended that women not be employed in the lead industry (Oliver, 1911). These observations, however, were based on exposure levels far above those considered acceptable today, and current research now focuses on substantially lower exposure levels.

The 1986 Lead AQCD provided evidence that lead, at high exposure levels, exerted significant adverse health effects on male reproductive functions. Several studies observed aberrations in both sperm count and morphology in men occupationally exposed to relatively high levels of lead (blood lead levels of 40-50 μg/dL). However, the effects of lead on female

reproductive function and fetal growth were suggestive but equivocal, perhaps due to the small sample sizes and inadequate controlling for potential confounding factors.

This section provides a critical review of the literature regarding the associations between exposure to environmental lead and reproductive outcomes. First, the evidence for the placental transfer of lead is reviewed; this is key to providing a basis and mechanism for fetal exposure. Second, the association between exposure and each outcome is reviewed. Outcomes of interest are reproductive function (fertility), spontaneous abortion, fetal growth, preterm delivery, and congenital anomalies. Each section below begins with a summary of the literature up to 1986, the year of the last EPA Air Quality Criteria Document. Then, key studies are reviewed and each section ends with a conclusion based on the evidence provided. The conclusion is based on the generally accepted "Causal Criteria" for bodies of epidemiologic literature (Hill, 1965; Susser, 1991).

6.6.2 Placental Transfer of Lead

In 1968, Barltrop (1968) demonstrated that lead crosses the placenta beginning as early as gestational week 12. He found that the rate of transfer subsequently increased to term. Lead accumulations were found in the bones, livers, blood, hearts, kidneys, and brains of stillborn and spontaneously aborted fetuses. These observations were replicated by numerous investigators; for example, Casey and Robinson (1978) found lead accumulations in the livers, kidneys, and brains of stillborn fetuses. Lead accumulations were also found in the livers, brains and kidneys of first trimester abort fetuses (Chaube et al., 1972), suggesting placental transfer earlier than 12 weeks of gestation. Newer findings, published since 1986, are reviewed below (also see Section 6.2.2.5.2).

Placental transfer of lead is confirmed by correlations of maternal blood lead concentrations, umbilical cord blood lead, and placental lead concentrations in a variety of settings. Umbilical cord blood reflects fetal blood. Early studies, prior to 1986, found correlation coefficients between maternal and umbilical cord blood lead ranging from 0.5 to 0.8, all of which were highly statistically significant. More recent studies also find significant correlations between maternal and fetal blood lead. For example, a prospective study in Kosovo, Yugoslavia recruited 1,502 women at mid-pregnancy in two towns — one with high exposure due to the presence of a lead smelter, refinery, and battery plant, and one with relatively low

exposure. The correlation between maternal blood lead (either at delivery or at mid-pregnancy) and cord blood lead ranged from 0.8 to 0.9 (Graziano et al., 1990). Among women with substantially lower levels of exposure (e.g., blood lead 1.9 µg/dL) the correlation between maternal and cord blood lead was 0.79 (Harville et al., 2005).

Chuang et al. (2001) propose that while maternal and cord whole blood lead are highly related, fetal exposure may be even more influenced by maternal plasma lead. Using data from a cohort of 615 women in Mexico City recruited in 1994-1995, these investigators used structural equation modeling to estimate the associations between whole blood lead, bone lead (cortical and trabecular), and the latent variable, plasma lead and cord blood lead. They found the strongest associations between whole blood lead and cord blood lead, even after accounting for plasma lead. The greatest contributors to plasma lead were bone lead and airborne lead. However, with declining exogenous lead exposure, these investigators note that the measurement of plasma and bone lead may become increasingly important in assessing fetal exposure.

These data provide little doubt of fetal exposure to lead via placental transport. Further, it appears that lead crosses the placenta throughout pregnancy, leading to continual exposure of the fetus. Indeed, there is evidence to suggest that maternal blood leads during the later half of gestation increase (Gulson et al., 2004; Hertz-Picciotto et al., 2000; Rothenberg et al., 1994; Sowers et al., 2002). The magnitude of the increase ranges from 14-40%, possibly due to the different starting blood leads in each study (Bellinger, 2005). The increase in blood lead in the later half of pregnancy may result from physiologic changes in maternal homeostasis during pregnancy and, in particular, to mobilization of lead stores from other body organs (Bellinger, 2005). Indirect evidence for such mobilization comes from the increased rate of bone turnover during the later half of gestation, prompted by the increased fetal need for calcium (Moline et al., 2000). Thus, both the epidemiological evidence and the biological plausibility of the associations support the role of maternal-fetal transfer of lead.

Additionally, in populations with greater lead burdens, the fetus may be at even greater increased risk for exposure and possible adverse effects of exposure. Among the variables associated with lead exposure in pregnant (and nonpregnant) women are: smoking and alcohol consumption (Graziano et al., 1990; Rhainds and Levallois, 1997), pica (Rothenberg et al., 1999), use of ethnic remedies and cosmetics (Al-Ashban et al., 2004; Centers for Disease Control and Prevention, 1993), and food preparation in inappropriately lead-glazed pottery

(Azcona-Cruz et al., 2000; Rothenberg et al., 2000). There is some evidence that low calcium intake is also associated with higher blood lead (Gulson et al., 2004; Hernandez-Avila et al., 2003; Hertz-Picciotto et al., 2000). Finally, the location where the mother resides (or resided as a child) may increase blood lead (Graziano et al., 1990). Blood leads are elevated among U.S. immigrants, especially those who migrated from countries where lead is still used as a gasoline additive (Centers for Disease Control and Prevention, 2000); indeed, blood leads are inversely associated with the number of years since migration (Centers for Disease Control and Prevention, 2000; Klitzman et al., 2002; Rothenberg et al., 1999).

In conclusion, the epidemiologic evidence indicates that lead freely crosses the placenta, resulting in continued fetal exposure throughout pregnancy. Indeed, the evidence is strong that exposure increases during the later half of pregnancy. Exposure to the fetus is more pronounced in high-risk populations, especially those who migrated from countries still using lead as a gasoline additive.

6.6.3 Effects of Lead on Reproductive Function

6.6.3.1 Effects on Male Reproductive Function

Male reproductive function is measured using the reproductive history of the male (i.e., number of pregnancies fathered), time to pregnancy and direct measures of semen quality (usually sperm count, motility and morphology). Most studies relating lead exposure to male reproductive function are based on data collected in the occupational setting linked to population birth registries and on studies directly collecting questionnaire exposure and outcome data.

6.6.3.1.1 Sperm Count, Motility and Morphology

Recent publications which purport a decline in sperm concentration, motility, and morphology seek the explanation in the rising use of man-made chemical endocrine disruptors (Auger et al., 1995; Fisch et al., 1997; Farrow, 1994; Gyllenborg et al., 1999; Kavlock et al., 1996; Keiding et al., 1994; Kieding and Skakkebaek, 1996; Lerchl, 1995; Olsen et al., 1995; Sherins, 1995). Several studies from the 1970s and early 1980s suggest aberrations in both sperm count and morphology in men exposed to relatively high levels of lead. In the earliest study, Lancranjan et al. (1975) found decreased sperm counts and an increased prevalence of morphologically abnormal sperm among workers heavily exposed to lead (mean blood lead

74.5 μg/dL) as well as those moderately exposed (mean blood lead 52.8 μg/dL). These findings have been corroborated by results of studies in the U.S. (Cullen et al., 1984) and Italy (Assennato et al., 1986) which describe similar effects in workers with blood leads above 60 μg/dL.

More recently, corroborating data was described in a comprehensive review by Apostoli et al. (1998). In studies of men with blood leads above 40 μg/dL, decreases in sperm count and concentration, motility and morphologic aberrations were found. Chowdhury et al. (1986) found a significant decrease in sperm count and motility and an increase in the number of sperm with abnormal morphology in 10 men with occupational lead exposure; the average blood lead in the exposed group was 42.5 μg/dL compared to 14.8 μg/dL in the unexposed. Similar results were found in a group of 30 lead-exposed factory workers compared to controls (Lerda, 1992). In a large study of male lead smelter workers, Alexander et al. (1996a) found a decreasing trend of sperm concentrations with increasing lead exposure. In this cohort, 152 workers provided blood specimens and 119 also provided semen samples. Geometric mean sperm concentrations were 79.1, 56.5, 62.7, and 44.4 million cells/mL for blood leads of <15, 15-24, 25-39, and ≥40 μg/dL, respectively. Long-term body lead burden was estimated from current blood lead concentrations and historical blood lead monitoring data. Using this measure of long-term lead body burden, a similar trend was found for sperm concentration, total sperm count, and total motile sperm count. No associations were found for sperm morphology or serum concentrations of reproductive hormones. A study of traffic police in Peru, where leaded gasoline is still in use, found decreases in sperm morphology, concentration, motility and viability among men with blood lead ≥40 μg/dL compared to men with blood lead <40 μg/dL.

Using data from an international study of 503 men employed in the lead industry, Bonde et al. (2002) considered the lowest adverse effect level associated with perturbed semen parameters. Median sperm concentration was reduced by 49% in men with blood lead >50 μg/dL; regression analysis indicated a threshold value of 44 μg/dL. These investigators conclude that adverse effects on sperm quality were unlikely at blood leads <45 μg/dL.

In a population of couples undergoing either artificial insemination or in vitro fertilization, Benoff et al. (2003a,b) found higher concentrations of lead in seminal fluid in the male partner among couples who did not conceive, compared to those who did conceive. While not directly measuring the adverse effects of lead on sperm per se, these data suggest a possible mechanism for the transfer of lead from paternal exposure to the fetal environment. Hernandez-Ochoa et al.

(2005) also provide evidence that lead concentrations in seminal fluid may be a better indicator of exposure than blood lead. Mean blood lead in this sample was lower than in most other studies, 9.3 µg/dL. Decreases in sperm concentration, motility, morphology, and viability were correlated with seminal fluid lead or lead in spermatozoa, but not with blood lead.

Overall, the available evidence suggests a small association between exposure to lead, usually in the workplace, and perturbed semen quality. It appears that sperm count and morphology (% normal forms) may be decreased at exposures >45 µg/dL. Future research should focus on studies of men exposed to lower levels of lead, as exposures in the very high range are associated primarily with occupational exposure. These studies should also account for variables known to be associated with semen quality and which may also be associated with exposure, e.g., social class, other environmental exposures such as heat and vibration, and lifestyle variables such as cigarette smoking and alcohol use.

6.6.3.1.2 Time to Pregnancy

Time to pregnancy represents a sensitive measure of fecundity. Time to pregnancy is important because it measures the end effect of perturbed reproductive function. While it is important and necessary to understand the associations between prenatal exposures and endocrine abnormalities and semen characteristics, they represent possible antecedents to the occurrence of pregnancy. Previous reports demonstrate good validity and reliability for reports of time to pregnancy in both males and females and when time to recall has been both long and short (Weinberg et al., 1993, 1994).

One advantage to the use of this parameter, as compared to just an infertility measure, is that it does not require categorization of men into fertile and infertile groups. Among couples that succeed in establishing pregnancy, there is considerable variability in the time between discontinuation of contraception and conception (Weinberg et al., 1994). With the possible exception of cigarette smoking and age, very little is known regarding this intercouple variability. Delays in time to pregnancy may be indicative of a range of reproductive abnormalities of both partners, including impaired gametogenesis, hormonal disruptions, and very early unrecognized pregnancy loss. Time to pregnancy has the menstrual cycle as its natural unit and is thus measured in integer units of menstrual cycles.

Usually, time to the most recent pregnancy is taken as the outcome (Baird et al., 1986). The measure of exposure in these studies usually is the fecundity density ratio, which is similar to an incidence density ratio. Fecundity density ratios can be interpreted as the risk of pregnancy among the exposed during an interval, compared to the risk of pregnancy among the unexposed during the same interval. In such studies, the intervals of interest are menstrual cycles. Fecundity density ratios less than one indicate reduced fecundity (i.e., longer time to pregnancy) among the exposed compared to the unexposed, while those greater than one indicate enhanced fecundity (i.e., shorter time to pregnancy) in the exposed. Usually fecundity density ratios are calculated using discrete time Cox proportional hazards regression models.

Several recent studies evaluate time to pregnancy when the male partner is occupationally exposed to lead. The Asclepios Project, a large European collaborative cross-sectional study, evaluated time to pregnancy in 1,108 men of whom 638 were exposed to lead (Joffe et al., 2003). The reference group consisted of lead workers for whom exposure did not coincide with time of pregnancy. The investigators only included pregnancies which resulted in live births. Fecundity density ratios were 1.12 (95% CI: 0.84, 1.49), 0.96 (95% CI: 0.77, 1.19), 0.88 (95% CI: 0.70, 1.10) and 0.93 (95% CI: 0.76, 1.15) for blood leads <20, 20-29, 30-39, and ≥40 μg/dL, respectively. These results indicate that no association was found between blood lead and delayed time to pregnancy. Similar results were found when duration of exposure or cumulative exposure was used as the exposure metric.

A separate report was published in the Italian group of men included in the Asclepios project (Apostoli et al., 2000). Blood lead at the time closest to conception was used as the measure of exposure. Lead-exposed men (n = 251) who had experienced at least one completed pregnancy were compared to nonexposed men (n = 45). Contrary to what was expected, time to pregnancy was significantly shorter among couples in which the male partner was exposed to lead compared to those in which the male partner was not exposed. In secondary analyses, time to pregnancy was longer among men with the highest blood lead (i.e., ≥40 μg/dL). Limiting the analysis solely to exposed men, time to pregnancy was longer among men with higher blood leads.

Among 502 couples identified by Sallmen (2000) from the Finnish Institute of Occupational Health in which the male partner was exposed to lead, time to pregnancy was reduced among those with blood leads >10 μg/dL compared to those with blood leads

≤10 µg/dL. However, when blood lead was stratified, no concentration-response relationship was found. Fecundity density ratios were 0.92 (95% CI: 0.73, 1.16), 0.89 (95% CI: 0.66, 1.20), 0.58 (95% CI: 0.33, 0.96) and 0.83 (95% CI: 0.50, 1.32) for exposures of 10-20, 21-30, 31-40, and ≥40 µg/dL, respectively. In this study, blood leads close to the time of conception were available on 62% of men, while in 38% it was estimated using blood leads obtained at other points or based on job descriptions.

Among 280 pregnancies in 133 couples in which the male partner was employed in a battery plant, 127 were conceived during exposure while the remainder conceived prior to exposure (Shiau et al., 2004). Time to pregnancy increased with increasing blood lead, especially when blood leads were ≥30 µg/dL. Fecundity density ratios were 0.50 (95% CI: 0.34, 0.74) and 0.38 (95% CI: 0.26, 0.56) for blood leads 30-39 and >39 µg/dL, respectively. In 41 couples, one pregnancy occurred prior to exposure and one during exposure – time to pregnancy during exposure was significantly longer. Of note, this is the only study to estimate decreases in time to pregnancy when blood lead was below 40 µg/dL; time to pregnancy increased by 0.15 months for each 1 µg/dL increase in blood lead between 10 and 40 µg/dL.

6.6.3.1.3 Reproductive History

Population-based birth registries in the Scandanavian countries provide data on medically diagnosed pregnancies. These registries provide a basis for linking occupational data on lead exposure obtained by place and duration of employment or by direct measures of blood lead relative to the timing of marriage or conception. Using a roster of men employed in three battery plants in Denmark, Bonde and Kolstad (1997) matched all births to the 1,349 employees when they were age 20-49 years. A control group of 9,656 men who were not employed in a lead industry was chosen. No associations were found between employment or, among those employed in the lead industry, duration of employment in the lead industry and birth rate.

A similar study in Finland (Sallmen, 2000) examined the association between conception and blood lead among men monitored for occupational exposure at the Finnish Institute of Occupational Health (n = 2,111). Men were categorized as probably exposed and possibly exposed based on their measured blood lead in relation to the time of marriage. A nonexposed group of 681 men with blood lead ≤10 µg/dL was similarly evaluated. Among men in the probable exposure group, the risk of failing to achieve a pregnancy increased with increased

blood lead in a monotonic concentration-response fashion. Compared to the nonexposed, the risk ranged from 1.3 to 1.9 for blood leads 10-20 µg/dL and >50 µg/dL, respectively.

Lin et al. (1996) linked records from the Heavy Metal Registry in New York State to birth certificates from the New York State Office of Vital Statistics for the period 1981 to 1992. Exposure was defined as having at least one blood lead measurement above 25 µg/dL and identified 4,256 men. A reference group of 5,148 men was frequency matched for age and residence. The exposed group had fewer births than expected, and was especially pronounced among men employed in the lead industry for over 5 years.

Among 365 men occupationally exposed to metals, Gennart et al. (1992) identified 74 exposed continuously for more than 1 year and with at least one blood lead measurement >20 µg/dL. Compared to a reference group with no occupational exposure, the probability of at least one live birth was significantly reduced. Fertility decreased with increasing duration of exposure but no concentration-response relationship with blood lead was found (possibly due to the small sample size of exposed men).

A study of men exposed to lead in a French battery plant (Coste et al., 1991) reported no effect on fertility. However, this study did not adequately control for potentially confounding variables, particularly those related to the women. Further, nonexposed workers were defined as those with no blood leads recorded which likely resulted in exposure misclassification.

One potential mechanism to explain the associations between lead exposure and male reproductive outcomes may be through an effect of lead on circulating pituitary and testicular hormones. Several studies have evaluated this hypothesis in groups of workers (Braunstein et al., 1978; Cullen et al., 1984; Erfurth et al., 2001; Ng et al., 1991; Rodamilans et al., 1988). In general these studies find perturbations in concentrations of follicle stimulating hormone, luteinizing hormone, and testosterone. Although many of these studies were limited by small sample sizes, lack of control groups, and admixtures of exposure, taken together, they provide evidence for this possible mechanism.

6.6.3.2 Genotoxicity and Chromosomal Aberrations

The potential genotoxicity and ability to induce chromosomal aberrations speak to the mechanisms by which lead is a potential reproductive toxin. Two possible mechanisms by

which lead may affect reproduction are through affinity with proteins and ability to mimic the actions of calcium (Silbergeld et al., 2000).

Data from occupational studies regarding the effects of lead on chromosomes are contradictory; however, the bulk of evidence suggests that there may indeed be a genotoxic effect. Early studies in occupational groups find associations between lead exposure and increased frequency of sister chromatid exchanges (Grandjean et al., 1983; Huang et al., 1988; Leal-Garza et al., 1986; Maki-Paakkanen et al., 1981). Similar results were found in a group of environmentally-exposed children with blood leads ranging from 30 to 63 μg/dL (Dalpra et al., 1983). Increased frequencies of chromosomal aberrations, particularly chromatid aberrations, were found in battery plant workers and were correlated with increased blood lead (Huang et al., 1988). A more marked increase was found when blood leads were above 50 μg/dL. Other occupational studies find similar associations (Al-Hakkak et al., 1986; Forni et al., 1976, 1980; Nordenson et al., 1978; Schwanitz et al., 1970). Other studies find no evidence of chromosomal aberrations when blood leads ranged from 38 to 120 μg/dL (Bauchinger et al., 1977; Maki-Paakkanen et al., 1981; O'Riordan and Evans, 1974; Schmid et al., 1972; Schwanitz et al., 1975). More recently, two studies in battery plant workers (mean blood lead 40.1 μg/dL) and controls (mean blood lead 9.8 μg/dL) found an increase in high-frequency cells and sister chromatid exchanges among the workers, indicating the cytogenetic toxicity of lead (Duydu et al., 2001, 2005). An increase in sister chromatid exchanges, although not statistically significant, was also found in individuals exposed to lead and/or alcohol and tobacco (Rajah and Ahuja, 1995, 1996). In the Lithuanian populations exposed to either environmental or occupational lead, a higher incidence of sister chromotid exchanges and chromosomal aberrations was found (Lazutka et al., 1999), although these populations were also exposed to other potentially genotoxic substances. Recent data also indicates that lead may inhibit DNA repair responses among lead-exposed workers (Karakaya et al., 2005).

Occupational exposure to lead, particularly when blood leads were high (i.e., over 40 μg/dL) was associated with increased mitotic activity in peripheral lymphocytes and with an increased rate of abnormal mitosis (Forni et al., 1976; Minozzo et al., 2004; Sarto et al., 1978; Schwanitz et al., 1970).

6.6.3.2.1 Issues Concerning Studies of Male Fecundity Related to Lead Exposure

In examining studies of fecundity and fertility, several issues relating to interpretation and bias must be addressed. Infertility usually is defined as 12 months of continuous unprotected intercourse without pregnancy. Fecundity represents both a characteristic of the individuals and a characteristic of a couple, meaning that both partners must be biologically able to procreate. Thus, one possible explanation for observations of reduced fecundity related to occupational lead exposure in the male partner is the exposure he "takes home" via transport of dust on clothing and shoes, ultimately resulting in an effect related to the female partner. Other possible interpretations need to account for measurement error, especially related to the outcomes of reproductive history and time to pregnancy, bias in the selection of subjects for study, and the control for potentially confounding variables.

Both reproductive history and time to pregnancy are subject to errors of recall and rely on the veracity of the subject. Several studies have evaluated recall and veracity of the male partner using the female partner as the "gold standard." In general, these find good reliability between the male and female (Weinberg et al., 1993, 1994). Nevertheless, it is possible, at least for studies using men as the sole informant, that the number of pregnancies a man has fathered is underreported. If reporting is nondifferential with regard to lead exposure, then associations will generally be biased towards the null value; however, since characteristics such as social circumstances, ethnicity, and age may affect both exposure and reporting, it is difficult to evaluate the role of bias.

It was not clear from many of the studies that men with medical conditions which affect fecundity/fertility were excluded. Further, several prescription and over-the-counter medications also affect fecundity as does a history of surgery in the genital area (e.g., varicocele). To the extent that these conditions are related to the absence of employment in lead-industries, then the results may be subject to a type of "healthy worker" effect. Because it is unclear whether many of these studies asked about these conditions, this cannot be ruled out as a possible source of bias.

In retrospective studies it is often useful to use the outcome of the most recent pregnancy in the primary analysis. The reason for this is to reduce any possible recall bias. This type of bias may also be an issue in studies which use occupational registry data, i.e., men may have fathered an additional pregnancy after employment in the industry ceased.

Variables considered potential confounders in studies of fertility and fecundity include sociodemographic characteristics (e.g., age, ethnicity, education, occupation); prenatal and recent lifestyle variables such as cigarette smoking, alcohol use, and medication use; exposures through occupation and hobby, and recent medication use. Also important in these studies is control for factors which may affect the partner's fertility, e.g., cigarette smoking. Many of the studies reviewed did not carefully measure or adjust for confounding variables.

The issues presented above potentially limit the interpretation of results from studies examining the association of lead exposure with male fecundity and fertility. Nevertheless, most studies find small associations between lead exposure at high levels (i.e., ≥45 μg/dL) and slightly reduced male fecundity or fertility.

6.6.3.3 Effects on Female Reproductive Function

Few data directly address the effects of lead exposure on fecundity in the female. A recent retrospective study of time to pregnancy among wives of lead workers provides limited support that lead exposure is associated with increased time to pregnancy. Fecundity density ratios were 0.92 (95% CI: 0.72, 0.16), 0.89 (95% CI: 0.66, 1.20), 0.58 (95% CI: 0.33, 0.96), and 0.83 (95% CI: 0.50, 1.32) for blood leads in the male partners of 10-20, 21-30, 31-38 and ≥39 μg/dL compared to <10 μg/dL, respectively. Note however, that exposure here is measured in the male partners and not the females.

Time to pregnancy was evaluated in 121 women biologically monitored for lead exposure at the Finnish Institute of Occupational Health between 1973 and 1983 (Sallmen et al., 1995). Fecundity did not differ with level of exposure (defined as <10 μg/dL, 10-19 μg/dL and ≥20 μg/dL), but among women with blood leads between 29 and 50 μg/dL, there was a suggestion of reduced fecundity (longer time to pregnancy). However, only a small number of subjects (n = 8) were exposed in this range.

In the limited number of studies, there is little evidence regarding the associations between lead exposure and fertility in the female to draw any conclusions at this time.

6.6.4 Spontaneous Abortion

6.6.4.1 Spontaneous Abortion and Maternal Exposure to Lead

Historical observations suggest increased rates of spontaneous abortion among lead-exposed women, particularly those employed in cottage industries (Rom, 1976). Two early studies in a smelter town in Sweden (Nordstrom et al., 1978a, 1979) suggest elevated rates of spontaneous abortion among female employees at the smelter and among female residents living in close proximity to the smelter. Neither of these studies used biological markers of lead exposure. Moreover, the Swedish smelter study included other exposures such as arsenic, zinc, and cadmium; thus the conclusions for these analyses should be tempered.

In contrast, a prospective study in and around a smelter town in Port Pirie, Australia (McMichael et al., 1986) did not find an association between blood lead concentration and spontaneous abortion. However, it was likely that complete ascertainment of spontaneous abortions was not obtained (Rowland and Wilcox, 1987) since most women were recruited for this study after the first trimester of pregnancy. A retrospective cohort study in two towns in the former Yugoslavia (Murphy et al., 1990) showed no associations between lead exposure and spontaneous abortion in the first reported pregnancy. One of these towns was a smelter town with relatively high lead exposure (at recruitment during mid-pregnancy, the mean blood lead concentration was 17.1 μg/dL, while in the control town the mean blood lead was 5.1 μg/dL). A similar study in Poland (Laudanski et al., 1991) evaluated the association between lead-exposed and nonexposed areas for their reproductive histories. Among women in the exposed areas, 11% reported having at least one prior spontaneous abortion, compared to 19.5% of women in the unexposed areas.

Two studies in Finland (Lindbohm et al., 1991; Taskinen, 1988) used hospital registry data to ascertain women with either spontaneous abortions or livebirths. Either maternal job histories (Taskinen, 1988) or both maternal and paternal job histories were obtained from a registry of occupational blood lead measurements. Neither study found evidence of an association between maternal exposure and spontaneous abortion. In the Lindbohm et al. (1991) study, maternal exposure was extrapolated from the occupation of the father.

In Bulgaria, pregnant women residing in or near lead smelting areas or petrochemical plants were prospectively followed for pregnancy outcomes (Tabacova and Balabaeva, 1993). The investigators compared blood leads in those women with spontaneous abortions and those

without. Blood lead concentrations in cases were significantly higher than in controls (mean blood lead 7.1 µg/dL versus 5.2 µg/dL, respectively). However, this study did not fully describe the selection of women nor the definition for cases.

Women employed by the U.S. Forest Service and exposed to lead-based paint (to mark trees for clearing) were studied using self-reported questionnaires (Driscoll, 1998). Adjustment was made for potential confounders and generalized estimating equations were used to adjust for multiple pregnancies per woman. Significant associations were found for three types of paint containing lead pigment (odds ratios of 4.3 [95% CI: 2.0, 9.3], 2.0 [95% CI: 1.2, 3.3] and 1.8 [95% CI: 1.2, 2.6]). While these findings are intriguing, the response rate was only 59% (with no evaluation of selection bias) and the paint also contained solvents thought to be associated with spontaneous abortions.

Borja-Aburto et al. (1999) examined the association between blood lead concentrations and spontaneous abortions in a nested case-control study using incidence density methods and matching for age, calendar time of study entry, public versus private clinic, and gestational age at study entry. They ascertained 668 women during the first trimester of pregnancy in Mexico City. After contacting women biweekly to update pregnancy status, they found 35 cases (6.4%) of spontaneous abortion among women not lost to follow up. An odds ratio of 1.8 (95% CI: 1.1, 3.1) per 5 µg/dL increase in blood lead was observed after adjustment for spermicide use, active and passive smoking, use of alcohol and coffee, maternal age, education, income, physical activity, hair dye use, use of video display terminals, and medical conditions. Mean blood lead in cases (12.0 µg/dL, range 3.1-29 µg/dL) was slightly higher than in controls (10.1 µg/dL, range 1.3-26 µg/dL). Further, after categorizing blood lead into 5 µg/dL intervals, a concentration-response relationship was evident.

More recently, a small study of 57 female workers in a battery plant in China and 62 controls found that 6 spontaneous abortions occurred in the exposed group, compared to none in the controls (Tang and Zu, 2003). A long-term follow-up of survivors of acute plumbism (Hu, 1991) found increased risk of spontaneous abortions or stillbirths (odds ratio of 1.6 [95% CI: 0.6, 4.0]). Although the study was based on small numbers, the data suggest a persistent association between childhood exposure and outcomes later in life.

A review of eight studies (Borja-Aburto et al., 1999; Driscoll, 1998; Laudanski et al., 1991; Lindbohm et al., 1991; McMichael et al., 1986; Murphy et al., 1990; Tabacova and

Balabaeva, 1993; Taskinen, 1988) evaluating maternal exposure to lead (blood lead >30 μg/dL) and spontaneous abortion concluded that there was little evidence that lead exposure at these relatively high levels was associated with an increased risk in spontaneous abortions (Hertz-Picciotto, 2000). However, Hertz-Picciotto also concluded that methodological difficulties in most of these studies (i.e., small sample sizes, inadequate ascertainment of outcome, and possible residual confounding) limited the confidence in these data. Further, she noted that exposure in many of these studies was either measured in an ecologic fashion or biological measures were available, but they were not ascertained during a biologically meaningful period.

Collectively, there is little evidence to support an association between lead exposure in the female and spontaneous abortion. The only well-designed study which finds an association is that of Borja-Aburto et al. (1999); however, these results need to be confirmed in other populations. Studies of spontaneous abortion need be done carefully to avoid possible bias due to recall, use of pregnancies other than the first, and confounding. Retrospective studies, for example, should take full pregnancy histories, including probing for spontaneous abortions versus induced abortions versus stillbirths. In some cultures, for example, induced abortions are frowned upon and women may report spontaneous abortions instead. Additionally, some women may confuse a stillbirth with spontaneous abortion, especially if she is unable to adequately date her pregnancy using date of last menstrual period. Although the use of the most recent pregnancy may curtail problems of recall, other concerns dictate that the first pregnancy be used in studies of spontaneous abortion because the risk of subsequent spontaneous abortion depends on the history of spontaneous abortion. Finally, while few variables are known confounders of this relationship, the following should be controlled: maternal age, education and other socioeconomic indicators, cigarette smoking, and alcohol use. Several studies of spontaneous abortion did not properly adjust for these potentially confounding variables.

One final concern regards the type of spontaneous abortion. Very early spontaneous abortions, i.e., before a clinical pregnancy is diagnosed, may be missed; assuming, however, that both exposed and unexposed women have the same rates of early spontaneous abortions, this would bias the association towards the null. Indeed, this may be true, as many very early spontaneous abortions may be chromosomally abnormal and probably not attributable to lead exposure.

6.6.4.2 Spontaneous Abortion and Paternal Exposure to Lead

Three studies evaluated paternal exposure to lead and spontaneous abortion. Lindbohm et al. (1991), using national databases to identify pregnancy outcomes among 99,186 births in Finland, found no association between paternal employment in jobs with lead exposure and spontaneous abortion (odds ratio of 0.9 [95% CI: 0.9, 1.0]). In a follow up case-control study (Lindbohm et al., 1991b), they ascertained paternal exposure status during the period of spermatogenesis in 213 cases of spontaneous abortion and 500 controls. Exposure was ascertained using blood lead concentrations measured during spermatogenesis for 6% of men; for the remaining 94%, exposure was estimated using a regression model where the independent variables were blood leads measured either prior to or after the period of spermatogenesis. Blood lead (either measured or estimated) was not associated with spontaneous abortion. When analysis was restricted to men with measured blood lead, blood lead concentrations >30 μg/dL were associated with an increased odds of spontaneous abortion (odds ratio of 3.8 [95% CI: 1.2, 2.0]); however, this result was only based on 12 cases and 6 controls.

The third study (Alexander et al., 1996b) found no association between men employed in a lead smelter and spontaneous abortion. For men with "moderate" exposure jobs the estimated odds ratio was 0.8 (95% CI: 0.5, 1.5) and for those with "high" exposure jobs, the estimated odds ratio was 1.4 (95% CI: 0.7, 2.5). Further when blood lead 1 year prior to the pregnancy was used as the exposure measure, no increased odds of spontaneous abortion was found. These results, however, are based on a low participation rate in eligible workers (37%) and should be interpreted with caution. Overall, the available studies provide little evidence for an association between lead exposure in the male and spontaneous abortions.

6.6.5 Fetal Growth

The results of epidemiologic studies regarding the association between lead exposure and birth weight are inconsistent. Cross-sectional studies (Clark, 1977; Gershanik et al., 1974; Moore et al., 1982; Rajegowda et al., 1972) did not find significant correlations between blood lead and birth weight, nor did a study using placental lead as the exposure variable (Wibberley et al., 1977). A case-control study (Bogden et al., 1978) comparing 25 low birth weight babies (1,500-2,500 grams) to 25 controls (>2,500 grams) matched on maternal age, race and social class found a small, nonsignificant difference in maternal and cord blood leads. Mean maternal

blood lead concentrations were 16.2 ± 4.5 μg/dL and 15.3 ± 5.2 μg/dL and mean cord blood leads were 13.8 ± 4.4 μg/dL and 13.1 ± 4.3 μg/dL in cases and controls, respectively. A further study (Huel et al., 1981) found no differences in maternal and fetal hair lead concentrations between infants born small-for-gestational-age compared to those of normal birth weight.

In 1984, Needleman et al. (1984) reported on a cross-sectional study of 5,183 births of at least 20 weeks gestation in Boston, MA. No associations were found between the proportion of births under 2,500 grams and cord blood lead. Exposure levels in this study were relatively low for the time; cord blood leads ranged from <1 to 35 μg/dL. A reanalysis of these data found no relationship between cord blood lead and birth weight when birth weight was considered as a continuous variable (Bellinger, et al., 1991). However, when birth weight was categorized as low birth weight (<2,500 grams), small for gestational age (<10th percentile for gestational age), or intrauterine growth retarded (>2 standard deviations below the mean for gestational age), relative risks of 1.6 (95% CI: 1.0, 2.6), 1.2 (95% CI: 0.8, 1.6) and 1.9 (95% CI: 1.0, 3.4), respectively, were found for each 10 μg/dL increase in cord blood lead levels. Increased relative risks also were found for cord blood lead levels ≥15 μg/dL, compared to cord blood lead <15 μg/dL; however, only 83 of the 5,183 women had exposures in the high range, resulting in imprecise estimates. These data suggest that lead-related modest reductions in birth weight are perhaps plausible when birth weight is expressed as a function of gestational age.

The prospective study of lead exposure in and around Port Pirie, Australia (McMichael et al., 1986) followed 749 pregnancies of at least 20 weeks duration. Mean maternal blood leads at mid-pregnancy were 10.1 μg/dL and 7.0 μg/dL for women residing in Port Pirie and the surrounding communities, respectively. After excluding 9 sets of twins and 10 cases for which the maternal last menstrual period could not be ascertained, no relationship was found between either cord blood lead or maternal blood lead measured at mid-pregnancy or at delivery and birth weight in a multivariate regression model controlling for known determinants of birth weight.

A prospective study in two towns in Kosovo, Yugoslavia evaluated relationships between birth weight (adjusted for gestational age using last menstrual period) and (a) maternal blood lead at mid-pregnancy and delivery and (b) cord blood lead (Factor-Litvak et al., 1991). The towns were vastly different in exposure patterns, as one was the site of a lead smelter, refinery and battery plant (n = 401, mean mid-pregnancy blood lead 19.0 μg/dL) and one was relatively unexposed (n = 506, mean mid-pregnancy blood lead 5.6 μg/dL). No associations were found

between any of the biomarkers of lead and birth weight in either crude analyses or analyses adjusted for potentially confounding variables.

While the aforementioned studies generally found no association between environmental lead exposure and birth weight, three other studies have shown large reductions in birth weight related to lead exposure. These studies, however, have questionable study designs. Nordstrom et al. (1978b, 1979) in a series of ecologic analyses known as the Swedish Smelter Study, found significant reductions in birth weight between the offspring of women either working at or living in close proximity to the smelter. The 125 gram deficit in birth weight among the offspring of women living closest to the smelter was confined to those with parity three or more, an observation which does not appear to be biologically plausible. Moreover, the ecological nature of the study did not allow for individual measurements of blood lead or for control of potentially confounding variables. Hence, while suggestive, these data do not provide strong evidence for a causal association between lead exposure and birth weight.

In a cross-sectional study of 100 "normal" singleton births, a negative correlation was found between placental lead concentration and birth weight (Ward et al., 1987). Mean placental lead concentration in 21 infants weighing less than 3,000 grams was 2.35 ± 0.9 µg/g compared to 1.12 ± 0.4 µg/g in 10 infants weighting more than 4,000 grams. This study has several limitations. First, no statistical adjustment was made for multiple comparisons (many exposures were studied). Second, potentially confounding variables were not controlled. Third, only 31 of the 100 infants, representing the extremes of the birth weight distribution, were studied. Hence, this study also does not provide strong evidence for an association.

In Cincinnati, OH, the association between lead exposure and birth weight was examined in offspring of a cohort of young (mean maternal age = 22.7 years), inner city women, 85% African American, 86% on public assistance, with a mean IQ of 75 (Dietrich et al., 1987a). The mean gestational period of the neonates, as determined by physical examination, was 39.5 weeks. A decrement in birth weight of 172 grams was associated with an increase in blood lead from 10 to 30 µg/dL. Lead exposure in this group was relatively low with a mean blood lead of 8.0 ± 3.7 µg/dL. In a sample of women from this cohort, the interaction between blood lead and maternal age was significantly associated with birth weight; the effect varied from a decrease of 64 grams for 18 year old mothers to 660 grams for 30 year old mothers, as blood lead rose from 10 to 30 µg/dL (Bornschein et al., 1989). Although the Cincinnati study is highly

suggestive of an effect (especially an effect which varies by maternal age) three factors should be considered in the interpretation of their findings. First, length of gestation was estimated by examining the neurological and physical maturity of the neonate (Ballard et al., 1979); other investigators find assessment of gestational age using this scale overestimates gestational age in preterm infants (Constantine et al., 1987; Kramer et al., 1988; Shukla et al., 1987; Spinnato et al., 1984). Second, it is possible that the association between lead and birth weight differs by maternal characteristics such as race, ethnicity, and SES; however, no study has provided a population sufficiently heterogeneous to examine this possible source of difference. Finally, it is possible that confounding by unmeasured maternal lifestyle characteristics may account for the reported association.

A hospital-based study of cord blood lead and pregnancy outcomes in Quebec, Canada, between June 1993 and January 1995 found a slight increase in cord blood lead levels among infants with birth weight <2,500 grams (Rhainds et al., 1999). For those infants with birth weight <2,500 grams, the geometric mean blood lead was 1.8 μg/dL (95% CI: 1.6, 2.9) compared to 1.6 μg/dL (95% CI: 1.5, 1.7), 1.6 μg/dL (95% CI: 1.5, 1.7), and 1.5 μg/dL (95% CI: 1.5, 1.6) among those with birth weights 2,500-2,990, 3,000-3,499, and ≥3,500 grams, respectively. Although suggestive, the study did not control for potentially confounding variables. The investigators also measured cord blood levels of mercury and organochlorine compounds, and observed that mean levels of these toxicants were higher as well in infants who weighed <2,500 g.

More recently Irgens et al. (1998) using data from the Norwegian birth registry found that women occupationally exposed to lead (none/low compared to moderate/high) were more likely to deliver a low birth weight infant (odds ratio of 1.3 [95% CI: 1.1, 1.6]). No association was found for paternal occupational lead exposure. Parental occupational exposure to lead was not associated with low birth weight in the Baltimore-Washington Infant Study database (Min et al., 1996), although subgroup analysis suggested that high paternal exposure may be associated with small-for-gestational-age infants (odds ratio of 2.9 [95% CI: 0.9, 9.2]). Similar findings were reported by Lin et al. (1998) who compared offspring of lead-exposed workers with those of bus drivers. No associations were reported between lead exposure and low birth weight except among the group of men with blood lead levels >25 μg/dL for over 5 years (relative risk of 3.4 [95% CI: 1.4, 8.4]).

Using bone lead as the metric of exposure, Gonzalez-Cossio et al. (1997) found associations with tibia bone lead (but not with patella bone lead or umbilical cord blood lead) and reduced birth weight. Bone lead was measured one month after delivery. Infants with tibia bone lead in the highest quartile (≥15.15 μg lead / g bone mineral) were, on average, 156 g lighter than those in the lowest quartile (≤4.50 μg lead / g bone mineral). Further analyses of these data (Hernandez-Avila et al., 2002) found an association between infants in the highest quintile of tibia bone lead and shorter birth length (odds ratio of 1.8 [95% CI: 1.1, 3.2]).

Two studies have considered the relationship between lead exposure and head circumference (Hernandez-Avila et al., 2002). Among 233 women in Mexico City, high maternal patella bone lead was associated with increased risk of a low head circumference score at delivery (1.02 per μg lead / g bone mineral [95% CI: 1.01, 1.04]). Similar findings were reported by Rothenberg et al. (1999) who found a reduction in six-month head circumference of 1.9 cm (95% CI: 0.9, 3.0) as maternal blood lead rose from 1 to 35 μg/dL. This study, however was plagued by multiple comparisons as head circumference was measured nine times and prenatal blood lead six times – only one statistically significant result was found.

Potential confounders need to be adjusted for to properly assess the relationship between lead exposure and fetal growth. Factors consistently associated with fetal growth include gender, ethnic origin, maternal body build (i.e., pre-pregnancy weight, height), parity, SES, gestational weight gain and nutritional intake during pregnancy, maternal illness, and cigarette smoking (Kramer, 1987). Factors with less established associations include alcohol consumption (Kline et al., 1987; Kramer, 1987) and street drug use (Kline et al., 1987; Kramer, 1987; Zuckerman et al., 1989). To the extent that these factors are associated with blood lead as well as with fetal growth, they must be accounted for in the analysis.

Studies to date are inconsistent regarding the association between lead exposure and birth weight. Several large prospective studies find no association (Factor-Litvak et al., 1991; McMichael et al., 1990), while at least one (Bornschein et al., 1989) did find an association in specific subgroups of women. However, there is limited evidence (Bellinger et al., 1991) for an association between lead exposure and low birth weight (i.e., <2,500 g), small for gestational age (i.e., <10th percentile for gestational age), and intrauterine growth retardation (i.e., >2 standard deviations below the mean for gestational age). These prospective studies were all well-conducted, adequately measured exposure and outcome, and controlled for potential confounding

variables. They did, however, take place in very different populations, suggesting that the association between lead and fetal growth may depend on the population being studied. The Yugoslavia study (Factor-Litvak et al., 1991) took place in two towns in Kosovo, Yugoslavia, which were divergent on exposure and somewhat comparable on other variables. The Port Pirie study took place in a middle class area of Australia (McMichael et al., 1986). The Boston study (Bellinger et al., 1991) took place in a range of social strata in Boston; the exposure in the highest social group was attributable to renovation of older housing stock. Finally, in the Cincinnati study (Bornschein et al., 1989), the study sample was comprised of lower social class African Americans; the mean IQ of the mothers was 75. It is possible that in this latter study, there was some unmeasured variable which accounts for the observed interaction. Thus, the evidence suggests at most a small effect of lead exposure on birth weight and possibly a small association between lead exposure and several dichotomized measures of fetal growth.

6.6.6 Preterm Delivery

Early evidence regarding an association between environmental lead exposure and preterm delivery was inconsistent. In 1976, Fahim et al. found a preterm delivery rate of 13% in 254 pregnant women living near a lead mining community in Missouri, compared to 3% in 249 women living in a control location. These investigators also found higher concentrations of lead in amniotic membrane, but not higher placental or cord lead in preterm compared to term deliveries, regardless of the women's residential locale. This observation prompted other studies of lead and preterm delivery.

Of the cross-sectional studies, the three which show no association employed cord blood lead as the exposure measure and restricted gestational age (Angell and Lavery, 1982; Bellinger et al., 1991; Needleman et al., 1984; Rajegowda et al., 1972). In contrast, three other studies used different exposure markers (placental lead, maternal and cord blood lead, and maternal and fetal hair lead) and found statistically significant associations (Huel et al., 1981; Moore et al., 1982; Ward et al., 1987). Other studies evaluated pregnancy outcomes in relation to maternal delivery blood lead (McMichael et al., 1986; Rahman and Hakeem, 2003).

Of the prospective studies, the Cincinnati study (Bornschein et al., 1989) found no association between both maternal blood lead at mid-pregnancy or maternal blood lead during the neonatal period (10 days post delivery) and preterm delivery. However, gestational age was

estimated by examining the neurological and physical maturity of the neonates (which tends to overestimate gestational age) and not actual dates. In Port Pirie, Australia (McMichael et al., 1986), a concentration-response relationship between maternal delivery blood lead and preterm delivery was reported. Odds ratios ranged from 2.1 to 4.4 in women with blood leads of 7.7-10.6 μg/dL and >13.5 μg/dL, respectively, compared to those with blood lead <7.7 μg/dL. Savitz et al. (1990) used data from the National Natality Survey and found an odds ratio of 2.3 (95% CI: 0.7, 7.0) between maternal occupational exposure to lead and preterm delivery; however, the estimated odds ratio was based on only 7 cases. In the Yugoslavia study (Factor-Litvak et al., 1991) no associations were found between cord blood lead or blood lead measured at mid pregnancy or delivery and either preterm delivery (defined as delivery <37 completed weeks) or gestational age. A registry study in Norway (Irgens et al., 1998) which linked births between 1970 and 1993 to census-based occupation records found a slightly increased odds of preterm delivery among moderate/high lead-exposed women, compared to those with no or low exposure (odds ratio of 1.13 [95% CI: 0.98, 1.29]). Paternal exposure was not found to increase the risk of preterm birth.

An ecologic study in Canada (Philion et al., 1997) examined 30 years of birth records, corresponding to 9,329 births in a smelter city and a control city. Outcome variables were intrauterine growth retardation defined as small for gestational age. The odds ratio for intrauterine growth retardation in the smelter city compared to the control city was 0.83. Further analysis, stratifying time into 5-year intervals also revealed no associations.

A case control study in Mexico City (Torres-Sanchez et al., 1999) evaluated 161 preterm births and 459 full term births. Cord blood lead was significantly higher in the preterm group (9.8 ± 2.0 μg/dL) compared to the full term group (8.4 ± 2.2 μg/dL) only among primiparous women.

Using data from the Baltimore-Washington Infant Study database, Min et al. (1996) found a small association between paternal occupational exposure in the high range and preterm delivery with appropriate weight for gestational age (odds ratio of 2.1 [95% CI: 0.7, 6.5]) and preterm delivery with small for gestational age (odds ratio of 2.4 [95% CI: 1.9, 3.1]). Similar findings were reported by Lin et al. (1998). Comparing the offspring of lead exposed workers with those of bus drivers, they found an elevated relative risk for preterm delivery (3.0 [95% CI: 1.6, 6.8]) only among men with blood leads >25 μg/dL for over 5 years.

In contrast to fetal growth, few factors are consistently related to preterm delivery; thus in both developed and developing countries the majority of preterm deliveries remain unexplained (Kramer 1987; van den Berg and Oechsli, 1984). Factors which are inconsistently associated with preterm delivery include maternal age, SES, pre-pregnant weight, prior history of preterm delivery or spontaneous abortion, and cigarette smoking (Kline et al., 1987; Kramer, 1987). Thus, these factors must be evaluated as potentially confounding factors in studies of lead exposure and preterm delivery.

For preterm delivery, or reduced length of gestation, the evidence for an association with lead exposure is contradictory. Several of the prospective studies find no evidence of an association (Bornschein et al., 1989; Factor-Litvak et al., 1991) while one finds a concentration-response relationship (McMichael et al., 1986). Further, two well-done registry studies (Irgens et al., 1998; Savitz et al., 1990) find some evidence of an association, albeit the number of exposed cases was small. It seems unlikely that the association between lead exposure and preterm delivery is large, but, more research is clearly necessary.

6.6.7 Congenital Abnormalities

Needleman et al. (1984) found an association between cord blood lead and minor congenital anomalies among 4,354 infants born in a single hospital in Boston, MA. All data were obtained from hospital records, not from direct examination of the infants. The most common anomalies were hemangiomas, lymphangiomas, minor skin problems (tags and papillae), and undescended testicles. Blood lead levels were not found to be associated with individual anomalies.

More recently, a number of studies have considered parental lead related to occupational exposure and risk of congenital anomalies in the offspring. In Finland, Sallmen et al. (1992) evaluated the associations between congenital malformations and paternal exposure during the time of spermatogenesis. The overall estimated unadjusted odds ratio for men with blood lead levels >20 μg/dL was 2.4 (95% CI: 0.9, 6.5). Due to small sample sizes, the investigators could only adjust for one potentially confounding factor at a time; this resulted in odds ratios ranging from 1.9 to 3.2. Of note is the lack of consistency of malformations among the five men with the highest blood lead. The malformation observed included congenital heart disease, oral cleft, club foot, polydactyly, and anomalies of the adrenal gland. The breadth of these anomalies suggests

either that lead affects physical development throughout gestation or that this association represents a chance finding. Among 2,021 pregnancies, Alexander et al. (1996b) found slightly elevated odds ratios for congenital defects among men in the lead smelting industry with moderate exposure (odds ratio of 1.9 [95% CI: 0.6, 6.3]) and high exposure (odds ratio of 2.7 [95% CI: 0.7, 9.6]). These estimates are based on 30 birth defects and 12 stillbirths. No analyses were presented which considered individual birth defects. In Norway, neither maternal (odds ratio of 1.25 [95% CI: 0.8, 1.9]) nor paternal (odds ratio of 0.94 [95% CI: 0.8, 1.1]) occupational lead exposure was associated with serious birth defects (Irgens et al., 1998). Similar results were reported by Kristensen et al. (1993) between paternal lead exposure and birth defects, with the exception of a fourfold increase in the risk of cleft lip among male offspring.

The risk of parental lead exposure and neural tube defects was evaluated in a case-control study of 88,449 births (363 neural tube defects) over a 25-year period in Fylde, England (Bound et al., 1997). Women living in areas in which the water lead concentration was >10 μg/L were more likely to deliver a child with a neural tube defect. The association was consistent for anencephaly (n = 169) and spina bifida/cranium bifidum (n = 195), even after adjusting for social class. These authors posit that the association could be a direct effect of lead on neural tube closure or an indirect effect, the latter meaning a reduction in uptake of zinc (due to lead exposure) leading to a reduction in folate uptake. Irgens et al. (1998) partially confirmed these effects on neural tube defects in mothers occupationally-exposed to lead (relative risk of 2.87 [95% CI: 1.05, 6.38]), but not for paternal lead exposure.

The association between total anomalous pulmonary venous return and parental lead exposure during pregnancy (self reported, obtained from industrial hygiene measures, or from a job exposure matrix) was examined in the Baltimore-Washington Infant Study (Jackson et al., 2004). In this case-control study, maternal periconceptional (i.e., 3 months prior to conception through the first trimester) exposure to lead resulted in an estimated odds ratio of 1.57 (95% CI: 0.64, 3.47). For lead-exposed men, the estimated odds ratio was 1.83 (95% CI: 1.00, 3.42). Findings from this study support a possible association between paternal lead exposure and total anomalous pulmonary venous return**.**

Taken together, the evidence suggests few associations between periconceptional or prenatal exposure to lead and congenital anomalies. There is a suggestion of small associations

with high levels of exposure, but many of those studies relied on occupational histories rather than on actual measures of blood lead levels.

6.6.8 Summary of the Epidemiologic Evidence for the Reproductive and Developmental Effects of Lead

There is little doubt that maternal to fetal transmission of lead results from placental transport. This transport occurs throughout pregnancy and may increase in the later stages. Further, there may be populations with increased fetal susceptibility, including populations with high rates of smoking and alcohol use, those using ethnic remedies and cosmetics, and those who use lead glazed pottery. Low levels of calcium intake may also increase fetal exposure.

The available evidence suggests small associations between exposure to lead and male reproductive outcomes. These include perturbed semen quality and increased time to pregnancy. These associations appear at blood lead levels greater the 45 μg/dL, as most studies only considered exposure in the occupational setting. More research is needed regarding possible male reproductive effects at exposure levels in the lower (and currently more relevant) range. There are no adequate data to evaluate associations between lead exposure and female fertility.

With one exception, there is no evidence to suggest an association between either maternal or paternal lead exposure and increased risk of spontaneous abortions. One study in Mexico where the mean maternal blood leads were in the moderate range (i.e. 10-12 μg/dL) suggests an association.

To date, the evidence suggests at most a small association between lead exposure and birth weight and possibly small associations between lead exposure and several dichotomized measures of fetal growth. The reviewed studies occurred in very different populations, and the small associations may reflect some unmeasured or unknown confounding variable. It is unlikely that further epidemiologic research will fully resolve this question. However, several factors, such as maternal SES, maternal education, smoking prevention and reduced use of alcohol, related to lead exposure are associated with increases in birth weight (and decreases in blood lead) and are candidates for intervention.

Similarly, the evidence suggests at most a small association between lead exposure and preterm delivery or reduced length of gestation. The available data also suggest limited associations between either periconceptional or prenatal lead exposure and congenital anomalies.

There is a suggestion of small associations with high levels of exposure, but many of those studies relied on occupational histories rather than on actual measures of blood lead.

Overall, since the 1986 Lead AQCD, a substantial body of work has evaluated the associations between lead exposure and reproductive outcomes. It is now clear that lead clearly crosses the placenta during all trimesters and maternal exposure results in fetal exposure. For many other outcomes, the observed associations are relatively small, especially at the levels of exposure that are currently of interest. Nevertheless, there may be populations that are highly susceptible to lead-related reproductive effects, especially if they have additional risk factors for these outcomes.

6.7 GENOTOXIC AND CARCINOGENIC EFFECTS OF LEAD

6.7.1 Summary of Key Findings from the 1986 Lead AQCD

The 1986 EPA Lead AQCD reviewed five epidemiologic studies of occupationally exposed workers (Cooper and Gaffey, 1975; Davies, 1984; Selevan et al., 1985; Sheffet et al., 1982; McMichael and Johnson, 1982). These workers were exposed to inorganic lead compounds such as lead oxides and lead sulfides. The EPA noted that Cooper and Gaffey reported a significant increase in lung and gastrointestinal cancer among battery and smelter workers in the U.S. (standardized mortality ratios of 1.50 and 1.48 respectively among smelter workers, and 1.32 and 1.23 among battery workers). The EPA further noted that much of this exposure was by inhalation and ingestion of lead oxides, which are relatively insoluble, adding some plausibility to the occurrence of cancer at these two sites. Sheffet et al. (1982) provided some corroborating evidence for gastrointestinal cancer by finding a nonsignificant excess of stomach cancer among U.S. lead chromate pigment workers. However, Davies (1984) did not find any cancer excess among lead chromate pigment workers in the U.K. The EPA noted that Selevan (1984) found a significant excess of kidney cancer among U.S. lead smelter workers based on 6 cases. This finding was judged striking because it mimicked the findings of kidney cancer in animals. The EPA judged that the McMichael and Johnson (1982) study of lead poisoned workers was not particularly informative because the non-poisoned workers may have had substantial lead exposure and no details were given on how lead poisoning was determined.

In summary the EPA felt the evidence was insufficient, stating that "little can now be reliably concluded from available epidemiologic studies."

The studies by Cooper and Gaffey (1975) and Selevan (1984), which are both important because they are large occupational cohorts with documented high exposure, have been updated and are further reviewed below. A cohort study of U.K. battery workers (Malcolm and Barnett, 1982) is also reviewed below.

EPA in 1986 also presented data on human cytogenetic studies, reproducing data from an earlier 1980 International Agency for Research on Cancer (IARC) monograph for metals and metallic compounds (IARC, 1980). For lead, 10 chromosomal aberration studies were judged to be "positive" and 6 such studies were judged to be "negative." On the whole the EPA considered that "under certain conditions lead compounds are capable of inducing chromosomal aberrations in vivo and in tissue cultures." The EPA also reviewed more limited data from two human studies of sister chromatid exchange (Dalpra et al., 1983; Grandjean et al., 1983), one of which was positive and one negative.

6.7.2 Summary of Key Findings by the International Agency for Research on Cancer and the National Toxicology Program

IARC reviewed inorganic and organic lead compounds in its monograph number 87 in February of 2004 (IARC, 2005), and IARC concluded that inorganic lead compounds were probable human carcinogens (Group IIA). This classification is one step down from a classification as a "definite" human carcinogen (Group I). The IARC classification of inorganic lead compounds as probable human carcinogens was based on limited evidence in humans and sufficient evidence in animals. Also, IARC noted that there was insufficient information regarding organic lead compounds (e.g., tetraethyl lead) to make any judgment.

Regarding the human studies, IARC based its evaluation largely on six occupational cohort studies of highly-exposed workers, which were felt to be particularly informative (battery workers in U.S. and U.K., smelter workers in Italy, Sweden, and the U.S.). The IARC assessment focused on four cancer sites, lung, stomach, kidney, and brain. IARC noted that lung showed a significant elevation in one study (Lundstrom et al., 1997) and nonsignificant elevations in a number of others. However, the significant elevation of lung cancer in Lundstrom et al. appeared to be inextricably associated with arsenic in addition to lead exposure

(Englyst et al., 2001). IARC concluded that the strongest epidemiologic evidence for lead carcinogenicity was for stomach cancer, noting that four cohort studies showed a consistent 30-50% excess of stomach cancer vs. external referent populations. IARC noted that confounding by ethnicity, diet, *Helicobacter pylori* infections, or SES may have played a role in the stomach cancer excesses. Finally, IARC noted that while one cohort study showed a 2-fold excess of renal cancer (Steenland et al., 1992), the other studies showed no excess. Similarly, there were no consistent excesses of brain cancer, although one study did find a significant positive dose-response between glioma and blood leads, based on small numbers (Anttila et al., 1996).

The National Toxicology Program (NTP) in 2003 evaluated the carcinogenicity of lead and lead compounds. A summary of its evaluation can be found in NTPs Report on Carcinogens (www.ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s101lead.pdf), and the detailed evaluation is also available (NTP, 2004). NTP, like IARC, concluded that "lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals." The NTP considered that "the strongest epidemiologic evidence was for lung and stomach cancer, which are consistently but weakly associated with occupational and industries entailing lead exposure and with indices of individual lead exposure, including job history and biological monitoring of occupationally exposed and general populations. However, most studies of lead exposure and cancer reviewed had limitations, including poor exposure assessment and failure to control for confounders (other factors that could increase the risk of cancer, including lifestyle factors and concurrent occupational exposure to other carcinogens), and did not demonstrate relationships between the amount of exposure (concentration or duration, for example) and the magnitude of cancer risk." NTP, like IARC, also relied heavily on occupational cohort studies in its evaluation of the epidemiologic evidence. NTP (2003) noted that "the mechanisms by which lead causes cancer are not understood. Lead compounds do not appear to cause genetic damage directly, but may do so through several indirect mechanisms, including inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor-suppressor proteins."

Both the IARC and NTP evaluations of human evidence relied primarily on occupational studies of highly exposed workers, in which limited evidence of stomach and to some extent lung carcinogenicity was found. There are seven such studies with relatively large populations

(Anttila et al., 1995; Carta et al., 2005; Fanning, 1988; Gerhardsson et al., 1995a; Lundstrom et al., 1997; Steenland et al., 1992; Wong and Harris, 2000). A further study (Ades and Kazantzis, 1988) also addresses lead exposure in a large occupational cohort, although it is compromised by the strong correlation between arsenic and lead exposure in the cohort. It should be noted that the blood lead levels among these workers were generally three to five times higher than the blood lead levels in the two studies of the general U.S. population (Jemal et al., 2002; Lustberg and Silbergeld, 2002; both based on NHANES II) with environmental exposures. For example, mean blood levels in two studies of U.S. lead smelter workers averaged 56 µg/dL in Steenland et al. (1990) in 1976 and 80 µg/dL in Cooper et al. (1985) during the period 1947-1972. In contrast, blood levels in the U.S. population enrolled in NHANES II in late 1976-1980 averaged 14 µg/dL. General population blood lead levels have decreased markedly since the 1970s in many industrial countries with the banning of leaded gasoline. For example, in the U.S. in the early 1990s general population levels averaged 3 µg/dL according to NHANES III (www.atsdr.cdc.gov/toxprofiles/, see lead toxicological profile, page 409). Regarding the occupational studies, while exposure is well documented, exposure-response data are generally not available, making impossible any quantitative inference about likely cancer effects in low exposure groups based on these studies. The high exposure occupational cohorts are the most informative for deciding whether lead is likely to cause cancer, simply because high doses are more likely to show detectable effects than low doses, if effects exist. If lead does cause cancer, and assuming there is no threshold below which exposure does not cause cancer (which is generally true for human carcinogens), current low level exposures to the general public may result in some level of cancers related to lead exposure due to the potential exposure of a large number of people.

6.7.3 Meta-Analyses of Lead and Cancer

There have been two published meta-analyses of the carcinogenicity of lead and lead compounds. The major findings of these studies are summarized in Table 6-7.1. Steenland and Boffeta (2000) relied on eight occupational cohort studies of highly-exposed workers (seven cohort studies, one nested case-control), all of which had documentation of exposure levels. Meta-analyses were conducted for lung, stomach, kidney, and brain cancer. The combined lung cancer relative risk relative risk was 1.30 (95% CI: 1.15, 1.46), based on 675 lung cancer deaths.

Table 6-7.1. Results of Meta-Analyses Addressing the Association Between Lead Exposure and Cancer

	Risk Estimate (95% CI) for indicated outcome [Number of studies utilized in estimate]		
Meta-Analysis	**Lung Cancer**	**Stomach Cancer**	**Renal Cancer**
Fu and Boffetta (1995)	1.24 (1.16, 1.33) [n = 15]	1.33 (1.18, 1.49) [n = 10]	1.19 (0.96, 1.48) [n = 5]
Fu and Boffetta (1995)	1.42 (1.05, 1.92) [battery/smelter only]	1.50 (1.23, 1.83) [battery/smelter only]	1.26 (0.70, 2.26) [battery/smelter only]
Steenland and Boffetta (2000)	1.30 (1.15, 1.46) [n = 8 – cohort only]	1.34 (1.14, 1.57) [n = 8 – cohort only]	1.01 (0.72, 1.42) [n = 7 – cohort only]

However, the authors noted that the lung cancer findings were not consistent across studies, and were influenced highly by one study (Lundstrom et al., 1997) in which confounding by arsenic was likely. Exclusion of this study dropped the combined lung cancer relative risk to 1.14 (95% CI: 1.04, 1.73). The strongest positive evidence was for stomach cancer (relative risk 1.34 [95% CI: 1.14, 1.57], 181 observed deaths). There was little positive evidence for renal cancer (relative risk 1.01 [95% CI: 0.72, 1.42], 40 deaths), or brain cancer (relative risk 1.06 [95% CI: 0.81, 1.40]). All meta-analyses used fixed effects models, given that no evidence of heterogeneity was found across studies (there was significant heterogeneity for lung cancer when the Lundstrom et al. study was included, but not when it was excluded).

Fu and Boffetta (1995) conducted an earlier meta-analysis in which they reviewed 16 cohort and 7 case-control studies. Different numbers of studies were used for meta-analyses of different outcomes, dependent on whether that outcome was reported separately, among other factors. These authors focused their analysis on the occupational studies. Twelve of these studies were used in a meta-analysis of lung cancer, resulting in a combined relative risk of 1.29 (95% CI: 1.10, 1.50) (random effects model). There was significant heterogeneity of lung cancer results across studies. Meta-analyses using fixed effects (no significant heterogeneity between studies) resulted in relative risks of 1.33 (95% CI: 1.18, 1.49) for stomach cancer (10 studies), of 1.19 (95% CI: 0.96, 1.48) for kidney cancer (5 studies), and 1.41 (95% CI: 1.16, 1.71) for bladder cancer (5 studies). No meta-analysis was conducted for brain cancer. Separate analyses for stomach, lung, and kidney cancer were also conducted for those studies with the

highest occupational exposure to lead (3 to 5 studies of battery and smelter workers), which resulted in slightly higher relative risks. The authors concluded that "the findings from the workers with heavy exposure to lead provided some evidence to support the hypothesis of an association between stomach and lung cancer and exposure to lead. The main limitation of the present analysis is that the excess risks do not take account of potential confounders, because little information was available for other occupational exposures, smoking, and dietary habits. The excess risk of stomach cancer may also be explained, at least in part, by nonoccupational factors. For bladder and kidney cancers, the excess risks are only suggestive of a true effect because of possible publication bias.

6.7.4 Genotoxicity of Lead

The NTP reviewed in some detail the genotoxicity studies over the period 1970-2002. These studies are cross-sectional studies, mostly of occupationally exposed workers compared to a control population. Usually blood lead levels are available to document exposure. Outcomes consisted of chromosomal aberrations (CA), sister chromatid exchange (SCE), micronuclei formation (MN), and studies of DNA damage (often via the comet assay) and/or measures of the mitotic activity. Of these outcomes, only CAs have been shown to have a positive relationship to subsequent cancer (Hagmar et al., 2004, Rossner et al., 2005). SCEs are generally considered a marker of exposure to environmental agents which have some effect on DNA, but are not thought to necessarily predict cancer risk. MN and DNA damage are thought to indicate genotoxicity with unknown effect on cancer risk. These outcomes are somewhat informative regarding the possible human carcinogenicity of lead but are clearly secondary to direct information on cancer risk from epidemiologic studies.

The most recent studies of the genotoxicity of lead are summarized in Annex Table AX6-7.1. Of eleven studies of chromosomal aberrations (CA), six were judged to show a positive relationship between CA and lead, four were judged negative, and one was neither clearly positive or negative. In general, these studies were done in the 1970s and 1980s; only one dates from the 1990s. There were nine studies of sister chromatid exchange. Of these, four were judged positive, three negative, and two could not be judged clearly one way or the other. It is notable that the positive studies were generally the most recent. There were four MN studies, all of which were judged positive. Finally, there were nine studies of DNA damage

and/or mitotic activity. These varied in the specific outcome, although many used a comet assay to measured oxidative damage to DNA. Eight of these nine studies were judged positive in the sense that increased DNA damage or mitotic activity was related to lead exposure, while one was judged negative.

Since the NTP review, there have been three additional cytogenetic studies which are informative regarding lead (Palus et al., 2003, Minozzo et al., 2004, and Fracasso et al., 2002), as well as one mutation study (Van Larebeke et al., 2004). All four of these studies (two of DNA damage one of MN, and one of a specific mutation frequency) were positive in significantly linking lead exposure to the outcome. The results of these studies as well as those reviewed by the NTP are summarized in Table 6-7.2.

Table 6-7.2. Results of Epidemiologic Studies on the Genotoxicity of Lead Exposure[a]

	Results		
Studied Outcome	**Positive**	**Mixed**	**Negative**
Chromosomal Aberrations (CA)	6	1	4
Sister Chromatid Exchange (SCE)	4	2	3
Micronucleus Formation (MN)	5	0	0
DNA Damage/Mitosis	10	0	1
Gene Mutation	1	0	0

[a] Results summarize the overall findings of epidemiologic studies addressing the potential genotoxic effects of lead exposure. Some studies addressed multiple aspects of genotoxicity; for these studies, their results for each of the listed categories of genotoxic outcomes are presented separately.

While the overall the evidence from cytogenetic studies is mixed, more recent studies which were focused on DNA damage or mitotic activity have tended to be largely positive. However, it is not known whether these outcomes predict subsequent cancer risk.

6.7.5 Review of Specific Studies on the Carcinogenicity of Lead Since the 1986 Lead AQCD

6.7.5.1 Introduction

The epidemiologic studies of lead exposure and cancer are listed in Table 6-7.3. The most relevant studies focus on exposure through occupational sources, wherein the most intense exposure to lead can be expected to occur. This exposure predominantly involves inorganic lead species. Relevant studies are discussed below, beginning with the most key studies of the general population will then be presented followed by a brief summary of other relevant studies examining the occupational studies.

6.7.5.2 Key Studies of Occupational Populations in the U.S.

There are seven key occupational studies based on highly exposed worker populations; these are all cohort studies with adequate numbers to address lung and/or stomach cancer. There are two cohorts based in the U.S. and five based outside it. Studies reviewed in this section are summarized in Annex Table AX6-7.2.

Steenland et al. (1992) followed up 1,990 male U.S. lead smelter workers, employed from 1940 to 1965, through 1988. Standardized mortality ratios indicated an excess of lung, stomach, kidney, and bladder cancer, but these excesses did not reach statistical significance. Focusing on a subgroup of workers classified as highly lead exposed based on air-monitoring records yielded a statistically significant excess for kidney cancer (standardized mortality ratio of 2.39 [95% CI: 1.03, 4.71]), although it did not appear to increase with increasing duration of exposure. Estimates for the other cancers (standardized mortality ratio of 1.11 [95% CI: 0.82, 1.47] for lung; 1.28 [95% CI: 0.61, 2.34] for stomach; 1.33 [95% CI: 0.48, 2.90] for bladder) showed little change with restriction to the high-exposure group. While neither arsenic nor cadmium exposure could be controlled for, 1975 NIOSH monitoring data indicated less intense exposure to airborne cadmium or arsenic than to lead. Lead averaged 3.1 mg/m^3 and arsenic 14 $\mu g/m^3$, compared to current OSHA standards of 0.05 mg/m^3 for lead and 10 $\mu g/m^3$ for arsenic. It is notable that a 1996 review of studies (Steenland et al., 1996) on arsenic-exposed workers concluded that significantly elevated rates of lung cancer were concentrated in studies where average exposures greatly exceeded OSHA standards (e.g., hundreds of $\mu g/m^3$). No data on workers' smoking status were available.

Table 6-7.3. Epidemiologic Studies of Lead Exposure and Cancer in Specific Populations, by Geographic Region and Study Design[a]

	Epidemiologic Study Design		
Specific Study Population	**Cohort**	**Nested Case-control**	**Case-control**
United States			
Battery and lead production workers	Cooper and Gaffey (1975), Cooper et al. (1985), Wong and Harris (2000)	Cooper et al. (1989), Wong and Harris (2000) (same publication as cohort study)	
Copper workers (Utah)	Rencher et al. (1977)		
Lead and zinc pigment plant workers	Sheffet et al. (1982)		
Lead smelter workers (Idaho)	Selevan et al. (1985), Steenland et al. (1992)		
Sample of deaths due to cancer vs. noncancer deaths (Illinois)			Mallin et al. (1989)
Brain cancer			Cocco et al. (1998a)
Central nervous system cancer			Cocco et al. (1998b)
Stomach cancer			Cocco et al. (1999)
NHANES II cohort mortality follow-up, general U.S. population	Jemal et al. (2002), Lustberg and Silbergeld (2002)		
Canada			
Population-based cases			Risch et al. (1988)
Specific cancers versus all cancers			Siemiatycki et al. (1991)
Europe			
Glass workers (Finland)	Sankila et al. (1990)		
Registry-derived liver cancer cases vs. stomach cancer or myocardial infarctions (Finland)		Kauppinen et al. (1992)	
Workers via Cancer Registry (Finland)	Anttila et al. (1995)	Anttila et al. (1996)	
Renal-cell cancer vs. population controls (Germany)			Pesch et al. (2000)
Laryngeal cancer among persons with no history of lead exposure (Greece)			Kandiloris et al. (1997)

Table 6-7.3 (cont'd). Epidemiologic Studies of Lead Exposure and Cancer in Specific Populations, by Geographic Region and Study Design[a]

Specific Study Population	Epidemiologic Study Design		
	Cohort	Nested Case-control	Case-control
Europe (cont'd)			
Glass workers (Italy)	Cordioli et al. (1987)		
Lead and zinc miners: females only (Sardinia)	Cocco et al. (1994b)		
Lead and zinc miners: male only (Sardinia)	Cocco et al. (1994a), Carta et al. (1994); Carta et al. (2003*)*		
Lead and zinc smelter workers (Sardinia)	Cocco et al. (1996)		
Lead and zinc smelter workers (Sardinia, but different from Cocco et al. 1996)	Cocco et al. (1997)		
Glass workers (Sweden)	Wingren and Englander (1990)	Wingren and Axelson (1985, 1987, 1993)	
Copper and lead smelter workers (Sweden)	Gerhardsson et al. (1995a)		
Copper and lead smelter workers (Sweden) (Lundström: full cohort; Englyst: sub-cohort)	Gerhardsson et al. (1986), Lundström et al. (1997), Englyst et al. (2001)		
Lead-acid battery workers (U.K.)	Dingwall-Fordyce and Lane (1963), Malcolm and Barnett (1982)		Fanning (1988)
Chromate (including lead-chromate) workers (U.K.)	Davies (1984a, 1984b)		
Zinc, cadmium, and lead smelter workers (U.K.)	Ades and Kazantzis (1988)	Ades and Kazantzis (1988) (same publication as cohort study)	
Asia			
Gliomas vs. noncancer patients (China)			Hu et al. (1998)
Meningiomas vs. noncancer patients (China)			Hu et al. (1999)
Gall bladder cancer vs. gallstone patients (India)			Shukla et al. (1998)
Prostate cancer cases versus benign prostate hyperplasia cases and normal controls (India)			Siddiqui et al. (2002)

[a] Within regions, study populations are listed in chronological order based on the earliest published study on that specific worker population. Publications considered to be key studies are italicized.

Wong and Harris (2002) extended follow-up on the battery and smelter worker cohort previously reported on by Cooper et al., 1985 through 1995, an additional 15 years. With the additional follow-up, standardized mortality ratios for lung, tracheal, or bronchial cancer decreased to 1.14 (95% CI: 0.99, 1.30) for battery workers but showed little change for smelter workers at 1.22 (95% CI: 1.00, 1.47). A significantly elevated standardized mortality ratio for stomach cancer (1.53 [95% CI: 1.12, 2.05]) persisted among battery workers, with a lesser elevation among smelter workers (1.33 [95% CI: 0.75, 2.20]). Among other cancers, only thyroid cancer among all workers combined showed a significantly elevated standardized mortality ratio (3.08 [95% CI: 1.33, 6.07]). Cancer mortality did not increase with earlier year of hire for lung, stomach, or thyroid cancer. Lung and stomach cancer mortality peaked among workers with 10 to 19 years of factory employment and declined with longer employment duration. Thyroid cancer mortality occurred exclusively among workers with 20 or more years of exposure. As with earlier analyses based on this cohort, concomitant exposures to other compounds could not be controlled for, but as these were likely to be most intense among lead production workers, whose standardized mortality ratios were similar to or lower than those for battery workers, any bias resulting from such exposure probably was toward the null. No data were available to assess the possible role of smoking, diet, or other potential nonoccupational risk factors in the results.

A nested case-control analysis was also conducted to further explore stomach cancer mortality within workers employed at the Philadelphia lead battery plant in the cohort (Wong and Harris, 2000). Among 30 workers who died of stomach cancer and 120 age-matched controls, job title histories were used to estimate duration of employment and cumulative exposure based on job-specific intensities of exposure. Duration of employment and estimated degree of lead exposure showed no elevation among workers who died of stomach cancer, nor did mortality increase across increasing tertiles of lead exposure. Little information appeared to be available on potential confounders. The authors suggested that in light of historically higher stomach cancer rates in Ireland and Italy and the observation of a higher proportion of Irish and Italian immigrants among lung cancer cases in the case-control study, differences in ethnicity may have contributed to the elevated standardized mortality ratios seen in the cohort as a whole. The recent IARC Working Group (IARC, 2005) concluded that, based on the ethnic composition

of the control population (23% Irish or Italian), confounding by race could account for only part of the observed association, however.

The extended follow-up and nested case-control analyses on the original Cooper et al. (1985) cohort thus continued to provide evidence for some increase in lung and stomach cancer among these lead workers, but no consistent evidence of increasing cancer risk with increasing exposure within the lead worker cohort itself, especially for stomach cancer.

Fanning (1998) studied deaths due to specific cancer types among U.K. battery and other factory workers. High to moderate lead exposure resulted in odds ratios for lung and digestive cancer of 0.93 and 1.13, respectively, with the latter elevation due mainly to stomach cancer (odds ratio of 1.34). No odds ratios reached nominal statistical significance, and no associations were noted for other cancer types. The excess of digestive cancer deaths was restricted to the 1926 to 1965 period, during which lead exposures would have been most intense. Odd ratios for other cancers did not vary by period. Because each cancer case group was compared with a control group consisting of subjects who died from all other causes, including other cancers, odds ratios would have been biased downward if some of these other deaths also were lead-related. However, most deaths were due to nonmalignant respiratory or circulatory diseases other than hypertension, mitigating the potential impact of such a bias.

Anttila et al. (1995) linked 20,700 Finnish workers whose blood lead was monitored during 1973 to 1983 by the Finnish Institute of Occupational Health to the Finnish Cancer Registry. Exposure was subdivided according to highest peak blood level measured: low (0 to 0.9 μmol/L [0 to 18.6 μg/dL]), moderate (1.0 to 1.9 μmol/L [20.7 to 39.4 μg/dL]), and high (2.0 to 7.8 μmol/L [41.4 to 161.6 μg/dL]). The total cohort showed no elevation in total or site-specific cancer mortality, based on an standardized mortality ratio analysis. Among male workers with moderate exposure, incidence of total respiratory cancer and lung cancer both were elevated (standardized incidence ratio of 1.4 [95% CI: 1.0, 1.9 for both]). Risks of total digestive, stomach, bladder, and nervous-system cancer also were modestly elevated. However, risks did not increase in the high-exposure group. Risks of mortality for all cancer for both men and women (relative risk 1.4 of [95% CI: 1.1, 1.8]) and lung or tracheal cancer (relative risk of 2.0 [95% CI: 1.2, 3.2]) were even stronger when a person-year analysis was applied to compare workers with moderate lead exposure to those with low exposure. Again, risks did not increase in the highest exposure group. This exposure group was smaller than the others, however, which

limited the power of analyses specific for high exposure workers. Thus, for example, the numbers of lung or tracheal cancer deaths among men in the low-, moderate-, and high-exposure groups were 25, 34, and 11, respectively, for the person-year-based analyses.

It should be noted that for cancer, cumulative exposure, particularly during the earlier part of the follow-up period, might be more relevant than peak exposure, although the two were reported to be highly correlated (Anttila et al., 1995). Case-referent substudies of lung cancer used different exposure criteria (Anttila et al., 1995). Odds ratios increased most consistently with increasing cumulative exposure to lead. Among histologic subtypes, significantly elevated risk for squamous-cell cancer of the lung (odds ratio of 4.1 [95% CI: 1.1, 15]) for the highest blood lead group persisted after adjustment for smoking, although with additional adjustment for engine exhaust and solvent exposure, the risk declined (odds ratio of 3.4 [95% CI: 0.9, 13]). Results for female workers are not considered, as too few cancers (3 total) occurred to permit meaningful conclusions. Although the follow-up period was relatively short, the lung cancer association was analyzed in much greater detail than in most studies, and smoking was adjusted for, while the association between lead exposure and lung cancer weakened with control for engine exhaust and solvent exposure, the odds ratio remained well above 1. The highest odds ratio of all was observed for estimated risk of lung cancer among workers with peak blood lead levels of at least 0.8 μmol/L [≥16.6 μg/dL] who were exposed to engine exhaust (odds ratio of 14.9 [95% CI: 1.3, 178]; 11 cases). If engine exhaust was acting as an effect modifier, directly controlling for it might not have been appropriate. The exhaust could have served as a source of organic lead, as well.

Gerhardsson et al. (1995a) followed up 664 male Swedish secondary lead smelter workers, tracing their cancer morbidity from 1969 to 1989. Compared to the population of the surrounding county, the workers' standardized incidence ratio for all cancers was 1.27 (95% CI: 0.91, 1.74), based on 40 tumors. Standardized incidence ratios for cancers at all specific sites except the brain were elevated, notably those for the respiratory system (1.32 [95% CI: 0.49, 2.88]), stomach (1.88 [95% CI: 0.39, 5.50]), and colon (1.46 [95% CI: 0.30, 4.28]). Because of the small numbers of tumors (only 6, 3, and 3, respectively, even for the aforementioned sites), the reliability of estimates for most sites is limited. Restricting analyses to workers in the highest quartile of lead exposure based on routine blood lead monitoring data yielded a higher standardized incidence ratio for total gastrointestinal cancer (2.43 [95% CI: 1.11, 4.62];

9 tumors), but not respiratory cancer. Availability of blood lead measurements is an advantage of this study, along with a lead-exposed worker population unlikely to have much exposure to arsenic, chromium, or cadmium. However, the cases were too few for detailed exposure-response analyses by cancer type. Lack of data on smoking further restricts interpretation of the results.

Lundström et al. (1997) followed 3,979 Swedish smelter workers from 1928 to 1987. Workers were further subdivided into those with high cumulative blood lead scores (mean times years exposed >10 μmol/L), and those exposed to "lead only" (excluding those from departments thought to have significant exposures to other potential carcinogens, such as arsenic, or little exposure to lead). The lung cancer standardized mortality ratio was 2.8 (95% CI: 2.0, 3.8) for the total cohort, 2.8 (95% CI: 1.8, 4.5) for the high-exposure subgroup, and reportedly similar for the subgroup exposed to lead only. With adjustment for a 15-year latency period, lung cancer standardized incidence ratios likewise differed little between the total cohort and high-exposure subgroup; however, among workers with exposure to lead only, the standardized incidence ratio rose from 3.1 (95% CI: 1.7, 5.2; 14 cases) for all workers to 5.1 (95% CI: 2.0, 10.5; 7 cases) for those with the highest exposure. With a 15-year latency period, elevated standardized incidence ratios also were observed for cancer of the brain and nervous system (1.6 [95% CI: 0.4, 4.2]) and renal pelvis, ureter, or bladder (1.8 [95% CI: 0.8, 3.4]) among the high-exposure subgroup. Non-respiratory cancers were too infrequent (5 total) in the high-exposure lead-only subgroup for meaningful analysis. This study's size, extensive follow-up, and ability to integrate blood-based and job-based exposure indices give it unusual power. The apparent increase in cancer risk with higher cumulative lead exposure that appeared when workers thought to be potentially exposed to other metals, such as arsenic and nickel, were excluded also appeared to strengthen the evidence for a specific link between lead and respiratory cancer. A subsequent study by Englyst et al. (2001), however, cast doubt on the efficacy of the "lead only" grouping.

Englyst et al. (2001) conducted additional analyses on one element of the Lundström et al. (1997) cohort. A total of 1,093 workers from the smelter's lead department was followed up through 1997. Significantly elevated lung cancer standardized incidence ratios were observed in all subcohorts, including the subcohort who had never worked in arsenic-exposed areas (3.6 [95% CI: 1.2, 8.3]; 5 cases). This subcohort is the same as the "lead-only" subgroup evaluated by Lundström et al. (1997). A review of detailed job histories obtained for all workers

with lung cancer, however, indicated that 13 of the 15 had "considerable" exposure to arsenic as well as lead, including all but 1 in the "lead only" subcohort.

Carta et al. (2003) followed up the mortality of 918 Sardinian lead smelter workers from 1972 through 2001. Smelter workers as a whole displayed an overall cancer mortality no higher than expected based on regional rates (standardized mortality ratio of 1.01). Cancer-specific standardized mortality ratios were, however, nonsignificantly elevated for cancers of the lung (1.21) and stomach (1.22) as well as for lymphoma and leukemia (1.82). Use of blood and ambient lead monitoring data available by department and task to categorize estimated exposure yielded a statistically significant upward trend with increasing lead exposure for lung cancer; no significant trend was seen for the other cancers, although in light of the small number of gastric cancer and lymphoma/leukemia deaths (4 and 6, respectively) interpretation of dose-response is problematic for these outcomes.

6.7.5.3 Key Studies of the General Population

There are two key general population cohort studies in which lead exposure is assessed via blood lead levels (see Annex Table AX6-7.3 for additional details). Jemal et al. (2002) conducted the first biomarker-based general population cohort study of lead exposure and cancer. The study employed the subsample of 3,592 white U.S. participants in NHANES II (1976 to 1980) who had undergone blood lead level determinations at time of entry. Deaths among this population were enumerated through 1992 by linkage to the National Death Index (NDI) and Social Security Administration Death Master File. Median blood lead levels in this population were 12 μg/dL. Adjusted for age, smoking, drinking, region, year, and gender, risk of mortality from any cancer rose across quartiles of blood lead level, but this trend was not statistically significant. The trend across quartiles was not consistent in gender-specific analyses, although relative risks were elevated for the highest quartile of blood lead level in both men and women (relative risk 2.0 for men and 1.6 for women). The relative risk for lung cancer based on comparison of subjects with blood lead levels above or below the median was 1.5 in the combined population, with higher risk observed among women (2.5 [95% CI: 0.7, 8.4]) than men. The highest relative risks were observed for cancer of the esophagus (3.7 [95% CI: 0.2, 89]), pancreas (3.6 [95% CI: 0.6, 19.8]), and stomach (2.4 [95% CI: 0.3, 19.1]); no elevations were noted for cancers of other sites.

The lack of statistically significant results reflects the small number of deaths during follow-up, which limited the study's power; of the nine major sites examined, the number of deaths ranged between 5 and 16 for all sites except the lung. Detailed exposure-response analyses were restricted to all cancers combined, although potential effects could have been strongly target-organ specific. In addition, the use of quartile cut points based on the distribution of lead concentrations estimated for the total U.S. population resulted in relatively small numbers in the referent group (lowest exposure quartile) for males and in the high-exposure quartile for females. Use of a biomarker provided an objective measure of lead exposure. Nevertheless, reliance on a single blood lead measurement produces less reliable estimates than would be obtained through multiple measurements and precludes addressing temporal changes in lead exposure over the follow-up period. Lack of control for exposure to occupational carcinogens other than lead and potential residual confounding by duration and intensity of tobacco smoking also could have biased the results, especially for men. Lustberg and Silbergeld (2002) carried out another biomarker-based general population study based on the same NHANES II mortality cohort used by Jemal et al. (2002). This study did not exclude nonwhites, however (thus gaining 524 subjects) and employed more extensive adjustment for potential confounding factors than the Jemal et al. (2002) analyses (i.e., education, body mass index, and exercise were included in the regression models, although alcohol intake was not). In addition, persons with blood lead levels of 30 μg/dL or higher were excluded in order to restrict comparisons to levels below the OSHA standard for lead exposure. Persons with levels below 10 μg/dL served as the referent group. Survival analyses adjusted for potential confounders found a relative risk for cancer mortality of 1.5 (95% CI: 0.9, 2.5) for those with blood lead levels of 10 to 19 μg/dL, compared with those with levels below 10 μg/dL, rising to 1.7 (95% CI: 1.0, 2.8) for those with levels of 20 to 29 μg/dL. Separate analyses of lung-cancer and non-lung-cancer deaths yielded estimates of increased risk for moderate- or high-exposure groups, compared with the referent population, both for lung cancer and non-lung cancer. However, none of the estimates reached the $P < 0.05$ level of statistical significance, and the results for non-lung cancers showed no evidence of an exposure-response relationship.

As with Jemal et al. (2002), the use of a biomarker for exposure and the prospective design of the study are strengths. Its attempts to control for potential confounders were more extensive, and its choice of cut points for the referent category yielded more males in the referent

group, although that group still included less than 20% of the study population. However, it is notable that blood lead levels rose significantly with smoking level. The models included terms for former smoking, current light smoking, and current heavy smoking (>1 pack per day). Nevertheless, some degree of residual confounding due to smoking might have remained, which could have contributed to the estimated risk of lung cancer for the highest exposure category (relative risk of 2.2 [95% CI: 0.8, 6.1]). Such residual confounding would have had less effect on the results for non-lung cancer. As noted regarding the other NHANES-based study, however, mortality due to cancers of other sites was too uncommon to allow for reliable site-specific comparisons. In the Lustberg and Silbergeld analysis, all cause and cardiovascular mortality increased monotonically with blood lead level, which might indicate residual confounding from SES or smoking affecting both heart disease and cancer.

6.7.5.4 Other Lead Studies

There are a variety of other epidemiologic studies of lead exposure, which are less important than the key studies above but which offer some information. Studies reviewed in this section are summarized in Annex Table AX6-7.4. Rencher et al. (1977) compared Utah copper smelter workers' mortality with that of miners for the same company. Workers in lead-exposed operations had a higher proportional mortality due to respiratory cancer in general and lung cancer specifically than did other workers, with or without control for smoking status. Among lead-exposed workers, those who developed lung cancer had significantly higher estimated lead exposure than the rest. Workers with lung cancer also had significantly higher estimated exposure to arsenic and sulfur dioxide, however, and these exposures were not adjusted for.

Ades and Kazantzis (1988) conducted a cohort study of lung cancer mortality among 4,393 U.K. zinc, lead, and cadmium smelter workers. Smelter workers had a lung cancer standardized mortality ratio of 1.25 (95% CI: 1.07, 1.44) compared with national rates, based on 182 lung cancer deaths Potential effects of lead could not be adjusted for arsenic exposure or other exposures due to inadequate numbers. Cancer-specific standardized mortality ratios were calculated for production and maintenance workers from an Italian lead and zinc smelter followed from 1950 to 1992 by Cocco et al. (1997). Deaths from lung,, stomach, and all cancer were not elevated over regional rates. Cocco et al. (1996) followed 1,060 Sardinian lead and zinc smelter workers whose glucose-6-phosphate dehydrogenase (G6PD) phenotype had been

measured from 1973 through 1991. Despite the thought that G6PD-deficient workers might be more vulnerable to the depletion of red blood cell glutathione associated with lead toxicity, mortality from cancer and from all causes was slightly lower among G6PD-deficient workers than among G6PD-normal workers. Follow-up was subsequently extended through 2001 by Carta et al. (2003).

Three European studies followed up cohorts of glass workers. Cordioli et al. (1987) studied 468 Italian glass workers. Workers producing low-quality glass containers were classified as being exposed to lead. A small elevation in mortality from all cancer (standardized mortality ratio of 1.3 [95% CI: 0.8, 1.8]) among glass workers was driven by significant excesses in lung cancer (2.1 [95% CI: 1.1, 3.6]) and laryngeal cancer (4.5 [95% CI: 1.2, 11.4]). The small number of deaths among exposed workers (28 total, 13 lung, and 4 laryngeal cancer) limited the study's statistical power. Sankila et al. (1990) compared the incidence of cancer in 1,803 male and 1,946 female Finnish glass workers with that of the national population. Glassblowers were considered to be a lead-exposed subgroup. Modest elevations in lung cancer risk were observed among glass workers for both men (standardized incidence ratio of 1.3 [95% CI: 1.0, 1.7]) and women (1.1 [95% CI: 0.5, 2.3]). However, the increased risk of lung cancer was not specific to glassblowers. In the final study, Wingren and Englander (1990) compared mortality in Swedish glass workers from work areas with airborne lead levels ranging from <0.001 up to 0.110 mg of lead/m^3, noting a significant elevation for pharyngeal cancer (standardized mortality ratio of 9.9 [95% CI: 1.2, 36.1]) and nonsignificant elevations for lung and colon cancer compared to national rates.

Wingren and Axelson (1985, 1987, 1993) conducted a case-control analysis comparing stomach, colon, and lung cancer mortality among Swedish glass workers with that of the surrounding regional populations. A small early study of three parishes (Wingren and Axelson, 1985) was expanded to include 11 parishes, thus encompassing most of the Swedish glass-work industry (Wingren and Axelson 1987). Mortality from cancer of the lung (odds ratio of 1.7 [90% CI: 1.1, 2.5]), stomach (1.5 [90% CI: 1.1, 2.0]), and colon (1.6 [90% CI: 1.0, 2.5]) all were elevated among glass workers as a whole (Wingren and Axelson, 1987). Among specific classes of glass workers, glassblowers had the highest odds ratios (2.3, 2.6, and 3.1 for lung, stomach, and colon cancer, respectively). When the data were analyzed according to level of estimated metal exposure, no consistent dose-response trend with lead was found for lung cancer, and the

association with stomach cancer was weaker for lead than for arsenic, copper, and other metals. In general in this study it was difficult to separate the independent cancer effects of different metals.

Sardinian lead and zinc miners were studied in a set of three papers published in 1994. Carta et al. (1994) studied a small group of workers and Cocco et al. (1994a,b) expanded coverage to follow 1,741 male and 526 female workers from two mines. Number of cancer deaths were small. This study was limited because exposure characterization focused only on silica and radon daughters; no lead exposure specific analyses were performed.

Davies (1984b) followed up 57 pigment factory workers who had been diagnosed with nonfatal lead poisoning, finding a small excess of lung cancer deaths (relative risk of 1.45), but with only 4 deaths in the lead-poisoned group this result did not reach statistical significance.

Mallin et al. (1989) used death certificates for Illinois males to compare deaths from seven specific cancers with a control group of 3,198 randomly selected deaths from other causes. Based on occupations from death certificates, the odds ratio for cancer of the brain (3.0, $p < 0.05$) was significantly elevated in white male glass workers (as well as physicians and communications workers). No significant association was observed for other cancer sites, including lung and stomach. This isolated association is not consistent with the results for Swedish glass workers summarized above. The National Cancer Institute, NIOSH, and the National Center for Health Statistics have assembled a database that integrates industry, occupation, and cause of death information from death certificates in 24 states. This resource provides a very large sample size for case-control analyses of occupational exposures, but results are limited by a lack of detailed work history and no control over confounders. Cocco et al. (1998a) matched all 27,060 brain cancer deaths occurring among persons aged 35 or older during 1984 to 1992 with four gender-, race-, age-, and region-matched deaths from nonmalignant causes. A job-exposure matrix was used to assign subjects to low, medium, or high probability and intensity of exposure. Risk of brain cancer mortality increased consistently with rising intensity of lead exposure among African American men but not among the other three race-gender groups. Cooco et al. (1998b) broadened the study to CNS cancer deaths, and computed odds ratios for specific industries and occupations rather than particular substances. Statistically significant associations were found with some industries and some race/sex groups, but little inference can be made about lead carcinogenicity from these data.

In the third 24-state death-certificate study, 41,957 stomach cancer deaths were matched with 83,914 deaths due to nonmalignant causes (Cocco et al., 1999). A job-exposure matrix was used to assign subjects to low, medium, or high probability and intensity of exposure to lead and 11 other chemicals. Elevated odds ratios occurred among white women (1.53 [95% CI: 1.10, 2.12]), African-American men (1.15 [95% CI: 1.01, 1.32]), and African-American women (1.76 [95% CI: 0.74, 4.16]) with high probability of lead exposure. Odds ratio in the moderate-probability group were elevated only for African-American women (1.37 [95% CI: 0.58, 3.21]), and not elevated for any exposure group among white males. Risk showed no consistent increase with intensity of exposure in any group. The absence of any association with lead exposure among the largest race-gender group, white males, is notable, as is the general absence of association with intensity of exposure. More consistent elevations of odds ratios for stomach-cancer mortality were observed for inorganic dust and nitrosamines than for lead.

Anttila et al. (1996) presented a nested case-control analysis of 26 Finnish male workers with central nervous system (CNS) cancer and 200 controls, using the same Finnish occupational cohort as in Anttila et al. (1995). For CNS cancer incidence, odds ratios rose with increasing peak lifetime blood lead level; however, the trend was not statistically significant. Odds ratios for glioma mortality rose consistently and significantly with increasing peak and mean blood lead level, as well as duration of and estimated cumulative lead exposure. A strength of this study is the availability of blood lead measurements. Limitations include the small number of cases (10 gliomas among workers with complete exposure information), short follow-up time (maximum of 15 years), potential selection bias due to low response rates (60% for cases, 56% for controls), and possible coexposures such as solvents or other metals.

Risch et al. (1988) compared 826 Canadian men with histologically confirmed bladder cancer with 792 Canadian population controls. Reported occupational exposure to lead yielded a significantly elevated smoking-adjusted odds ratio (2.0 [95% CI: 1.2, 3.5]) and a significant trend with duration of exposure. Of 17 other exposures examined, only one (tar and asphalt) was significantly associated with bladder cancer. These analyses relied on self-reported exposure, with the potential for inaccurate recall. Siemiatycki et al. (1991) conducted a case-control study in Canada using 3,730 cases of various histologically confirmed cancers. Occupational exposure to 293 substances, including lead, was estimated from interview data. Elevated odds ratios were noted for cancer of the lung (1.1 [90% CI: 0.9, 1.4]), stomach (1.2 [90% CI: 1.0, 1.6]), bladder

(1.3 [90% CI: 1.0, 1.6]), and kidney (1.2 [90% CI: 1.0, 1.6]). Strengths of this study are adjustment for smoking and other potential risk factors and reliance on interview-obtained exposure data, further evaluated by experts. Limitations include potential confounding by the other 292 occupational exposures and low quantitative detail regarding lead exposure.

Kauppinen et al. (1992) conducted a nested case-control study in Finland, matching 344 primary liver cancer deaths by age and gender to 476 stomach cancer deaths and 385 myocardial infarct deaths. No association was found between lead and liver cancer, which was not an a priori site of interest. Use of a control group with stomach cancer, which some other studies have linked to lead exposure, may have biased results toward a negative association.

In a Chinese hospital-based case-control study, Hu et al. (1998) compared 218 patients with histologically confirmed primary gliomas with 436 patients with non-neurological, nonmalignant disease, matched by age, gender, and residence. An odds ratio could not be calculated for occupational exposure to lead because no glioma patients reported such exposure.

In a parallel study, Hu et al. (1999) compared 183 patients with histologically confirmed primary meningiomas with patients with non-neurological, nonmalignant disease, matched by age, gender, and residence. Reported occupational exposure to lead was associated with risk of meningioma in both men (odds ratio of 7.20 [95% CI: 1.00, 51.72]) and women (5.69 [95% CI: 1.39, 23.39]). Some elevation of odds ratios occurred in most of the 14 occupational exposures examined, including exposure to cadmium. Malczyk et al. (1999) measured urinary lead concentrations in 24 Polish bladder cancer cases. Ten out of the 24 cases had urinary lead levels above 90 μg/L, thus exceeding the upper limit of the range estimated as normal for a healthy person (10-90 μg/L). Results are limited by the lack of any measurements done on persons without bladder cancer from the same area.

Pesch et al. (2000) compared occupational exposure to potential carcinogens among 935 Germans newly diagnosed with renal-cell cancer and 4,298 controls selected from regional population registries and matched by age, gender, and area of residence. Lifetime job histories and information on smoking habits and other potential risk factors were collected by interview. Cumulative exposure to lead, as well as cadmium, solder fumes, welding fumes, and metals in general, was estimated based on previously published job exposure matrices and grouped into four ascending categories; separate estimates of lead exposure were calculated based on British- and German-developed matrices. After adjustment for age and smoking, odds ratios for renal

cancer were elevated in men (1.5 [95% CI: 1.0, 2.3]) and women (2.6 [95% CI: 1.2, 5.5]) with the highest lead exposure, compared with the low-exposure groups based on the British matrix. When exposure was based on the German matrix, the odds ratio was less elevated among men (1.3 [95% CI: 0.9, 2.0]); no results for women were reported. Strengths of the study are its size and population base. The primary limitation is uncertainty regarding the specificity of the results for lead. Significant associations also were noted for exposure to cadmium, solder fumes, and organic solvents among men, for example, but no analyses attempting to account for other exposures were reported. It is thus unclear how much of the observed risk associated with lead exposure may be secondary to exposure to cadmium or other agents.

Siddiqui et al. (2002) compared blood lead levels in Indian men with prostate cancer or benign prostatic hyperplasia to levels seen in normal controls of similar SES. Lead levels were significantly higher in both prostate cancer and benign prostatic hyperplasia cases than in controls, while zinc levels were lower.

Kandiloris et al. (1997) found similar blood lead levels but lower aminolevulinic acid dehydratase (ALAD) activity in 26 laryngeal carcinoma cases compared to 53 controls from the same hospital. Shukla et al. (1998) found significantly higher mean bile lead in 38 newly diagnosed, histologically confirmed gall bladder cancer cases compared to 58 patients with gallstones diagnosed at the same Indian hospital surgical unit (58.38 ± 1.76 mg/L versus 3.99 ± 0.43 mg/L). Cancer cases also showed elevated cadmium and chromium levels.

6.7.6 Confounding of Occupational Lead Studies Due to Other Occupational Exposures: Arsenic, Cadmium

A number of studies of lead workers come from smelters, where exposures to other metals are common. Of particular concern are other lung carcinogens, especially arsenic (workers exposed to high levels of arsenic historically have had a lung cancer relative risk of 3-4, see Steenland et al. 1996), but also cadmium. Glass workers are also of limited use for inference about lead effects, as they are also typically exposed to arsenic, cadmium, chromium, and nickel, all of which are lung carcinogens (e.g., see Wingren and Axelson, 1993).

In some smelters, measurements have been taken which indicate clearly that exposures to these other carcinogens was minimal and the main suspect is lead (e.g., Steenland et al., 1992). In others, however, one is unable to disentangle the effects of arsenic and lead (Ades and

Kazantis, 1988, Lundstrom et al., 1997). As a result, these studies cannot yield strong evidence regarding the possible relation between lung cancer and lead specifically. The study by Lundstrom et al., 1997 is particularly important in this regard, because it had a high relative risk of 2.8 (95% CI: 2.0, 3.8), and had an important effect in raising the overall result when included in meta-analyses (e.g., Steenland and Boffetta [2000], where exclusion of the Lundstrom et al. study lowered the estimated combined lung cancer relative risk from 1.30 to 1.14). A subsequent publication by Englyst et al. (2001) indicated that the smelter workers studied by Lundstrom et al. (1997) were likely to have had significant exposure to arsenic, and the authors concluded that it was impossible to separate the effects of lead and arsenic.

6.7.7 Confounding of Lead Studies: Smoking and Other Factors

The most informative studies of lead carcinogenicity are those comparing highly exposed workers to general populations. In these comparisons one must consider typical differences between worker populations and the general populations, in particular differences due to smoking and diet. Smoking can be a major confounder for lung cancer, while diet or SES can be a confounder, albeit weaker, for stomach cancer.

Regarding smoking, it has been shown both theoretically and empirically that confounding due to smoking differences between workers and the general population will typically account for an observed relative risk of approximately 1.1 to 1.2, with a possible maximum of about 1.4 (Axelson and Steenland, 1988; Siemiatycki et al., 1988). Furthermore, most occupational cohort studies are retrospective and have little information on smoking, making it impossible to control directly for potential confounding by this strong risk factor. As noted above, the lung cancer relative risk in the meta-analysis of Steenland and Boffetta (2000), after excluding the Lundstrom et al. study, was 1.14 (95% CI: 1.04, 1.73), based on seven occupational cohort studies, six of which used a non-worker external referent population, and none of which controlled for smoking as a confounder. This relatively small excess relative risk could plausibly be due to confounding by smoking. Unfortunately the occupational cohort studies were usually not followed by nested-case control studies of lung cancer which could have controlled for smoking, and furthermore they usually did not involve internal exposure-response analyses, wherein confounding by smoking is usually minimal. An exception was the lung cancer case-control study conducted by Anttila et al. (1995) within a large cohort of Finnish

workers with known blood lead levels. In this case-control study smoking-adjusted lung cancer odds ratios were increased among workers with higher estimated cumulative blood lead or higher peak blood lead exposure compared to workers with the lowest exposure, and the authors noted that smoking actually appeared to be a "weak negative confounder" for the high peak blood lead group. Also, in one large population-based case-control study with extensive information on other cancer risk factors, there remained an elevated odds ratio for lung cancer with substantial lead exposure after controlling for smoking (Siemiatycki et al., 1991). Hence there is some evidence that confounding by smoking does not explain the modest excess lung cancer risk seen in many studies.

Diet high in salt or smoked meats, *Helicobacter pylori* infection, and SES are possible confounders for stomach cancer. Those of highest SES compared to those of lower SES have been shown to have a relative risk of about 3 (Tomatis, 1990). None of the occupational cohort studies, in which again stomach cancer in workers was compared to the general population, controlled for these potential confounders. However, these potential confounding factors are much less powerful risk factors in respect to stomach cancer than smoking is with respect to lung cancer, and hence are unlikely to account for relative risks higher than perhaps 1.1 or at most 1.2. Given that the occupational cohort studies had a combined relative risk of 1.34 (95% CI: 1.14, 1.57) in the meta-analysis of Steenland et al. (2002) and 1.33 (95% CI: 1.18, 1.49) in that of Fu and Boffetta (1995), it seems unlikely that confounding by these factors can fully account for the excess stomach cancer risk observed in the occupational studies.

6.7.8 Summary of Epidemiologic Evidence for the Genotoxic and Carcinogenic Effects of Lead

The availability of studies of cancer in lead-exposed populations was relatively limited at the time of the 1986 Lead AQCD. The number and range of studies has notably expanded since that time, including extended follow-ups of major extant cohorts, new cohort and case-control studies, and analyses addressing not only cancer but genotoxicty. These new human data greatly expand our knowledge of possible lead carcinogenicity. Animals studies are primarily based on dermal exposure to lead acetate. While the animal studies clearly show a carcinogenic effect, they are of less relevance here because human exposures are usually to inhaled lead oxides.

Studies of genotoxicity consistently link lead exposed populations with DNA damage and micronuclei formation, although less consistently with the more established indicator of cancer risk, chromosomal aberrations. Epidemiologic studies, particularly those of the high exposed occupational cohorts, are the most informative for determining whether lead causes cancer, because in general we assume that any cancer effect will be strongest and most easily detected when exposure is highest. There are only two general population cohort studies at ambient levels, and these are of the same population (NHANES II in the late 1970s). These general population studies at lower exposure levels show internal dose-response trends but suffer at times from small numbers for site-specific analyses or lack of site-specific analyses altogether and, also, from possible residual confounding by SES and smoking.

The strongest evidence in the key occupational studies linking lead exposure to actual human cancers is that for cancers of the lung and those of the stomach. Of seven large occupational cohort studies available (Ades and Kazantzis, 1988; Anttila et al., 1995; Carta et al., 2005; Gerhardsson et al., 1995; Lundstrom et al., 1997; Steenland et al., 1992; Wong and Harris, 2000), for example, all showed results consistent with an increase in lung cancer risk among lead-exposed workers, and in four of these studies the association was statistically significant. Further, where workers could be categorized as to their level of lead exposure, the greatest magnitude of association for lung cancer was usually seen for the highest exposure category. However, the modest elevation of lung cancer risk seen in most relevant studies is in the range of possible confounding due to smoking or other occupational exposures, particularly arsenic, which precludes the evidence from these studies being seen as conclusive. In particular, the one occupational study with the highest lung cancer risk (Lundstrom et al.) has been subsequently shown to be highly confounded by arsenic, and without this study, the combined evidence for a lung cancer elevation across studies is considerably reduced (e.g., the estimated relative risk falls from 1.30 to 1.14). A moderate elevation of stomach cancer is also found in most studies of occupationally exposed populations with applicable data on this outcome. As with lung cancer, it is possible that other risk factors such as intake of smoked meats or *H. pylori* infection could have contributed to the observed associations, but the observed elevation (meta-analysis of 1.33 or 1.34) coupled with the known effect of diet makes it unlikely that the elevation in stomach cancer is entirely due to confounding by diet . Data for other sites such as kidney, brain, and

bladder show some indications of an excess, but the results across studies are not consistent and are based on small numbers.

The epidemiologic data reviewed above from key high lead exposure occupational studies suggest a relationship between lead exposure and cancers of the lung and the stomach. These are supported by two meta-analyses. This is limited by potential confounders such as other occupational exposures (arsenic, cadmium), smoking, and dietary habits. General population cohort studies in which low lead exposure was assessed via blood levels and adjusted for confounders showed trends for a relationship, but were limited by relatively small numbers for site-specific analysis. A cancer assessment on lead has not been conducted using the U.S. EPA Guidelines for Cancinogen Risk Assessment (U.S. Environmental Protection Agency, 2005). However, the most recent IARC (2005) review concluded that inorganic lead compounds were probable human carcinogens (Group IIA), based on limited evidence in humans and sufficient evidence in animals. This classification is one step down from a classification as "definite" human carcinogen (Group I).

6.8 EFFECTS OF LEAD ON THE IMMUNE SYSTEM

6.8.1 Summary of Key Findings of the Effects of Lead on the Immune System from the 1986 Lead AQCD

The 1986 Lead AQCD concluded that studies conducted in laboratory animal models provided evidence for immunosuppressive effects of lead; however, evidence for such effects in humans was lacking. Since then, the epidemiological study of immunological effects of lead has progressed considerably. The currently available epidemiologic and clinical observations are consistent with the greater body of evidence derived from studies in experimental animals indicating that lead can suppress cellular and humor immunity and decrease host resistance to infection agents and tumor cells (see Section 5.9). Findings from the epidemiologic studies suggest that lead exposure (as reflected in blood lead concentration) may be associated with effects on cellular and humoral immunity. These effects include changes in serum immunoglobulin levels (e.g., elevated serum IgE); perturbation of peripheral lymphocyte phenotype profiles, including decreases in peripheral blood T-cell abundance and changes in

T-cell:B-cell abundance ratios; suppression of lymphocyte activation; and suppression of neutrophil chemotaxis and phagocytosis.

Available studies of associations between lead exposure and immunological outcomes are summarized in Annex Tables AX6-8.1 and AX6-8.2. In general, while the studies provide support for associations between lead exposure and immunological outcomes, the studies have numerous limitations that complicate the assessment of the strength of the associations and causation. Furthermore, the health consequences of outcomes that have been associated with lead exposure are uncertain. All studies have been cross-sectional in design and most included relatively small cohorts. The studies implemented varying degrees of quantitative analysis of potential covariables and confounders. In most studies, a detailed analysis of covariables and confounding was lacking, and many of the reports offered no analysis of covariables or confounding. Covariables that were considered (but not consistently) in multivariate analyses or controlled by stratification included age, sex, race, smoking habits, alcohol consumption, and illness and/or medications that might affect the immune system. Studies that offer the strongest designs are discussed in greater detail below.

6.8.2 Host Resistance

Associations between lead exposure and host resistance have not been rigorously examined in humans. Two analyses of illness surveys in children (Rabinowitz et al., 1990) and lead workers (Ewers et al., 1982) have been reported, which suggest a possible association between increasing blood lead concentrations (>10 μg/dL) and illness incidence or prevalence. Both studies relied on personal surveys for assessment of illness and neither study considered covariates or confounders in the analyses.

6.8.3 Humoral Immunity

Studies of biomarkers of humoral immunity in children have consistently found significant associations between increasing blood lead concentration and serum immunoglobulin levels, with increasing serum IgE in association with increasing blood lead concentration (Table 6-8.1; Karmaus et al., 2005; Lutz et al., 1999; Sun et al., 2003). These effects were evident at blood lead concentrations <10 μg/dL. Increasing serum IgE levels also have been observed with increasing blood lead concentration (blood lead ≥30 μg/dL) in association with

Table 6-8.1. Summary of Results of Selected Studies of Associations Between Lead Exposure and Serum Immunoglobulin Levels

Study	Subjects	n[a]	Blood Lead (µg/dL)		IgA	IgE	IgG	IgM
			Mean (SD)	Range				
Children								
Annesi-Maesano et al. (2003)	neonates	374	67 (48)[b]	NR	NR	+[c]	NR	NR
Karmaus et al. (2005)	children, 7–10 yr	331	3	1–5[e]	o	+	o	o
Lutz et al. (1999)	children, 9 mo–6 yr	270	NR	1–45	NR	+	NR	NR
Sarasua et al. (2000)	children, 6–35 mo	372	7	~2–16[d]	+	NR	+	+
Sun et al. (2003)	children, 3–6 yr	73	NR	~3–40	NR	+	–	–
Adults								
Heo et al. (2004)	batter manufacture workers	606	~22 (~10)[e]	NR	o	+	o	o
Pinkerton et al. (1998)	smelter workers	229	39[f]	<2–55	o	NR	–	o
Sarasua et al. (2000)	general population	433	4.3	~1–10[d]	o	NR	o	o

-, decrease; +, increase; o, no effect; NR, not reported, Ig, serum immunoglobulin level

[a] total number of subjects (including reference group)
[b] infants cord blood (maternal blood lead mean was 96 µg/dL (SD 58)
[c] in association with increasing neonatal hair lead
[d] 5–95th percentile range
[e] mean of age-group means and SDs
[f] median

occupational exposures to lead (Heo et al., 2004). Outcomes for other immunoglobulin indices in adults have been less consistent (Pinkerton et al., 1998; Sarasua et al., 2000).

Possible associations between lead exposure and biomarkers of humoral immunity in children have been examined in several cross-sectional studies (Annesi-Maesano et al., 2003; Karmaus et al., 2005; Lutz et al., 1999; Reigart and Graher, 1976; Sarasua et al., 2000; Sun et al., 2003; Wagnerova et al., 1986). Four studies warrant particular attention because they examined a relatively low range of blood lead concentrations and applied multivariate analyses to the data in attempts to control for possible covariables (Karmaus et al., 2005; Lutz et al., 1999; Sarasua et al., 2000; Sun et al., 2003). Three studies found significant associations between increasing blood lead concentration and serum IgE levels (Karmaus et al., 2005; Lutz et al., 1999; Sun et al., 2003). The reported percent increase in serum IgE levels measured in these studies ranged from approximately 50 to 400% The Lutz et al. (1999) study measured serum IgE and IgG (against Rubella) in 270 children (age range 9 months to 2 years; blood lead range 1-45 μg/dL). The observed blood lead-age-IgE relationship is shown in Figure 6-8.1. The highest IgE levels (mean 211 IU/mL, SD 441, n = 17) were observed in children who had blood lead concentrations in the range 15–19 μg/dL; by comparison, mean IgE levels were blood lead concentrations in the range of 15–19 μg/dL; by comparison, mean IgE levels were 52 IU/mL (SD 166) for subjects who had blood lead concentrations <10 μg/dL (n = 174). The Karmaus et al. (2005) study measured serum IgA, IgE, IgG, and IgM levels in 331 children (age range 7-10 years). Blood lead concentrations were lower in this study than in the Lutz et al. (1999) study (1–5 μg/dL). A multivariate linear regression analysis revealed a significant association between blood lead ($p < 0.05$) and serum IgE, however, the change in serum IgE level was not monotonic with increasing blood lead concentration (Figure 6-8.2). The highest IgE levels (adjusted mean 59 IU/L) were observed in the children who had blood lead concentrations ranging from 2.8–3.4 μg/dL (n = 86) and >3.4 μg/dL (n = 82). Sun et al. (2003) measured serum IgE, IgG, and IgM levels in children, ages 3–6 years (blood lead concentration range 2.6–44 μg/dL, n = 73). A nonparametric comparison of immunoglobulin levels between low (<10 μg/dL) and high (≥10 μg/dL) blood lead strata revealed significantly higher IgE levels (Figure 6-8.3) and significantly lower IgG and IgM levels in the high blood lead stratum.

The study by Annesi-Maesano et al. (2003) provides further suggestive evidence for an association between lead exposure and increasing IgE levels. The study included 374

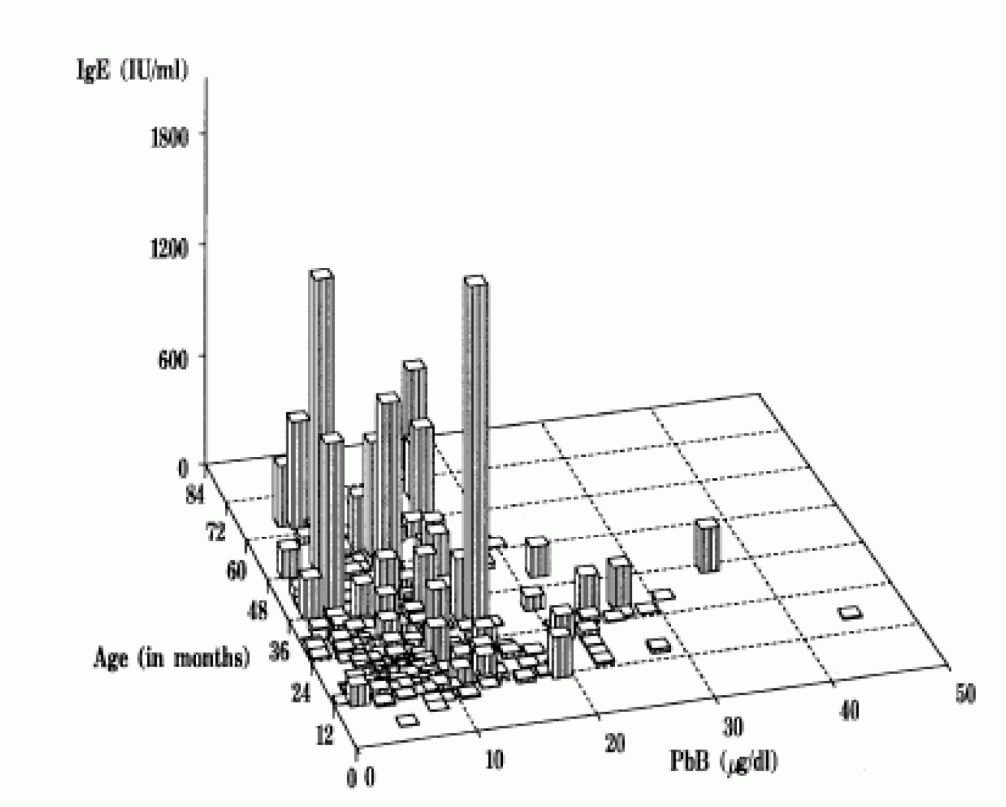


Figure 6-8.1. Relationship between blood lead concentration (PbB), age, and serum IgE level in children. Spearmen partial correlation between blood lead and serum IgE is 0.22 p = 0.0004, n = 221).

Source: Lutz et al. (1999).

mother-infant pairs who had relatively high mean blood lead levels (maternal mean 96 μg/dL, SD 58; infant cord 67 μg/dL, SD 48). Serum IgE level was significantly associated with increasing infant hair lead ($p < 0.001$), but not with cord blood lead or placental lead level. The association between IgE and hair lead levels was evident in a subset of mother-infant pairs, in which mothers were classified as nonallergenic, and was unrelated to maternal smoking (i.e., urinary cotinine).

The ATSDR Multisite Lead and Cadmium Exposure Study (ATSDR, 1995) is one of the largest studies to assess humoral immune status in association with lead exposures; however, it did not include an assessment of IgE. The study included a cross-sectional analysis of serum IgA, IgG, and IgM levels in 1,561 subjects (age range 6 months to 75 years) who resided in areas

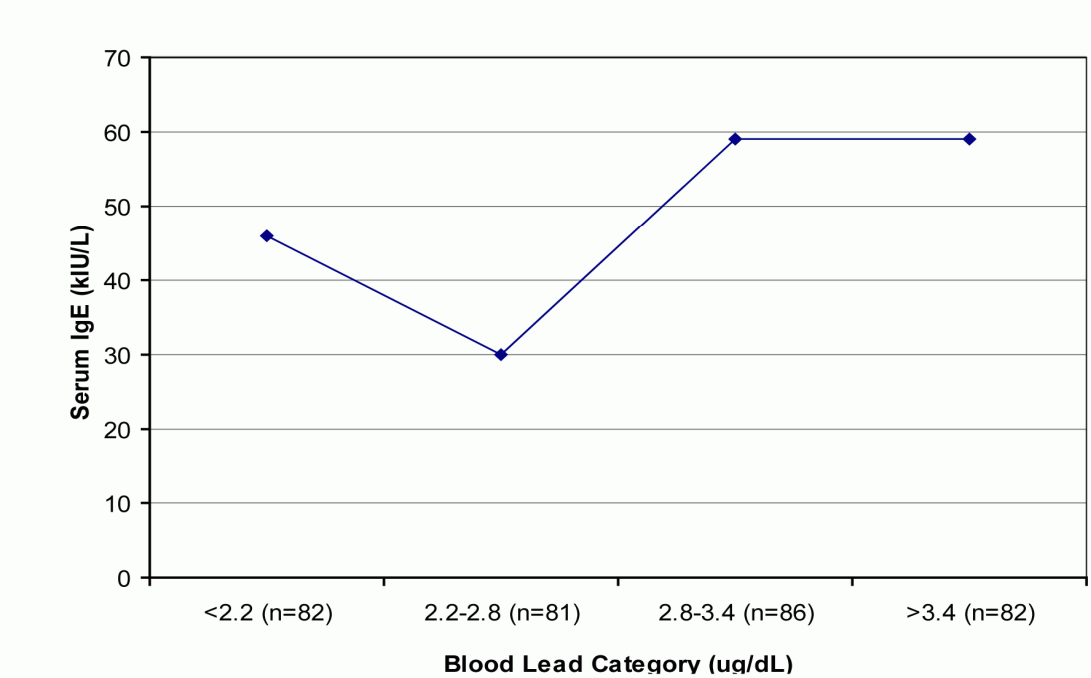


Figure 6-8.2. Relationship between blood lead concentration and serum IgE level in children. Mean serum IgE levels (standard deviations not reported) are adjusted for age, number of infections in the previous 12 months, exposure to passive smoke in the previous 12 months, and serum lipids (sum of cholesterol and triglycerides). Means of serum IgE levels in blood lead categories were significantly different (F-test p = 0.03).

Source: Karmaus et al. (2005).

impacted by lead mining and/or smelting operations and in 480 demographically-matched controls (Sarasua et al., 2000). A multivariate linear regression analysis of immunoglobulin levels and blood lead concentration (exposed and control groups combined) revealed associations between increasing blood lead and increasing serum IgA, IgG, and IgM levels in subjects 6–35 months of age (blood lead 5th–95th percentile range 1.7–16 µg/dL, Figure 6-8.4).

Possible associations between lead exposure and biomarkers of humoral immunity also have been examined in several cross-sectional studies of lead workers (Alomran and Shleamoon, 1988; Anetor and Adeniyi, 1998; Ayatollahi, 2002; Coscia et al., 1987; Ewers et al., 1982; Heo et al., 2004; Kimber et al., 1986; Pinkerton et al., 1998; Ündeger et al., 1996). Outcomes from

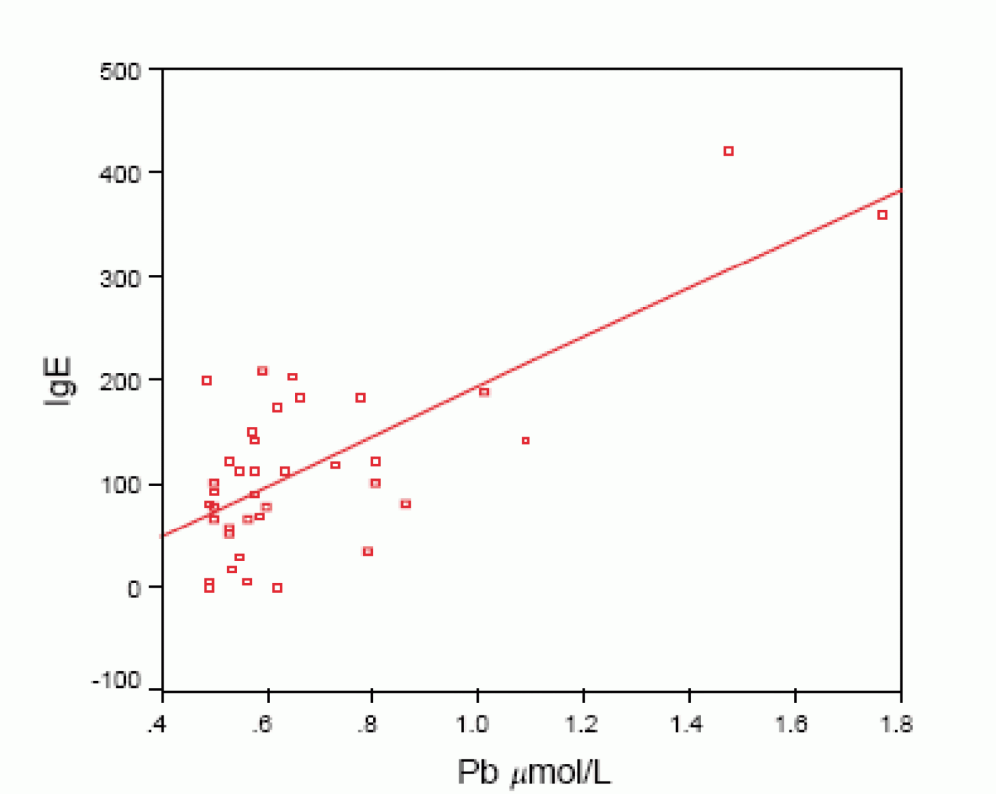


Figure 6-8.3. Relationship between blood lead concentration (lead) and serum IgE level in lead children. Mean serum IgE levels in female children whose blood lead concentrations were in the range 10–40 µg/dL (20.4 IU/L; n = 16) were significantly higher than for children whose blood lead concentrations <10 µg/dL (13.1 IU/L; n = 17).

Source: Sun et al. (2003).

these studies, with respect to humoral immune parameters, measured as serum and/or salivary immunoglobulin levels, are mixed. Some studies finding positive associations with blood lead (Heo et al., 2004), negative associations (Anetor and Adeniyi, 1998; Ewers et al., 1982; Pinkerton et al., 1998), or no (or mixed) effects (Alomran and Shleamoon, 1988; Kimber et al., 1986; Queiroz et al., 1994b; Sarasua et al., 2000; Ündeger et al., 1996).

Based on study design considerations (e.g., cohort criteria, size, treatments of covariates), three studies warrant particular attention (Heo et al., 2004; Pinkerton et al., 1998; Sarasua et al., 2000). Of these, only Heo et al. (2004) assessed serum IgE levels consistent with outcomes reported in children, increasing blood lead concentration was significantly associated with

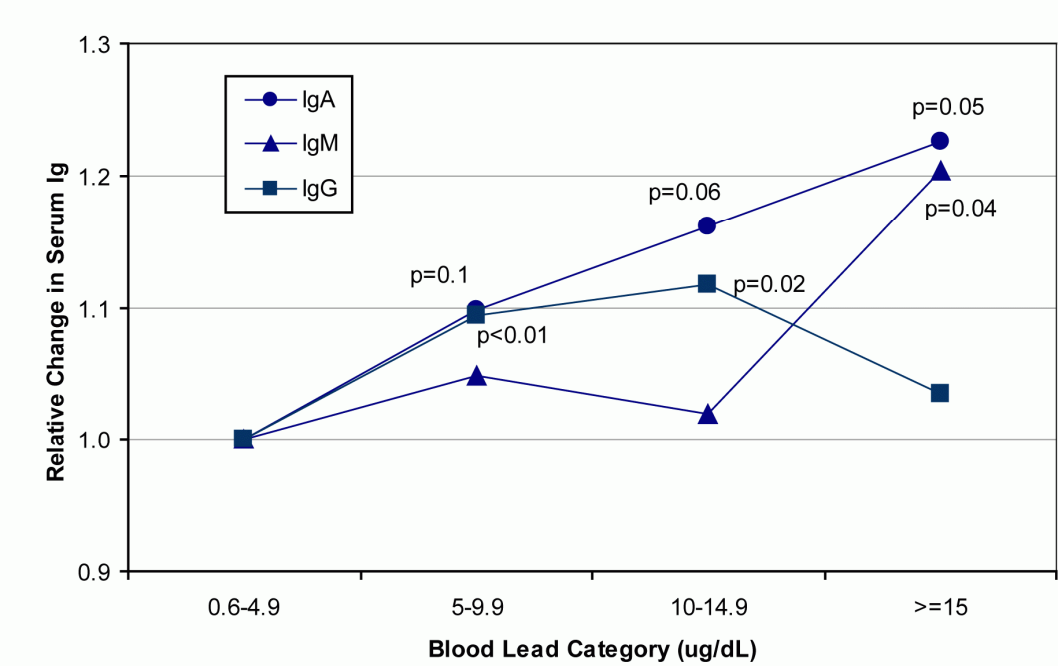


Figure 6-8.4. Relationship between blood lead concentration and serum immunoglobulin (Ig) levels in children. Shown are relative changes in serum Ig levels, adjusted for age, sex, and exposure location. P-values reflect comparison to <5 µg/dL blood lead category mean (<5 mg/dL, n = 165; 5-9.9 µg/dL, n = 136; 10–14.9 µg/dL, n = 47; ≥15 µg/dL, n = 24).

Source: Sarasua et al. (2000).

increasing serum IgE levels (Figure 6-8.5). The study measured serum IgE, IL-4 and IFNγ in 606 battery manufacture workers. Serum IgE levels were significantly higher in the blood lead stratum (≥30 µg/dL) compared to lower strata (<10 or 10–29 µg/dL) for the age strata 30–39 years, ≥40 years, and for all ages combined.

Although the Pinkerton et al. (1998) study did not assess IgE outcomes, it offers the strongest study design of the three for assessment of other immunoglobulin classes. Although it is a relatively small cross-sectional study, it considered immune illnesses and immune suppressant drugs in the construction of the cohorts and examined a relatively large number of potential covariates in the data analysis. Serum immunoglobulin levels were measured in male smelter (n = 145) workers and hardware workers (n = 84). Excluded (by blind evaluation) from the study cohorts were individuals who had "serious" illnesses of the immune system, who were

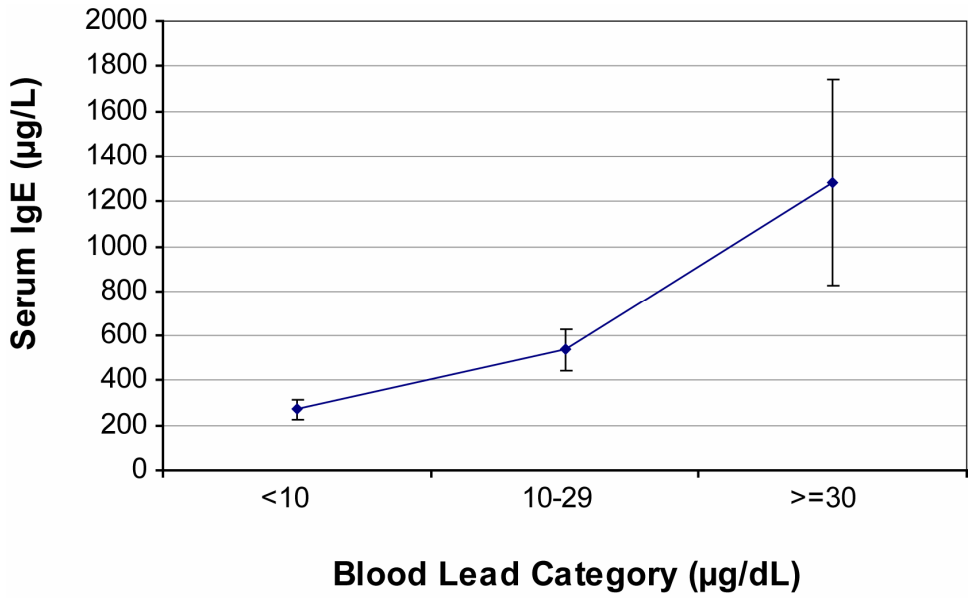


Figure 6-8.5. Relationship between blood lead concentration and serum IgE level in lead workers. Mean serum IgE levels in high blood lead category were significantly higher for all ages (shown), and within age categories ≥40 years and 30-39 years, but not within age category <30 years.

Source: Heo et al. (2004).

taking immune suppressant drugs, or who had chemical exposures (other than to lead) that might affect immune function. Median blood lead concentrations were 39 µg/dL (range 15–55) in the lead workers and <2 µg/dL (range <2–12) in the reference group. Covariate-adjusted (logistic regression) geometric mean serum IgA, IgG, and IgM, and salivary IgA levels in the lead workers were not significantly different from the reference group; however, the adjusted regression coefficient for serum IgG and time-integrated (but not current) blood lead concentration was negative and significant.

The Sarasua et al. (2000) study, described above for its assessment of children, also included a cross-sectional analysis of serum IgA, IgG, and IgM levels in adults (age 16–75 years, n = 433; blood lead 5th–9th percentile range 1–10 µg/dL) and found no significant associations between blood lead and serum immunoglobulin levels (serum IgE outcomes were not assessed).

Also germane to the evidence for effects of lead on humoral immunity in humans are the results of a clinical study in which serum immunoglobulin levels were repeatedly measured in a lead smelter worker who underwent CaEDTA therapy three times per week for a period of

10 weeks (Sata et al., 1998). Serum IgA, IgG, and IgM were significantly higher when assessed 24 h after each CaEDTA treatment compared to assessments made prior to treatment. Furthermore, serum IgG levels were significantly negatively correlated with blood lead concentration during the treatment period. Before-treatment and after-treatment blood lead concentration means were 45.1 (SD 16.0) and 31.0 (SD 9.8), respectively.

6.8.4 Cell-mediated Immunity

Studies of biomarkers of cellular immunity in children have found significant associations between increasing blood lead concentration and decreases in T-cell abundance, with corresponding increases in B-cell abundance (Karmaus et al., 2005; Sarasua et al., 2000; Zhao et al., 2004). These effects have been observed in children whose blood lead concentrations were below 10 µg/dL (Karmaus et al., 2005; Sarasua et al., 2000), although not all studies (e.g., Lutz et al., 1999) have found such associations at higher blood lead concentrations (e.g., 10–45 µg/dL). Studies of occupational lead exposures have also found associations between increasing blood lead concentration and changes in T-cell abundance (Fischbein et al., 1993; Pinkerton et al., 1998; Sata et al., 1997). Effects were observed in association with blood lead concentrations below 25 µg/dL (Fischbein et al., 1993) and in populations whose blood lead concentrations ranged from approximately 7 to 55 µg/dL (Pinkerton et al., 1998; Sata et al., 1997). Outcomes from these studies are qualitatively summarized in Table 6-8.2 and are discussed in greater detail below.

Several cross-sectional studies have examined possible associations between lead exposure and biomarkers of cellular immunity in children (Karmaus et al., 2005; Lutz et al., 1999; Sarasua et al., 2000; Zhao et al., 2004). Three studies (Karmaus et al., 2005; Sarasua et al., 2000; Zhao et al., 2004) found significant associations between increasing lead exposure and decreases in T-cell abundance (Table 6-8.2). The largest study (Sarasua et al., 2000) examined abundance of total lymphocytes, T-cells ($CD3^+$), B-cells ($CD20^+$), NK cells, and $CD4^+$ and $CD8^+$ T-cell phenotypes in infants, children, and adolescents. Associations between increasing blood lead concentration and increasing B-cell abundance (% and number), and decreasing T-cell abundance (%) were found for children 6–35 months of age (n = 312), after adjustment for age, sex, and study site (of four mining/smelting sites). Comparison of adjusted

Table 6-8.2. Summary of Results of Selected Studies of Associations Between Lead Exposure and Serum Lymphocyte Abundances

Study	Subjects	n[a]	Blood Lead (µg/dL)		T[b]	T_H[c]	T_C[d]	T_{HC}[e]	T_M[f]	NK[g]	B[h]
			Mean (SD)	Range							
Children											
Karmaus et al. (2005)	children, 7–10 yr	331	3	1–5[i]	–	o	–	NR	o	o	–
Lutz et al. (1999)	children, 9 mo–6 yr	270	NR	1–45	o	NR	NR	NR	NR	NR	o
Sarasua et al. (2000)	children, 6–35 mo	372	7	~2–16[i]	–	o	o	NR	NR	o	+
Zhao et al. (2004)	children, 3–6 yr	73	NR	~3–40	o	–	+	–	NR	NR	o
Adults											
Fischbein et al. 1993)	firearms instructors	87	31 (4)[j]	NR	–	–	o	NR	NR	o	+
Pinkerton et al. (1998)	smelter workers	229	39[k]	<2–55	o	o	o	o	+	o	+
Sarasua et al. (2000)	general population	433	4.3	~1–10[i]	o	o	o	o	NR	o	o
Sata et al. (1997)	lead stearate workers	99	19	7–50	o	o	+	NR	–	NR	o

–, decrease; +, increase; o, no effect; NR, not reported; SD, standard deviation.

[a] total number of subjects (including reference group)
[b] T-cells ($CD3^+$)
[c] T-helper cells ($CD4^+$)
[d] Cytotoxic T-cells ($CD8^+$)
[e] $CD4^+CD8^+$
[f] T-memory cells ($CD45RO^+$, $CD45RA^+$)
[g] Natural killer cells (e.g., $CD16^+$, $CD56^+$)
[h] B-cells (e.g., $CD19^+$, $CD20^+$)
[i] 5–95th percentile range
[j] high exposure group
[k] median

means for outcomes across blood lead strata revealed that the differences were significant for the ≥15 μg/dL stratum only, compared to the <5 μg/dL stratum. The Karmaus et al. (2005) study examined children in the age range 7–10 years (n = 331) who had blood lead concentrations <5 μg/dL. In addition to age and sex, regression models relating outcomes to blood lead concentration included exposure to environmental tobacco smoke and infections in the previous year as covariates. Similar to the Sarasua et al. (2000) study, Karmaus et al. (2005) found significant associations between blood lead concentration and decreased T-cell abundance ($CD3^+$, $CD3^+CD8^+$) and increased B-cell ($CD19^+$) abundance (for the blood lead quartile 2.2-2.8 μg/dL; Figure 6-8.6). Zhao et al. (2004) examined lymphocyte phenotype abundance in children in the age range 3–6 years (n = 73) and found significantly lower % abundance of T-cell phenotypes $CD3^+CD4^+$, $CD4^+CD8^+$ and significantly higher abundance of $D3^+CD8^+$ cells in children whose blood lead concentrations were ≥10 μg/dL compared to <10 μg/dL. Lutz et al. (1999) found no significant associations between blood lead concentration and age-adjusted T-cell ($CD3^+$) or B-cell (CD19+) abundance or abundance of various other lymphocyte phenotypes (i.e., $CD2^+$, $CD25^+$, $CD28^+$, $CD71^+$) in children whose blood lead concentrations were 10–14, 15–19, or 20–45 μg/dL compared to <10 μg/dL.

A larger set of studies have evaluated potential associations between lead exposure and biomarkers of cellular immunity in adults (Basaran and Ündeger, 2000; Cohen et al., 1989; Coscia et al., 1987; Fischbein et al., 1993; Kuo et al., 2001; Mishra et al., 2003; Pinkerton et al., 1998; Sarasua et al., 2000; Sata et al., 1998, 1997; Yücesoy et al., 1997b; Ündeger et al., 1996). Four studies warrant particular attention because they implemented relatively stronger study designs (i.e., cohort criteria, size, treatment of covariates): Fischbein et al., 1993; Pinkerton et al., 1998; Sarasua et al., 2000; and Sata et al., 1998). With one exception (Sarasua et al., 2000), all were studies of relatively small occupational cohorts. The Sarasua et al. (2000) study included a cross-sectional analysis of abundance of total lymphocytes, B-cells, NK cells, and $CD4^+$ and $CD8^+$ T-cell phenotypes in individuals (n = 433), age 16–75 years. Associations were not found between blood lead concentration and either B-cell or T-cell abundance, after adjustment for age, sex, and study site (of four mining/smelting sites). The study did detect significant associations among these variables in infants and children (see above discussion of cellular immunity outcomes in children). However, all three occupational studies found

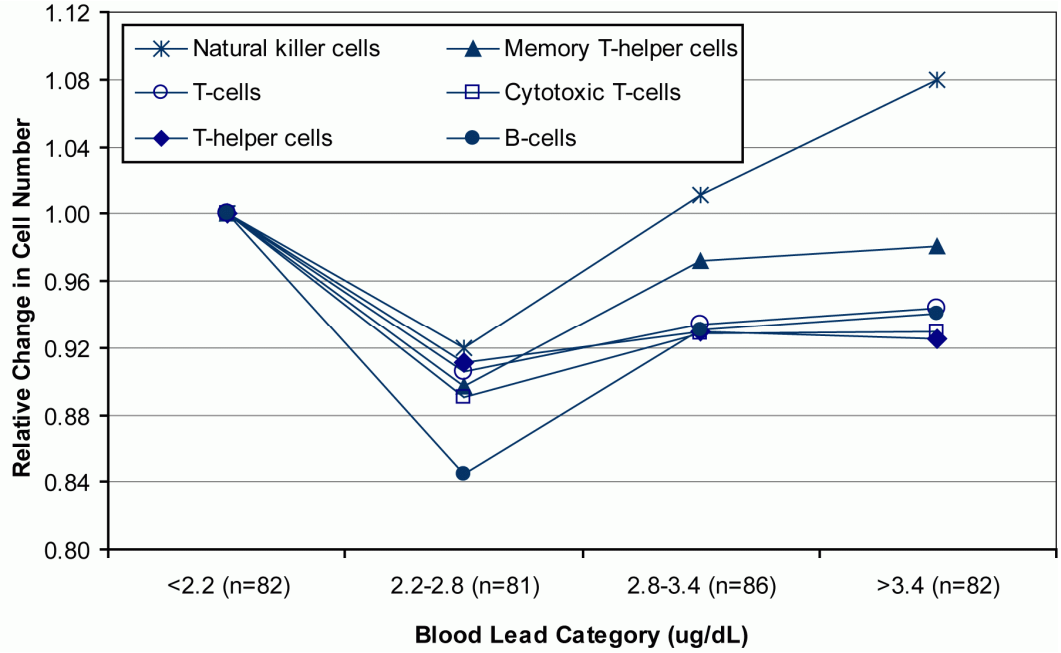


Figure 6-8.6. Relationship between blood lead concentration and T- and B-cell abundances in children. Shown are relative changes in covariate-adjusted absolute cell numbers (cells/µL) compared to the lowest blood lead group; adjusted for age, number of infections in the previous 12 months, exposure to passive smoke in the previous 12 months, and serum lipids (sum of cholesterol and triglycerides). Abundances for T-cells, cytotoxic T-cells, and B-cells in the 2.2-2.8 µg/dL group were significantly different ($p \leq 0.05$) from the <2.2 µg/dL group. Receptor phenotypes assayed were: T-cells, CD3+; T-helper cells, CD3+CD4+; cytotoxic T-cells, CD3+CD8+; memory T-helper cells, CD4+CD45RO+; natural killer cells, CD16+CD56+; B-cells, CD3+CD5+CD19+.

Source: Karmaus et al. (2005).

significant associations between increasing blood lead concentration and changes in abundanceof circulating T-cells with either no effect or an increasing B-cell abundance (Fischbein et al., 1993; Pinkerton et al., 1998; Sata et al., 1997). The strengths of the Pinkerton et al. (1998) study have been described previously with respect to outcome measures for humoral immunity. The study included male smelter workers (n = 145, mean blood lead 39 µg/dL; range 15–55) and hardware workers (n = 84, mean <2 µg/dL, range <2–12). Covariate-adjusted significant outcomes were an increase in B-cell ($CD19^+$) abundance (% and number) and increases in $CD4^+CD45RA^+$ cell

abundance (%, number) in association with increasing blood lead concentration. Covariate-adjusted mean levels of monocytes (%), and T-cells (% $D4^+CD8^+$, $CD8^+CD56^+$) were lower in lead workers compared to the reference group.

The Fischbein et al. (1993) study examined a small group of firearms instructors (n = 51) and age-matched reference subjects (n = 36). Fifteen of the instructors had blood lead concentration ≥25 µg/dL (mean 31.4, SD 4.3), the mean of the remaining 21 subjects was 4.6 µg/dL (SD 4.6). Mean blood lead concentration of the reference group was reported as <10 µg/dL. Increasing blood lead concentration was significantly associated with decreasing covariate-adjusted T-cell ($CD4^+$) abundance (Figure 6-8.7). Covariate-adjusted T-cell ($CD3^+$ % and number, $CD4^+$ % and number, $CD4^+CD8^+$ number) abundance was significantly lower and B-cell ($CD20^+$ cells % and number) abundance was higher in the instructors than in the reference group.

The Sata et al. (1998) study included male lead stearate manufacture workers (n = 71) and a nonexposed reference group (n = 28). Mean blood lead concentration was 19 µg/dL (range 7-50) in the lead workers (blood lead concentration for the reference group was not reported). Categorical covariate-adjusted lead exposure classification (exposed, not exposed) was significantly associated with lower T-cell ($CD3^+CD45RO^+$) number. Lead workers, relative to the reference group, had significantly lower covariate-adjusted mean $CD3^+CD45RO^+$ number and higher $CD8^+$ cells (%).

The above observations of decreasing T-cell abundance in association with lead exposure, as assessed from blood lead concentrations, is supported by results of several smaller cross-sectional studies, including Basaran and Ündeger (2000), Coscia et al. (1987), and Ündeger et al. (1996), as well as a clinical study in which T-cell and NK cell abundance was found to increase after CaEDTA chelation therapy of a lead smelter worker (Sata et al., 1997). Lower serum levels of the cytokines that function in the regulation of cellular immune responses, including IL-1β and IFN-γ, in lead workers compared to nonexposed subjects have also been observed (Yücesoy et al., 1997a).

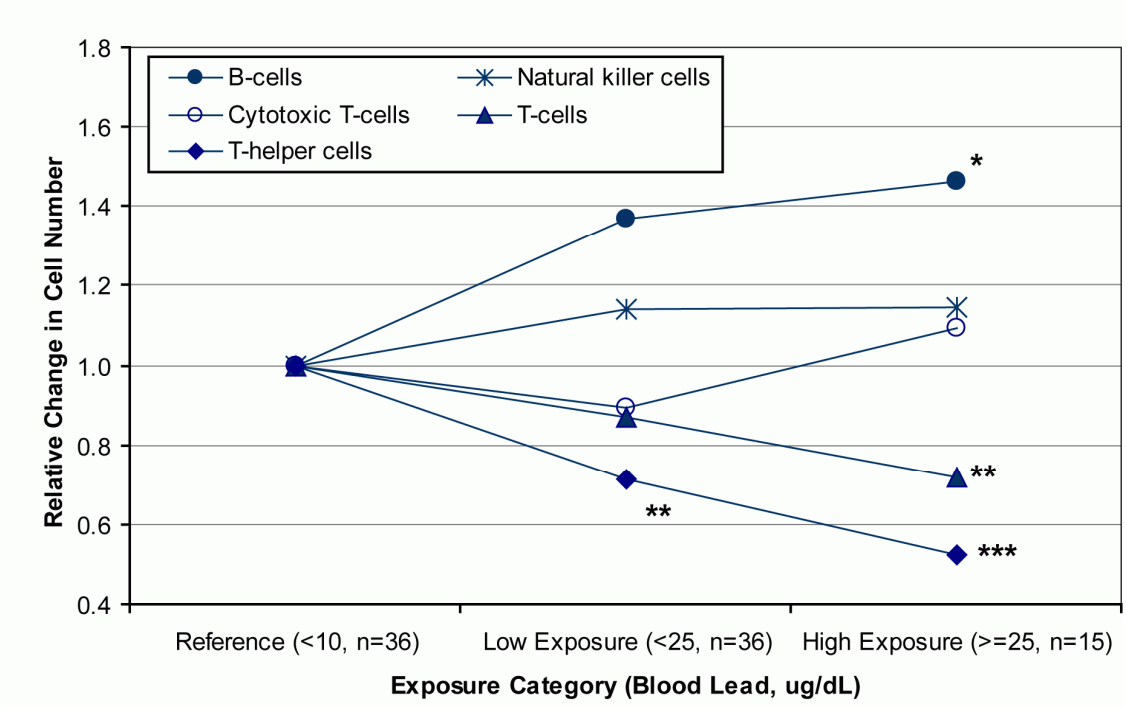


Figure 6-8.7. Relationship between lead exposure and T- and B-cell abundances in firearms instructors. Shown are relative changes in absolute cell numbers compared to the reference group. Comparisons of exposed relative to the reference group are shown as: * for $p < 0.05$; ** for $p < 0.01$; and * for $p < 0.002$. Receptor phenotypes assayed were: T-cells, CD3+; T-helper cells, CD4+; cytotoxic T-cells, CD8+; natural killer cells, CD16+; B-cells, CD20+. The CD4+/CD8+ ratio (not shown) was significantly lower in both the low exposure (1.38 [SD 0.5], $p < 0.002$) and higher exposure group (0.95 [SD 0.5], $p < 0.002$), compared to the reference group (1.95 [SD 0.66]).**

Source: Fischbein et al. (1993).

6.8.5 Lymphocyte Function

Limited evidence from occupational studies suggests that lead may suppress lymphocyte activation in humans. All available studies are of adults. Several studies have examined associations between lead exposure in adults and lymphocyte activation, assessed as a proliferative response to mitogens and/or antigens (Alomran and Shleamoon, 1988; Cohen et al., 1989; Fischbein et al., 1993; Kimber et al., 1986; Mishra et al., 2003; Pinkerton et al., 1998; Queiroz et al., 1994b). Results of these have been mixed. Three studies found no significant associations between blood lead concentrations in lead workers and lymphocyte proliferative

response to activating agents (; Kimber et al., 1986; Pinkerton et al., 1998; Queiroz et al., 1994b). Four studies found decreasing proliferative response with increasing blood lead concentration (Alomran and Shleamoon, 1988; Cohen et al., 1989; Fischbein et al., 1993; Mishra et al., 2003). The Alomran and Shleamoon (1988), Cohen et al. (1989), Mishra et al. (2003), and Queiroz et al. (1994b) studies, which found significant lead associations, included subjects who had relatively high blood lead levels (>60 µg/dL) compared to the Kimber et al. (1986) and Pinkerton et al. (1998) studies. The inclusion of subjects with higher lead concentrations may have contributed to the differences in outcomes.

As noted in the previous section, the Fischbein et al. (1993) and Pinkerton et al. (1998) studies are particularly noteworthy because of the strengths of the cohort selection and the data analyses which attempted to account for potential confounders. Also, these are the only reported studies that examined antigen-specific lymphocyte activation in humans. Mean blood lead concentrations in the two studies were similar 31 µg/dL (SD 4) in the Fischbein et al. (1993) study and 39 µg/dL (range 15–55) in the Pinkerton et al. (1998) study. Both studies found no significant associations between lead exposures (i.e., blood lead concentration) and antigen-specific lymphocyte proliferation, assessed in the Pinkerton et al. (1998) study with tetanus toxoid as the antigen and in the Fischbein et al. (1993) study with staphylococcus aureus as the antigen. However, the Fischbein et al. (1993) study also measured mitogen-induced lymphocyte proliferation (induced with PHA or PWM) and found a significantly lower proliferative response to the mitogens in association with lead exposure. This study also found a significant association between increasing blood lead concentration and decreasing proliferative response in mixed lymphocyte cultures (i.e., proliferative response of lymphocytes from exposed subjects when incubated with inactivated lymphocytes from a reference subject).

Inorganic lead has been shown by in vitro studies to perturb several aspects of lymphocyte function when introduced into primary isolates of human blood monocytes. Activated lymphocytes show altered lysosomal enzyme secretion and altered expression and secretion of cytokines (Bairati et al., 1997; Guo et al., 1996a; Hemdan et al., 2005). Lymphocytes activated with *Salmonella enteritidis* or to monoclonal antibodies of CD3, CD28 and CD40, and exposed to inorganic lead had suppressed expression of T-helper cell type T_H-1 cytokines, interferon (IFN-γ), interleukin (IL-1β), and tumor necrosis factor (TNF-α), whereas activation by CD antibodies increased secretion of T_H-2 cytokines, IL-5, IL-6, and IL-10 (Hemdan et al. 2005).

Inorganic lead also activates transcription factor NK-κβ in $CD4^+$ cells (Pyatt et al., 1996), an important regulator of T-cell activation, and increases expression of MHC class II surface antigens (HLA-DR), an important surface antigen in the $CD4^+$ response to exogenous antigens (Guo et al., 1996b). Lead increases antibody production in cultured human B-cells (McCabe and Lawrence, 1991). These observations suggest that they may perturb cellular immune function through a variety of mechanisms.

6.8.6 Phagocyte (Macrophage and Neutrophil) Function

Studies of lymphocyte and phagocyte (i.e., macrophage, neutrophil) function have found associations between blood lead concentrations and suppressed activation of macrophages in children whose blood lead concentrations ranged from 4 to 50 μg/dL (Pineda-Zavaleta et al., 2004). In addition, studies have observed suppressed PMNL chemotaxis in association with occupational exposures that resulted in blood lead concentrations of 12–90 μg/dL (Bergeret et al., 1990; Queiroz et al., 1994a, 1993).

Pineda-Zavaleta et al. (2004) examined mitogen (PHA)- and cytokine (INFγ)-induced activation of blood monocytes collected from 65 children (age range 6–11 years) who resided near an active lead smelter. Mean blood lead concentrations of subjects at three schools were: 7.0 μg/dL (range 3–25 μg/dL; 8,100 meters from smelter complex), 21 μg/dL (range 11-49 μg/dL; 1,750 meters from smelter), and 30 (range 10–48 μg/dL; 650 meters from smelter). Endpoints measured were nitric oxide and superoxide anion production, a response generally attributed to activated macrophages. Increasing blood lead concentration was significantly associated with decreasing PHA-induced nitric oxide production and increasing INFγ-induced superoxide anion production. The mitogen, PHA, activates macrophages indirectly through activation of lymphocytes, whereas INFγ, a cytokine released from CD44 (T_H1) cells, directly activates macrophages. Thus, one interpretation of this outcome is that lead suppressed T-cell mediated macrophage activation and stimulated cytokine-induced macrophage activation.

Possible associations between occupational lead exposure and PMNL chemotaxis and phagocytic activity have been explored in several small cross-sectional studies. Consistent findings are significantly reduced chemotactic response and phagocytic activity (i.e., respiratory burst, luminal uptake) in lead workers compared to reference groups. The largest study is that of Queiroz et al. (1994a, 1993) which evaluated PMNL function in several (possibly overlapping)

cohorts of lead battery manufacture workers (n = 60). Blood lead concentrations in the study groups ranged from 12 to 90 µg/dL. PMNL chemotaxis and lytic activity were significantly lower in the lead workers compared to the reference group. Bergeret et al. (1990) assessed PMNL chemotaxis and phagocytosis in a group of battery smelting workers (n = 34) and in a group of reference subjects (n = 34) matched to the lead worker group by age, sex, ethnic origin, smoking and alcohol consumption habits, and intake of antibiotics and NSAIDs. Mean blood lead concentrations were 71 µg/dL (SD 18) in the lead workers and 9 µg/dL (SD 4) in the reference group. Significantly lower PMNL chemotactic response to FMLP and phagocytic response in opsonized zymosan were significantly lower in the lead workers than in the reference group. Lead introduced into primary cultures of human PMNLs suppressed chemotaxis and phagocytosis (Governa et al., 1987).

6.8.7 Summary of the Epidemiologic Evidence for the Effects of Lead on the Immune System

Several studies have examined possible associations between lead exposures and biomarkers of immune function. Findings from the epidemiologic studies suggest that lead exposure (as reflected in blood lead concentration) may be associated with effects on cellular and humoral immunity. These effects include changes in serum immunoglobulin levels; perturbation of peripheral lymphocyte phenotype profiles, including decreases in peripheral blood T-cell abundance and changes in T-cell:B-cell abundance ratios; suppression of lymphocyte activation; and suppression of neutrophil chemotaxis and phagocytosis.

Studies of biomarkers of humoral immunity in children have consistently found significant associations between increasing blood lead concentration and serum Ig levels with increasing serum IgE in association with increasing blood lead concentration (Karmaus et al., 2005; Lutz et al., 1999; Sun et al., 2003). These effects were evident at blood lead concentrations below 10 µg/dL. Findings of studies of adults have been mixed with significant associations between blood lead (>30 µg/dL) and serum immunoglobulin levels (Heo et al., 2004; Pinkerton et al., 1998) and no association in a study group in which blood lead concentrations were <10 µg/dL (Sarasua et al., 2000).

Studies of biomarkers of cellular immunity in children have found significant associations between increasing blood lead concentration and decreases in T-cell abundance, with

corresponding increases in B-cell abundance (Karmaus et al., 2005; Sarasua et al., 2000; Zhao et al., 2004). These effects have been observed in children whose blood lead concentrations were below 10 µg/dL (Karmaus et al., 2005; Sarasua et al., 2000), although not all studies have found such associations at higher blood lead concentrations (e.g., 10–45 µg/dL; Lutz et al., 1999). Studies of occupational lead exposures have also found associations between increasing blood lead concentration and decreasing T-cell abundance (Pinkerton et al., 1998; Sata et al., 1997; Fischbein et al., 1993). Effects were observed in association with blood lead concentrations below 25 µg/dL (Fischbein et al., 1993) and in populations whose blood lead concentrations ranged from approximately 7 to 55 µg/dL (Pinkerton et al., 1998; Sata et al., 1997).

Studies of lymphocyte and phagocyte (i.e., macrophage, neutrophil) function have found associations between blood lead concentrations and suppressed activation of macrophages in children whose blood lead concentrations ranged from 4 to 50 µg/dL (Pineda-Zavaleta et al., 2004); suppressed PMNL chemotaxis in association with occupational exposures that resulted in blood lead concentrations of 12 to 90 µg/dL (Bergeret et al., 1990; Queiroz et al., 1994a, 1993), and suppressed mitogen-induced activation of peripheral lymphocytes in adults in association with occupational exposures that resulted in blood lead concentrations that ranged from 15 to 55 µg/dL (Fischbein et al., 1993).

6.9 EFFECTS OF LEAD ON OTHER ORGAN SYSTEMS

6.9.1 Biochemical Effects of Lead

6.9.1.1 Summary of Key Findings of the Biochemical Effects of Lead from the 1986 Lead AQCD

The 1986 Lead AQCD provided an extensive discussion of the effects of lead on heme biosynthesis and on quantitative relationships between exposure and effects in humans. Lead interferes with heme synthesis by inhibiting the enzymes δ-aminolevulinic acid dehydratase (ALAD) and ferrochelatase. As a consequence, heme biosynthesis decreases, relieving the rate-limiting enzyme of the heme synthesis pathway, δ-aminolevulinic synthetase (ALAS), from negative feedback inhibition by heme (Figure 6-9.1). The outcomes of decreased activity of ALAD and ferrochelatase, and increased activity of ALAS are increased urinary excretion of

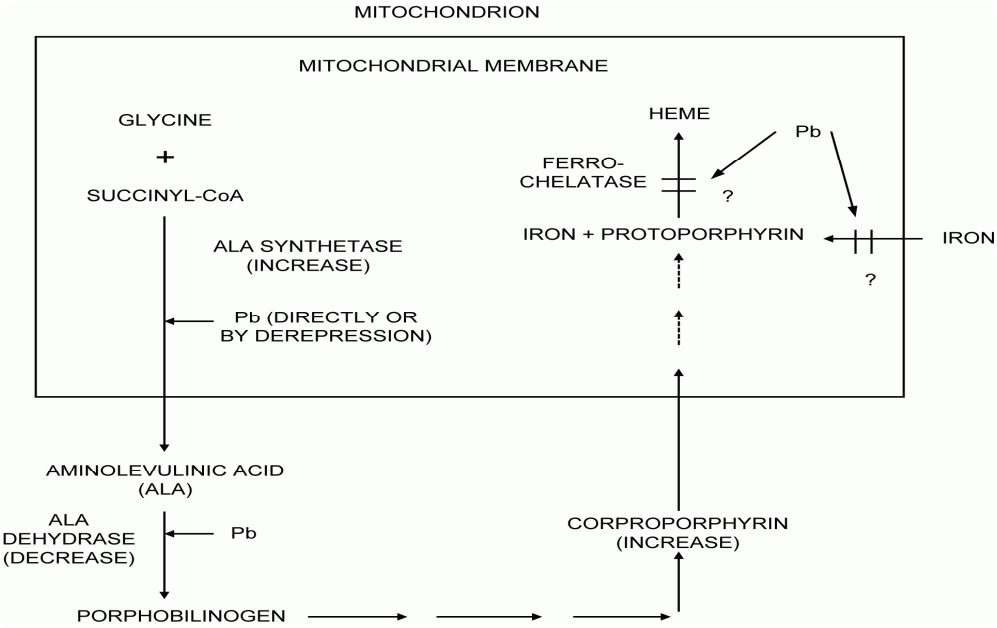


Figure 6-9.1. Effects of lead on heme biosynthesis.

Source: Derived from EPA (1986).

coproporphyrin (CP) and δ-aminolevulinic acid (ALA), increased level of ALA in blood plasma, and increased erythrocyte protoporphyrin (EP) levels.

Associations between lead exposure and blood ALAD activity and EP levels, and urinary ALA and CP excretion have been studied extensively in adults and children, and quantitative relationships between exposure and effect are well understood. Much of this information was available prior to completion of the 1986 Lead AQCD and is summarized in that criteria document (e.g., Alessio et al., 1976; Hernberg et al., 1970; Lilis et al., 1978; Piomelli et al., 1982; Roels et al., 1979; Selander and Cramer, 1970; Valentine et al., 1982). Numerous studies published since the 1986 AQCD provide additional support for the lead concentration-response relationships in humans described in the 1986 AQCD. The most pertinent studies are summarized in Annex Tables AX6-9.1 and AX6-9.2. The studies that provide the strongest basis for empirically-derived expressions relating blood lead concentration, blood ALAD activity, urinary ALA, and EP are listed in Table 6-9.1 and are discussed below.

Table 6-9.1. Blood Lead–Response Relationships for Heme Synthesis Biomarkers in Adults and Children

Study	n	Age	Blood Lead (µg/dL)	Regression Equation (r)	Blood Lead Change (µg/dL) Predicted to Halve or Double Effect Biomarker
ALAD Activity Decrease					
Roels and Lauwerys (1987)	143	10–13 yr	5–41	log[ALAD]= 1.864–0.015[blood lead] (r = 0.87)	20.1
Alessio et al. (1976, 1977)	169	Adult (m)	15–150	log[ALAD]=3.73–0.031[blood lead] (r = 0.87)	22.4
Hernberg et al. (1970)	158	Adult (m, f)	5–95	log[ALAD]=2.274–0.018[blood lead] (r = 0.90)	16.1
Morita et al. (1997)	58	Adult (m)	2–82	log[ALAD]=1.8535–0.00971[blood lead] (r = 0.76)	20.1
Urinary ALA Increase					
Roels and Lauwerys (1987)	37	10–13 yr	20–41	log[ALAU]=0.94+0.11[blood lead] (r = 0.54)	20.9
Alessio et al. (1976, 1977)	316	Adult (m)	10–150	log[ALAU]=1.25+0.014[blood lead] (r = 0.62)	49.5
Gennart et al. (1992)	183	Adult (m, f)	4–75	log[ALAU]=0.37+0.008[blood lead] (r = 0.64)	37.6
Oishi et al. (1996)	418	Adult (m, f)	10–99	log[ALAU]= -0.387+0.022[blood lead] (r = 0.71)	13.7
Selander and Cramer (1970)	150	Adult (m, f)	6–90	log[ALAU]= -1.0985+0.157[blood lead] (r = 0.74)	19.2
Roels and Lauwerys (1987)	39	Adult (m)	10–60	log[ALAU]=0.37+0.006[blood lead] (r = 0.41)	50.2
Roels and Lauwerys (1987)	36	Adult (f)	7–53	log[ALAU]=0.15+0.015[blood lead] (r = 0.72)	20.1

Table 6-9.1 (cont'd). Blood Lead–Response Relationships for Heme Synthesis Biomarkers in Adults and Children

Study	n	Age	Blood Lead (µg/dL)	Regression Equation (r)	Blood Lead Change (µg/dL) Predicted to Halve or Double Effect Biomarker
EP Increase					
Piomelli et al. (1982)	2,002	2–12	2–98	log[EP]=1.099+0.016[blood lead] (r = 0.509)	18.8
Roels and Lauwerys (1987)	51	10–13	15–41	log[EP]=1.321+0.025[blood lead] (r = 0.73)	12.0
Soldin et al. (2003)	4,908	0–17	<1–103	EP = -0.0015[PbB]^3+0.1854[blood lead]^2–2.7554[PbB]+30.911 (r = 0.999)	20.6
Alessio et al. (1976, 1977)	95	Adult (m)	10–90	log[EP]=0.94+0.0117[blood lead]	25.7
Alessio et al. (1976, 1977)	93	Adult (f)	10–70	log[EP]=1.60+0.0143[blood lead]	21.1
Gennart et al. (1992)	183	Adult (m)	4–75	log[EP]=0.06+0.019[blood lead] (r = 0.87)	15.8
Roels and Lauwerys (1987)	39	Adult (m)	10–60	log[EP]=1.41+0.014[blood lead] (r = 0.74)	21.1
Roels and Lauwerys (1987)	36	Adult (f)	7–53	log[EP]=1.23+0.027[blood lead] (r = 0.81)	11.1
Wildt et al. (1987)	851	Adult (m)	10–80	log[EP]=1.21+0.0148[blood lead] (r = 0.72)	20.3
Wildt et al. (1987)	139	Adult (f)	10–80	log[EP]=1.48+0.0113[blood lead] (r = 0.56)	20.6

ALA, δ-aminolevulinic acid; ALAD, δ-aminolevulinic acid dehydratase; ALAU, urinary δ-aminolevulinic acid; EP, erythrocyte protoporphyrin; PbB, blood lead concentration

Since completion of the 1986 Lead AQCD, a literature has developed on the effects of lead on serum and blood lipids, including cholesterol levels and indications of oxidative stress, in the form of lipid peroxides, depletion of erythrocyte reduced glutathione (GSH), and production of reactive oxygen species (ROS). These studies also are summarized in Annex Tables AX6-9.1 and AX6-9.2, and key findings are discussed below.

6.9.1.2 Heme Biosynthesis

6.9.1.2.1 ALAD Inhibition

Numerous studies published since completion of the 1986 AQCD have explored associations between lead exposure and inhibition of ALAD activity, as assessed from measurements of blood ALAD activity (Gurer-Orhan et al., 2004; Kim et al., 2002; Lee et al., 2000; Makino et al., 1997; Roels and Lauwerys, 1987; Schuhmacher et al., 1997), or urinary ALA excretion (Gennart et al., 1992; Oishi et al., 1996; Schuhmacher et al., 1997; Wildt et al., 1987; Soldin et al., 2003). Quantitative estimates derived from the larger, more recent studies are presented in Table 6-9.1. Blood lead concentration is inversely correlated with the log of blood ALAD activity and log of urinary ALA and quantitative estimates of the change in blood ALAD activity per unit change in blood lead concentration are consistent across studies. Halving of blood ALAD activity occurs with an increase in blood lead concentration of approximately 20 μg/dL in both children (Roels and Lauwerys, 1987) and adults (Morita et al., 1997). These estimates are consistent with earlier studies of adults (e.g., Hernberg et al., 1970) and children (e.g., Alessio et al., 1976, 1977), discussed in the 1986 AQCD. Greater variability is apparent in estimates of the change in urinary ALA per unit change in blood lead concentration (Table 6-9.1). This may be related, in part, to gender-heterogeneity in the relationship. Roels and Lauwerys (1987) estimated that urinary ALA doubles in association with a 20 μg/dL increase in blood lead concentration in females and 50 μg/dL in males. In a much larger study (Oishi et al., 1996), an analysis that combined data from males (n = 253) and females (n = 165) found that a doubling of urinary ALA occurred in association with a 14 μg/dL increase blood lead concentration. Urinary ALA excretion increases as a linear function of plasma ALA concentration (Oishi et al., 1996); thus, the gender heterogeneity for the blood lead-urinary ALA relationship may derive from a gender difference in the effect of lead on plasma ALA concentration or from differences in renal plasma clearance of ALA.

6.9.1.2.2 ALAD Polymorphism

ALAD is a polymorphic enzyme with two alleles (ALAD1 and ALAD2) and three genotypes: ALAD1,1, ALAD1,2, and ALAD2,2 (Battistuzzi et al., 1981). The corresponding phenotypes appear to have nearly identical catalytic properties (Battistuzzi et al., 1981). The predominant genotype is ALAD1,1 which has a prevalence of approximately 90% (Astrin et al., 1987; Battistuzzi et al., 1981; Hsieh et al., 2000; Shen et al., 2001). A higher percentage of erythrocyte lead was bound to ALAD in carriers of the ALAD2 allele (84%) compared to carriers of the ALAD1 allele (81%); however, no differences were evident in the distribution of lead between erythrocytes and plasma (Bergdahl et al., 1997), and there is no evidence that the ALAD genotype confers different sensitivity to inhibition of heme biosynthesis (Hsieh et al., 2000; Perez-Brava et al., 2004; Schwartz et al., 1997; Suzen et al., 2003).

6.9.1.2.3 Ferrochelatase Inhibition

Lead inhibition of ferrochelatase results in an accumulation of protoporphyrin IX in erythrocytes (EP, also referred to as zinc protoporphyrin, or ZPP, or iron protoporphyrin, FEP, depending on the method used to make the measurement). Numerous studies have examined relationships between blood lead concentration and EP levels in adults and children. Quantitative estimates based on the most pertinent studies are presented in Table 6-9.1. Results across these studies are similar. In both children and adults (males and females), a doubling of EP levels occurs in association with an increase in blood lead concentration of approximately 20 µg/dL (Piomelli et al., 1982; Soldin et al., 2003; Wildt et al., 1987). A pronounced gender difference in the relationship between EP and blood lead concentration was observed by Roels and Lauwerys (1987) which was not observed in the much larger study of Wildt et al. (1987).

Inhibition of ferrochelatase also gives rise to an increase in urinary coproporphyrin, with a similar relationship to blood lead concentration; a doubling of urinary EP occurs in association with an increase in urinary coproporphyrin of approximately 20 µg/dL (Alessio et al., 1976).

6.9.1.3 Effects on Blood Lipids

Associations between occupational exposure to lead and changes in blood lipid composition have been observed. These include increased levels of lipid peroxides in blood and/or serum (Ito et al., 1985; Jiun and Hsien, 1994; Sugawara et al., 1991) and increased serum

levels of total and HDL cholesterol (Kristal-Boneh et al., 1999). Increased levels of glucose-6-phosphate dehydrogenase (G6PD) in erythrocytes have also been observed in lead workers (Cocco et al., 1995; Gurer-Orhan et al., 2004).

Kristal-Boneh et al. (1999) measured serum total, HDL, and LDL cholesterol, and triglycerides in a group of male battery manufacture workers. Covariate-adjusted serum total-cholesterol and HDL cholesterol levels were 6% and 12% higher, respectively, in lead workers (n = 56, mean blood lead 42 μg/dL, SD 15) compared to reference group (mean blood lead: 2.7 μg/dL). Increasing blood lead concentration was significantly associated with increasing covariate-adjusted total cholesterol and HDL cholesterol. A similar outcome was found in a larger study (Ito et al., 1985) of male steel workers (n = 712, blood lead range 5–62 μg/dL). When stratified by age, total and HDL cholesterol levels in serum were 3.6% and 7.5% higher, respectively, in lead workers in the age range 40 to 49 years, compared to corresponding strata of the office workers (n = 155). Although a smaller study, the Kristal-Boneh et al. (1999) study considered a larger set of potential covariables (e.g., dietary fat, cholesterol, and calcium intakes, sport activities, alcohol consumption, cigarette smoking).

Oxidative changes in blood lipids (e.g., increased levels of lipid peroxides and malondialdehyde levels) as well as decreased levels of erythrocyte superoxide dismutase (SOD), catalase, G6PD, and GSH peroxidase, indicative of increased oxidative stress, have been observed in lead workers, in comparison to reference groups (Ito et al., 1985; Jiun and Hsien, 1994; Solliway et al., 1996; Sugawara et al., 1991). However, none of these studies have developed concentration-response relationships that take into account potential confounders. The largest study is that of (Ito et al., 1985), described above. When stratified by age, serum HDL cholesterol and serum lipoperoxide levels were 16% higher in the lead workers in the age range 40 to 49 years, compared to corresponding strata of the reference group. Serum lipoperoxide levels also appeared to increase as blood lead increased above 30 μg/dL, while erythrocyte SOD appeared to decrease with increasing blood lead concentration (a statistical evaluation was not reported).

Evidence for increased oxidative stress (increased reactive oxygen species) in lymphocytes of lead workers has also been reported (Fracasso et al., 2002). Peripheral lymphocytes collected from battery manufacture workers (n = 37, mean blood lead: 40 μg/dL) exhibited increased DNA strand breaks, higher production of ROS and lower GSH levels

compared to a reference group of office workers (n = 29, mean blood lead 4 μg/dL). The covariate-adjusted odds ratios (exposed versus not exposed) were 1.069 (95% CI: 1.020, 1.120) for increased DNA strand breaks and 0.634 (95% CI: 0.488, 0.824) for lower GSH levels.

6.9.2 Effects of Lead on the Hematopoietic System

6.9.2.1 Summary of Key Findings of the Effects of Lead on the Hematopoietic System from the 1986 Lead AQCD

The 1986 Lead AQCD concluded that lead decreases heme production and shortens erythrocyte survival; both effects contributing to lead-induced anemia in children and adults, which becomes evident in children at blood lead concentrations ≥40 μg/dL and, in adults, ≥50 μg/dL. The 1986 Lead AQCD also concluded that effects of lead on blood hemoglobin level extend below 50 μg/dL, with effects detected in lead workers at blood lead concentrations <25 μg/dL (Baker et al., 1979; Grandjean, 1979). More recent epidemiologic studies, summarized below, provide additional information on concentration-response relationships for hematopoietic effects of lead. The studies support the conclusion that clinical anemia can occur in children in association with blood lead concentrations >40 μg/dL (Schwartz et al., 1990). The newer studies suggest that perturbation of erythropoiesis, indicated by changes in serum erythropoietin, occurs in association with blood lead concentrations <40 μg/dL and in the absence of detectable changes in blood hemoglobin levels or hematocrit. Details regarding the design of these studies and outcomes are presented in Annex Tables AX6-9.3 and AX6-9.4. Outcomes of the most pertinent studies are discussed below.

6.9.2.2 Blood Hemoglobin Levels

Several studies reported since the completion of the 1986 Lead AQCD have explored associations between lead exposure and blood hemoglobin levels in children and adults. Consistent findings have been a lack of discernable depression of blood hemoglobin levels in study populations whose mean blood lead concentrations were ≤40 μg/dL (Table 6-9.2). Of note is the findings relating patella bone lead to both blood hemoglobin levels and hematocrit.

The Kosovo prospective study of pregnancy outcomes is one of the largest epidemiologic evaluations of associations between lead exposure and blood hemoglobin levels in infants and children (Graziano et al., 2004; Factor-Litvak et al., 1999, 1998). The study included pregnant

Table 6-9.2. Summary of Results of Selected Studies of Associations Between Lead Exposure and Blood Hemoglobin Levels

Study	Subjects	n[a]	Blood Lead (µg/dL)		Blood Hemoglobin	Comment
			Mean (SD)	Range		
Children						
Graziano et al. (2004)	ages: 4.5–12 yr	311	6–9, 31–39[b]	3–70	o	+ erythropoietin
Liebelt et al. (1999)	ages: 1–6 yr	86	18[c]	2–84	o	– erythropoietin
Adults						
Graziano et al. (1990)	pregnant women	1,502	5, 17[d]	2–43	o	– erythropoietin
Hu et al. (1994)	male carpenters	119	8	2–25	o	– in association with patella bone lead
Makino et al. (1997)	male VCS workers	1,573	13	1–39	+	(+) 1 g/dL per 10 µg/dL blood lead
Solliway et al. (1996)	male battery workers	100	10	23–63	o	– RBC count
Gennart et al. (1992)	battery workers	183	51 (8)	40–70	–	– hematocrit
Horiguchi et al. (1991)	male lead refinery workers	40	54 (16)	NR	–	– hematocrit
Poulos et al. (1986)	male lead workers	160	18–27 (5)[e]	NR	–	– hematocrit

-, decrease; +, increase; Hgb, hemoblogin; NR, not reported; PCV, packed cell volume SD, standard deviation; VCS, vinyl chloride stabilizer

[a] total number of subjects (including reference group)
[b] range of means of low and higher exposure groups
[c] median
[d] mean of low- and high-exposure groups
[e] range of group means (standard deviation estimated for up range based on reported standard error).

women (n = 1502) and their children (n = 311) who resided in one of two regions of Kosovo, Yugoslavia; one was heavily impacted by lead industries (high-lead area), the other had relatively little lead contamination (low-lead area). Mean blood lead concentrations of children (measured at birth and at intervals to 12 years of age) ranged from 30 to 40 μg/dL in the high-lead area and 6 to 9 μg/dL in the low-lead area. Mean blood hemoglobin levels in the low-lead and high-lead children, measured at 4.5, 6.5, 9.5, and 12 years of age, were not significantly different. These findings are consistent with those from a smaller cross-sectional study (n = 89; blood lead range 2 to 84 μg/dL, 84% <35 μg/dL) that also found no association between blood lead concentration and blood hemoglobin levels (Liebelt et al., 1999). Results from these two studies suggest that, in the absence of iron deficiency, lead exposures that result in blood lead concentrations <40 μg/dL do not produce detectable changes in blood hemoglobin levels in children.

Associations between lead exposure and blood hemoglobin levels in adults have been examined in numerous epidemiological studies (Froom et al., 1999; Gennart et al., 1992; Horiguchi et al., 1991; Hu et al., 1994; Makino et al., 1997; Poulos et al., 1986; Romeo et al., 1996; Solliway et al., 1996). The Graziano et al. (1990) and Makino et al. (1997) studies warrant particular attention because of the design (longitudinal), relatively large size (>1000 subjects), and relatively low blood lead levels of the subjects (<40 μg/dL). Both studies support the general conclusion that blood hemoglobin levels are not depressed in association with blood lead concentrations <40 g/dL. In the Kosovo prospective study, no discernable effect of lead on maternal blood hemoglobin levels was evident from a comparison of the high-lead exposure group (mean blood lead 17 μg/dL, range 7–43 μg/dL) with the low lead exposure group (mean blood lead 5.1 μg/dL, range 2–11 μg/dL). Makino et al. (1997) found a positive association between increasing blood lead concentration and increasing blood hemoglobin levels in a longitudinal survey of adult males (n = 1,573) who worked in pigment or vinyl chloride stabilizer manufacture (mean blood lead 13 μg/dL, range 1–39 μg/dL). A simple linear regression model predicted a 1 g/dL increase in blood hemoglobin per 10 μg/dL increase in blood lead concentration (typical level 10–20 g/dL).

Two other cross-sectional studies are also notable, because of design considerations and/or blood lead concentration ranges of the subjects. Solliway et al. (1996) observed no differences in mean blood hemoglobin levels in a comparison of adult male battery manufacture

workers (n = 34, mean blood lead 41 µg/dL, range 23–63 µg/dL) and a matched reference group (n = 56, mean blood lead 7 µg/dL, range 1–13 µg/dL). Hu et al. (1994) conducted a cross-sectional assessment of adult male carpentry workers (n = 119) whose blood lead concentrations were ≤25 µg/dL. Blood hemoglobin was not significantly associated with blood lead concentration. Of note, however, was the finding that increasing patella bone lead was significantly associated with decreasing blood hemoglobin levels. Covariate-adjusted blood hemoglobin levels were predicted to decrease by 1.1 g/dL per 37 µg/g increase (mean of first and fourth quartiles) in patella bone lead.

Studies of lead workers whose blood lead levels were higher than in the studies noted above have, in general, found lower blood hemoglobin levels in association with increasing blood lead concentrations; these include Gennart et al. (1992) with a blood lead range of 40–70 µg/dL, Horiguchi et al. (1991) with a mean blood lead level of 54 µg/dL (SD 16), and Poulos et al. (1986) with mean blood lead range of 21–27 µg/dL. In the latter study (Poulos et al., 1986), blood hemoglobin levels decreased by 0.6–0.9 g/dL per 10 µg/dL increase in blood lead (simple linear regression) in adult males. Analyses or adjustments for potential covariables were not reported for these studies.

6.9.2.3 Erythrocyte Volume and Number

Schwartz et al. (1990) conducted a concentration-response analysis of data collected at the Bunker Hill smelter site in Idaho in 1974, shortly after the failure of the smelter bag house resulted in extensive contamination of the surrounding area with uncontrolled smelter emissions. This analysis is unique in that it collected hematocrit measurements in children (n = 579, age range 1–5 years) who had relatively high blood lead levels (range 11–164 µg/dL, approximately 40% exceeded 40 µg/dL). A logistic model relating blood lead concentration and age to hematocrit predicted a 10% decrease in hematocrit (from 39.5 to 35.5%) in association with blood lead concentrations of 85, 115, and 145 µg/dL at ages 1, 3, and 5 years, respectively (Figure 6-9.2). A 10% probability of anemia (hematocrit <35%) was predicted in association with a blood lead concentration of approximately 20 µg/dL at age 1 year, 50 µg/dL at age 3 years, and 75 µg/dL at age 5 years (Figure 6-9.2).

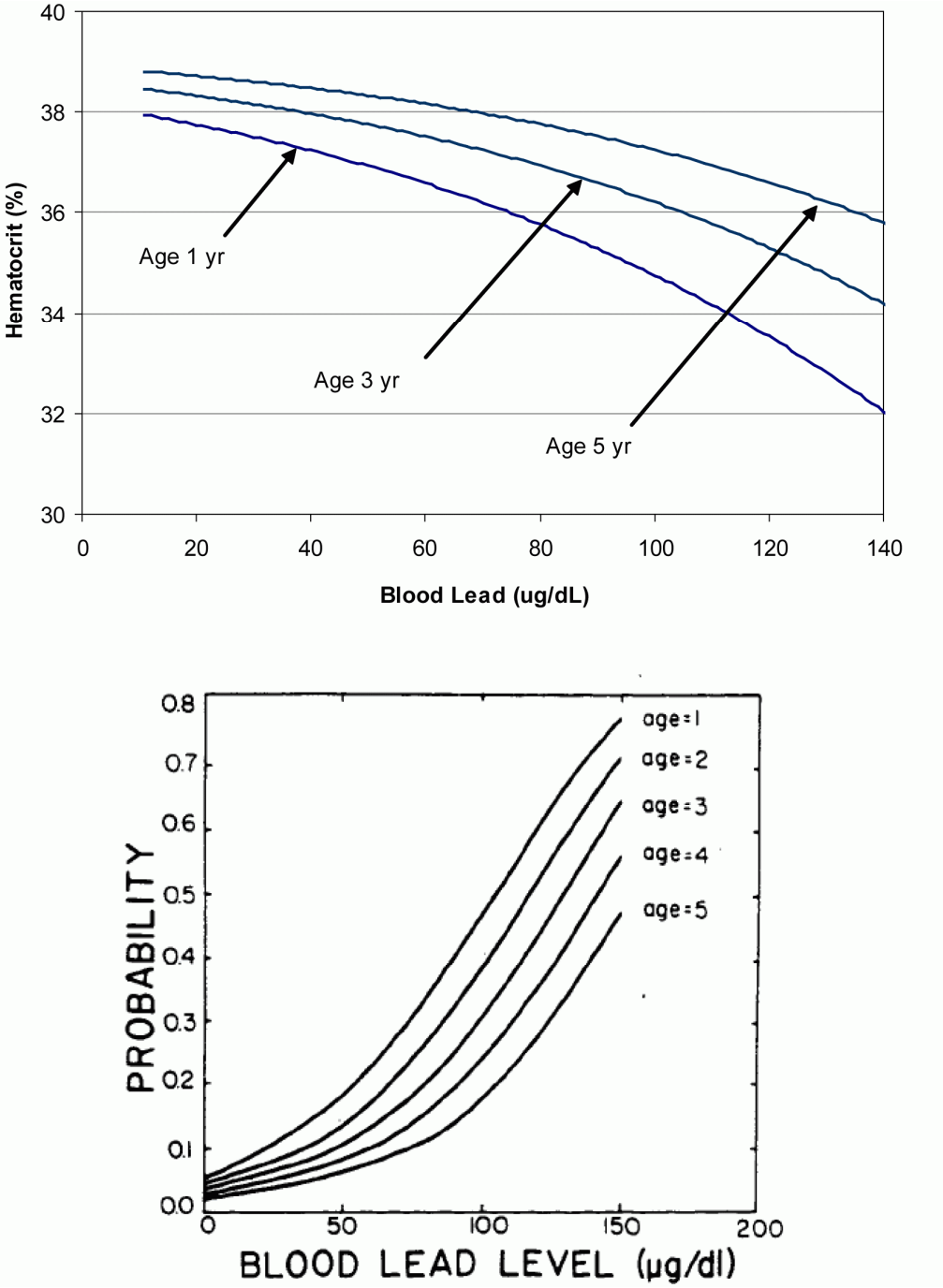


Figure 6-9.2. Relationship between blood lead and hematocrit in children. The top panel shows central tendency predictions based on a logistic regression model relating hematocrit and blood lead concentration, adjusted for age. The regression coefficients relating hematocrit and blood lead were (β = 0.0133 [SE 0.0041], p = 0.0005). The bottom panel shows corresponding concentration-response (hematocrit <35%) relationships.

Source: Schwartz et al. (1990)

Numerous studies of associations between lead exposure and erythrocyte volume (e.g., hematocrit) or number have been reported in adults (Gennart et al., 1992; Horiguchi et al., 1991; Hsiao et al., 2001; Hu et al., 1994; Makino et al., 1997; Osterode et al., 1999; Poulos et al., 1986; Solliway et al., 1996). The Hu et al. (1994) and Makino et al. (1997) studies examined groups of workers that had blood lead concentrations that were relatively low, compared to other studies, and found either no association or weak association between blood lead concentration and hematocrit and/or erythrocyte number. The Hu et al. (1994) cross-sectional study of carpentry workers (n = 119, blood lead concentration range 2–25 μg/dL) found no association between blood lead concentration and hematocrit; however, increasing patella bone lead was associated with a significant decrease in hematocrit. Covariate-adjusted blood hematocrit was predicted to decrease by 0.03% (95% CI: 0.01, 0.05) per 37 μg/g increase (mean of first and fourth quartiles) in patella bone lead. The Makino et al. (1997) longitudinal study of pigment and vinyl chloride stabilizer manufacture workers (n = 1,573; blood lead concentration range 1–39 μg/dL) found a positive association between blood lead concentration and hematocrit, and erythrocyte count. A simple linear regression model predicted an increase in hematocrit of 0.6 (typically 43) and an increase in erythrocyte count of $0.07 \times 10^6/mm^3$ (typically $4–7 \times 10^6/mm^3$) per 10 μg/dL increase in blood lead concentration.

Studies that included subjects who had higher blood lead concentrations (i.e., >40 μg/dL) have, in general, found negative associations between blood lead concentration and hematocrit Gennart et al., 1992; Horiguchi et al., 1991; Poulos et al., 1986; Solliway et al., 1996), with two exceptions, Hsiao et al. (2001) and Osterode et al. (1999). Hsiao et al. (2001) conducted an 11-year retrospective longitudinal analysis of blood lead concentration, hematocrit, and erythrocyte count in a group of battery manufacture workers (n = 30; mean blood lead concentration 30–60 μg/dL). A repeated measures regression analysis (generalized estimation equation) yielded a significant association between increasing blood lead concentration and increasing hematocrit and erythrocyte count. Osterode et al. (1999) measured erythrocyte number and packed cell volume in a group of lead workers (n = 20) and an age-matched reference group (n = 20). Mean blood lead concentration was 45.5 μg/dL (range 16–91 μg/dL) in the lead workers and 4.1 μg/dL (range 3-14 μg/dL) in the reference group. Mean erythrocyte number and packed cell volume in the lead workers and reference group were not different.

6.9.2.4 Erythropoiesis

Several studies have found associations between lead exposure and serum erythropoietin levels in children (Graziano et al., 2004; Liebelt et al., 1999) and adults (Graziano et al., 2001; Osterode et al., 1999; Romeo et al. 1996). A qualitative summary of outcomes from these studies are provided in (Table 6-9.3).

Two studies have examined possible association between lead exposure and serum erythropoietin levels in children. In the Kosovo prospective study (Factor-Litvak et al., 1999, 1998; Graziano et al., 2004) a significant association was evident between increasing blood lead concentration (3–70 μg/dL) and increasing serum erythropoietin levels after adjustment for age and blood hemoglobin levels (Figure 6-9.3). The association weakened with age; it was significant at ages 4.5 and 6.5 years, but not at ages 9.5 or 12 years. A multivariate linear regression model predicted a 36% increase in serum erythropoietin per 10 μg/dL increase (3-13 μg/dL, hemoglobin 13 g/dL) in blood lead at age 4.5 years, and an 18% increase per 10 μg/dL at age 6.5 years. These outcomes suggest that erythropoiesis is stimulated in children in association with increasing blood lead concentrations below 40 μg/dL and in the absence of depressed blood hemoglobin levels.

A smaller cross-sectional study examined serum erythropoietin levels in a group of children (n = 89), 1 to 6 years of age (Liebelt et al., 1999). The blood lead concentration range in the study group (2–84 μg/dL) was similar to that in the Graziano et al. (2004) study and, consistent with this study, Liebelt et al. (1999) found no association between blood lead concentration and serum hemoglobin levels. However, in contrast to the Graziano et al. (2004) study, blood hemoglobin-adjusted serum erythropoietin levels decreased in association with an increase in blood lead concentration (0.3 mIU/mL decrease per 10 μg/dL increase blood lead). The Liebelt et al. (1999) study did not include age as a covariate in the regression model, which was shown in the Kosovo prospective study to be a significant covariable in blood lead-serum erythropoietin relationship (Graziano et al., 2004); this may have contributed to the different outcome in the two studies. Liebelt et al. (1999) studied a convenience sample from a lead/primary care clinic (rather than a prospectively selected cohort) that specifically excluded children who had symptoms of severe iron deficiency, or were taking iron supplements or other bone marrow suppressing drugs. Iron status of the children in the Graziano et al. (2004) study was not reported. However, serum ferritin levels in the mothers, at mid-pregnancy, was not

Table 6-9.3. Summary of Results of Selected Studies of Associations Between Lead Exposure and Serum Erythropoietin

Study	Subjects	n[a]	Blood Lead (µg/dL)		Serum Erythropoietin	Comment
			Mean (SD)	Range		
Children						
Graziano et al. (2004)	ages: 4.5–12 yr	311	6–9, 31–39[b]	3–70	+	adjusted for age, blood Hgb
Liebelt et al. (1999)	ages: 1–6 yr	86	18[c]	2–84	–	adjusted for blood Hgb
Adults						
Graziano et al. (1990)	pregnant women	48	NR	2–40	–	stratified by blood Hgb
Osterode et al. (1999)	male lead workers	40	45	16–91	–	adjusted for blood PCV
Romeo et al. (1996)	male lead workers	141	30, 65[b,d]	30–92	–	no association with blood Hgb

–, decrease; +, increase; Hgb, hemoblogin; NR, not reported; PCV, packed cell volume SD, standard deviation.

[a] total number of subjects (including reference group)
[b] range of means of low and higher exposure groups
[c] median
[d] reference group mean was 10 µg/dL (range 3–20)

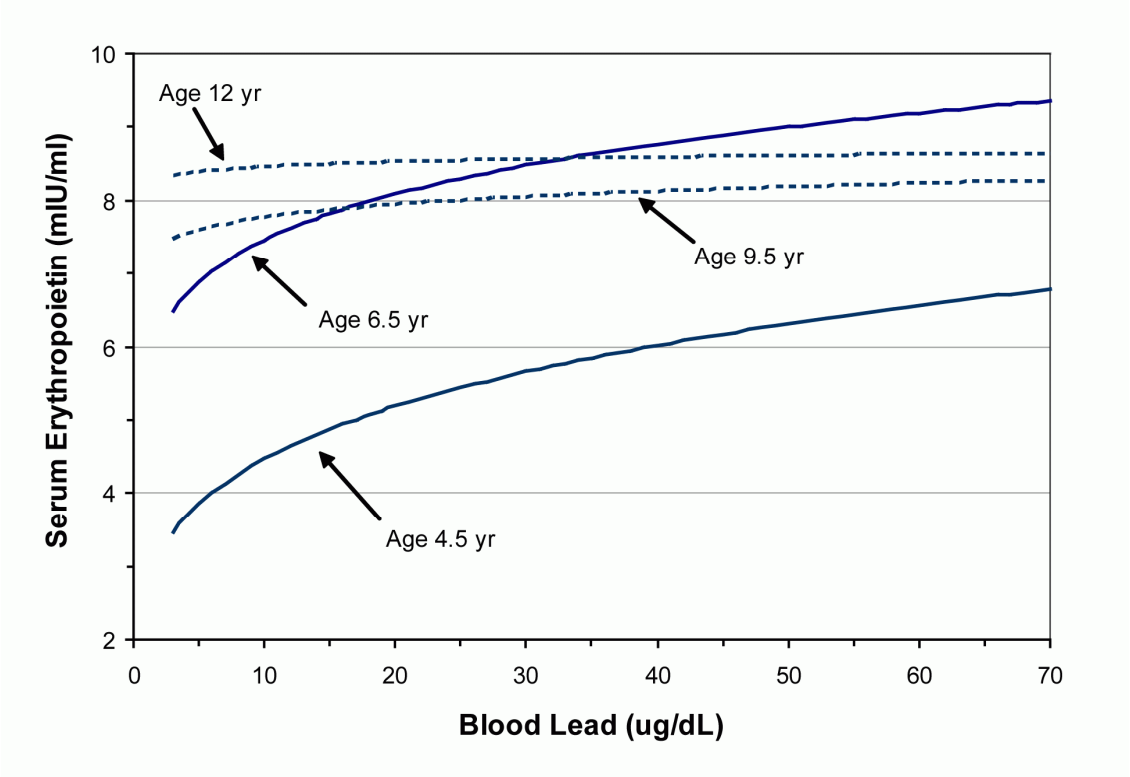


Figure 6-9.3. Relationship between blood lead and serum erythropoietin in children. Shown are central tendency predictions based a generalized estimating equation (for repeated measures) relating serum erythropoietin and cumulative lifetime average blood lead concentration, adjusted for age and blood hemoglobin levels (13 g/dL). The regression coefficients relating erythropoietin and blood lead were significant for ages 4.5 (β = 0.21 [95% CI: 0.13, 0.30], p < 0.0001) and 6.5 years (β = 0.12 [95% CI: 0.03, 0.20], p < 0.001).

Source: Graziano et al. (2004).

indicative of iron deficiency (Graziano et al., 1990). Although the direction of the outcome measure was different in the two studies, both studies (Graziano et al., 2004; Liebelt et al., 1999) found evidence for an effect of lead exposure on serum erythropoietin levels in the absence of significant lead-associated changes in blood hemoglobin levels.

Three studies have found associations between lead exposure and changes in erythropoiesis biomarkers in adults. As part of the Kosovo prospective study, serum erythropoietin was measured at mid-pregnancy and at term in a subset of women enrolled in the study (Graziano et al., 1991). The high- and low-lead cohorts were constructed from the six

highest and lowest mid-pregnancy blood lead concentrations, within each of four blood hemoglobin strata, ranging from 9.0 to 12.9 g/dL. Mean blood lead concentrations in the strata ranged from 17 to 39 μg/dL in the high-lead group and 2.4 to 3.6 μg/dL in the low lead group. Serum erythropoietin levels significantly decreased in association with increasing blood lead concentration, independently of an effect of blood hemoglobin (Figure 6-9.4). Romeo et al. (1996) also found an association between increasing blood lead concentration and decreasing serum erythropoietin, in the absence of discernable changes in blood hemoglobin levels, in a comparison of groups male lead workers (n = 28, blood lead range 30–92 μg/dL) and a similar-aged reference group (n = 113, mean blood lead 10 μg/dL, range 3–20). Osterode et al. (1999) examined several measures of erythropoiesis in a group of lead workers (n = 20, mean age 46 years) and in an age-matched reference group (n = 20). Mean blood lead concentration was 45.5 μg/dL (range 16–91) in the lead workers and 4.1 μg/dL (range 3–14) in the reference group. Mean blood hemoglobin levels in the lead worker and reference groups were not different. Lead workers with had blood lead concentrations ≥60 μg/dL had significantly lower circulating erythrocyte progenitor cells than the reference group. Also, erythrocyte progenitor cell number was significantly negatively correlated with blood lead concentration and urine lead concentration. Serum erythropoietin levels increased exponentially with decreasing packed blood cell volume in the reference group, but not in the lead workers (i.e., serum erythropoietin level was not significantly correlated with packed cell volume in the lead workers). Thus, unlike the reference group (blood lead concentration ≤14 μg/dL), lead workers appeared to have a suppressed erythropoietin response to declining blood cell volume.

Collectively, the results of the above studies suggest that lead exposure depresses serum erythropoietin levels, in the absence of significant depression in blood hemoglobin levels. Lead-induced nephrotoxicity may contribute to a suppression of erythropoietin levels in lead-exposed individuals. Although this cannot be entirely ruled out in these studies, both the Romeo et al. (1996) and Osterode et al. (1999) studies excluded people who had a history of hematological or kidney disease. Nevertheless, renal nephrotoxicity, including proximal tubular nephropathy, could have been a confounder in these studies which included subjects whose blood lead concentrations were >40 μg/dL.

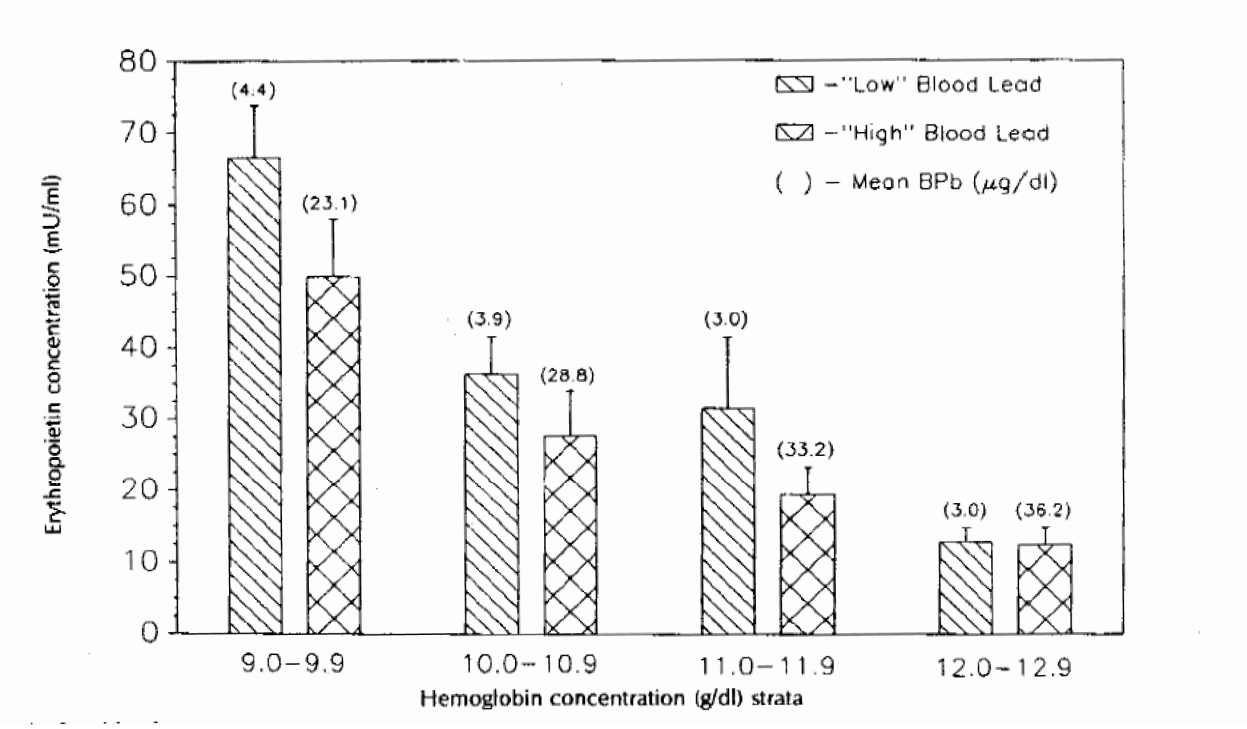


Figure 6-9.4. Association between blood lead concentration and serum erythropoietin in pregnant women. Shown are combined data for mid-pregnancy and delivery. Each bar represents the mean (±SD) of 12 subjects. ANOVA of the data at mid-pregnancy and at delivery showed blood lead effects (p = 0.049, p = 0.055, respectively) and blood hemoglobin effects (p = 0.0001. p = 0.009, respectively), with no significant interaction between the two variables.

Source: Graziano et al. (2001).

6.9.2.5 Other Effects on Erythrocyte Metabolism and Physiology

6.9.2.5.1 Erythrocyte Nucleotide Metabolism

Lead inhibits erythrocyte pyrymidine-5′nucleotidase (P5N) and adenine dinucleotide synthetase (NADS). Associations between increasing blood lead concentration and decreasing blood P5N and NADS activity have been observed in studies of lead workers (Kim et al. 2002; Mohammed-Brahim et al., 1985; Morita et al., 1997). Mean blood lead concentrations in these study groups were ≥35 μg/dL and ranged up to 80 μg/dL.

6.9.2.5.2 Erythrocyte Deformability

Horiguchi et al. (1991) compared the deformability of erythrocytes collected from adult male secondary lead refinery workers (n = 17, age range 24–58 years) with a reference group of male subjects (n = 13, age range 22–44 years). Erythrocyte deformability was assessed as microfilterability of erythrocytes under a negative (−10 cm H_2O) pressure head. Erythrocytes from the lead workers showed significantly lower deformability compared to the reference group. The mean blood lead concentration in the lead workers was 53.5 µg/dL (SD 16.1).

6.9.2.5.3 Erythrocyte Membrane Transport

Hajem et al. (1990) measured erythrocyte membrane activities of Na^+-K^+-ATAase, Na^+-K^+-co-transport, Na^+-Li^+-antiport, and passive Na^+ and K^+ permeability in erythrocytes collected from adult males (n = 122, geometric mean blood lead: 16 µg/dL, range 8.0–33.0) and hair lead was 5.3 µg/g (95% CI: 4.44, 6.23, range 0.9–60). Na^+-K^+-co-transport activity was negatively correlated with blood lead concentration but not with hair lead (geometric mean 5.3 µg/g, range 0.9–60), and Na^+-K^+-ATPase activity was negatively correlated with hair lead, but not with blood lead.

6.9.3 Effects of Lead on the Endocrine System

6.9.3.1 Summary of Key Findings of the Effects of Lead on the Endocrine System from the 1986 Lead AQCD

The 1986 Lead AQCD concluded that various endocrine processes may be affected by lead at relatively high exposure levels. These included effects on thyroid hormone levels (e.g., Refowitz, 1984; Robins et al., 1983), effects on male sex hormone levels (e.g., Braunstein et al., 1978), and impairment of the production of 1,25-dihydroxy vitamin D (1,25-OH-D) (e.g., Rosen et al., 1980). Effects on these endocrine systems were concluded to be apparent only at blood lead concentrations exceeding 30–40 µg/dL. The 1986 Lead AQCD concluded that studies from which the effects of lead on reproductive hormones in females could be assessed were lacking.

More recent epidemiologic studies have examined possible associations between lead exposure (as reflected by blood and/or bone lead levels) and various biomarkers of endocrine function, including the thyroid, male reproductive, and calcitropic endocrine systems. These studies have examined endocrine outcomes at lower blood lead ranges and in the absence of

overt clinical lead toxicity, and have more rigorously attempted to control for confounding factors. Evidence for lead effects on these systems, in association with blood lead concentrations below 30–40 μg/dL, remains absent. The strongest study designs have yielded no associations, or weak associations, between lead exposure and thyroid hormone status (Erfurth et al., 2001; Schumacher et al., 1998; Tuppurainen et al., 1988; Zheng et al., 2001). Similarly, studies of the male reproductive system that attempted to control for confounding effects of age, have yielded mixed outcomes (Alexander et al., 1998, 1996; Erfurth et al., 2001; Gustafson et al., 1989; McGregor and Mason, 1990; Ng et al., 1991). Results of a more recent epidemiologic study of the calcitropic endocrine system in children suggest that associations between serum vitamin D status and blood lead may not be present in calcium-replete children who have average lifetime blood lead concentrations below 25 μg/dL (Koo et al., 1991). In adults, exposures to lead that result in blood lead concentrations >40–60 μg/dL may increase, rather than decrease, circulating levels of 1,25-OH-D and PTH (Kristal-Boneh et al., 1999; Mason et al., 1990), possibly as a compensatory response to increased urinary calcium losses, secondary to impaired kidney function. Details regarding the design of these studies and outcomes are presented in Annex Tables AX6-9.5 and AX6-9.6. Outcomes of the most pertinent studies are summarized below.

6.9.3.2 Thyroid Endocrine Function

Several studies have examined possible associations between lead exposure and thyroid hormone status. Most of these have been studies of occupational exposures. The results of these studies have been mixed; some studies have found significant associations with lead exposure (e.g., blood lead concentration), but most studies have found none or relatively weak associations. In studies that have controlled for the effects of age, outcomes also have been mixed, with the strongest study designs finding none or weak associations between lead biomarkers and thyroid hormone status (Erfurth et al., 2001; Schumacher et al., 1998; Tuppurainen et al., 1988; Zheng et al., 2001). The strength of the association and, possibly, the direction of the effect (i.e., increase or decrease in hormone levels) may change with exposure duration or level (Robins et al., 1983; Tuppurainen et al., 1988). The overall picture that emerges is that those studies that have included subjects having blood lead concentrations exceeding 100 μg/dL have found depression of serum T3 and/or T4 levels, without a detectable increase in serum TSH. However, studies in which the blood lead distribution was dominated by

levels well below 100 µg/dL, have found either no effects or subclinical increases in serum T3, T4, with no change in TSH levels. Outcomes from the most pertinent studies are summarized qualitatively in Table 6-9.4 and are described in greater detail below.

Siegel et al. (1989) measured serum total thyroxine (TT4) and free thyroxine (FT4) in children ages 11 months to 7 years (n = 68) who were outpatients at a clinical care facility. Mean blood lead concentration in the study group was 25 µg/dL (range 2–77). In a simple (univariate) linear regression analysis, hormone levels were not significantly associated with blood lead concentration.

Zheng et al. (2001) measured concentrations of TT4 and transthyretin (TTR) in serum and cerebral spinal fluid (CSF) of adult hospital patients (n = 82) admitted for evaluation of CSF clinical chemistry (e.g., for head wounds, tumors, neurological symptoms). Mean blood lead concentration was 14.9 µg/dL (SD 8.3). Age-adjusted serum TT4 and TTR, and CSF TT4 were not significantly associated with blood lead concentration; however, increasing CSF lead concentration was associated with decreasing CSF TTR levels ($r = -0.30$, $p = 0.023$).

Possible associations between lead exposure and thyroid hormone status have been examined in several studies of lead workers (Dursun and Tutus, 1999; Erfurth et al., 2001; Gennart et al., 1992; Gustafson et al., 1989; Horiguchi et al., 1987; Lopez et al., 2000; Refowitz, 1984; Robins et al., 1983; Schumacher et al., 1998; Singh et al., 2000; Tuppurainen et al., 1988). Of these, six warrant particular attention because the design and/or analysis attempted to control for effects of age (Erfurth et al., 2001; Dursun and Tutus, 1999; Gustafson et al., 1989; Schumacher et al., 1998; Tuppurainen et al., 1988; Robins et al., 1983). Outcomes of these studies are summarized in Table 6-9.4. The largest studies were Erfurth et al. (2001), Schumacher et al. (1998), and Tuppurainen et al. (1988).

Erfurth et al. (2001) was a cross-sectional study of secondary smelter workers (n = 62) and a reference group of metal (not lead) workers (n = 26). Excluded from the study were individuals with ongoing thyroid disease or who were taking thyroid hormone supplements or other drugs that would interfere with thyroid hormone levels (e.g., beta-blockers). Median blood lead concentration in the lead workers was 31 µg/dL (range 8–93 µg/dL). Age-adjusted basal serum levels of FT3, FT4, and TSH were not associated with blood, urine, or finger bone lead levels. Thyroid releasing hormone (TRH)-induced TSH secretion (area under serum TSH concentration-time curve) was measured in an age-matched subset of the study group (9 lead

Table 6-9.4. Summary of Results of Selected Studies of Associations Between Lead Exposure and Thyroid Hormone Levels

Study	Subjects	n[a]	Blood Lead (µg/dL)		T3	T4	TSH
			Mean (SD)	Range			
Children							
Siegel et al. (1989)	children, 11 mo–7 yrs	68	25	2–77	NR	o	NR
Adults							
Dursun and Tutus (1999)	metal powder manufacture workers	57	17.1 (9.0)	1–36	+	+	o/o[b]
Erfurth et al. (2001)	secondary smelter workers	88	31.1[c]	4–93	o	o	o
Gustafson et al. (1989)	secondary smelter workers	42	39.4 (2.1)	NR	o	+	o
Robins et al. (1983)	brass foundry workers	47	NR	16–127	NR	–	NR
Schumacher et al. (1998)	primary smelter workers	151	24.1	15>40%	o	o	o
Tuppurainen et al. (1988)	battery manufacture workers	176	55.9 (23.8)	5–134	–	–	o
Zheng et al. (2001)	general population	82	14.9 (8.3)	NR	NR	o	NR

–, decrease; +, increase; o, no effect; NR, not reported; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone

[a] Total number of subjects (including reference group)
[b] basal/thyroid releasing hormone-stimulated
[c] median

workers and 11 reference subjects) and was not significantly different in the two groups. The Schumacher et al. (1998) study measured serum FT4, TT4, and TSH levels in a group of male workers (n = 151) at the Trail British Columbia smelter complex. Excluded from the study were individuals who had ongoing clinical thyroid disease. Mean blood lead concentration in the study group was 24 μg/dL (15% >40 μg/dL). Covariate-adjusted (age, alcohol consumption) hormone levels were not significantly associated with current blood lead concentration or 10-year average blood lead concentrations. Prevalence of abnormal hormone values was also unrelated to blood lead concentration.

Tuppurainen et al. (1988) measured serum total triiodothyronine (TT3), FT4, TT4, and TSH levels in a group of male battery manufacture workers (n = 176). Mean blood lead concentration was 56 μg/dL (range 14–134 μg/dL). Although, hormone levels were not significantly associated with blood lead concentrations, increasing exposure (i.e., employment) duration was significantly associated with decreasing FT4 ($r^2 = 0.071$, $p = 0.001$) and TT4 ($r^2 = 0.059$, $p = 0.021$) levels. The r^2 was not improved by including age or blood lead as covariables. Strength of the association was greater when the analysis was restricted to workers who had an exposure duration >7.6 years (FT4: $r^2 = 0.33$, $p < 0.002$; TT4: $r^2 = 0.21$, $p < 0.001$). Consistent with the results of the Tuppurainen et al. (1988) study, Robins et al. (1983) found a significant association between increasing blood lead concentration and decreasing FT4 ($r^2 = 0.085$, $p = 0.048$) in a group of brass foundry workers (n = 47). The blood lead range in the subjects was 16–127 μg/dL. When stratified by race (black, white) the association was significant in the black stratum ($r^2 = 0.21$, $p = 0.03$), but not in the white stratum ($r^2 = 0.05$, $p = 0.27$). The strength of association was not changed by including age in the regression model. Both the Robins et al. (1983) and Tuppurainen et al. (1988) included subjects with blood lead concentrations >100 μg/dL.

Blood lead concentrations were lower in the Dursun and Tutus (1999) and Gustafson et al. (1989) studies than in the above studies, and both studies found significant associations between lead exposure and increasing serum TT4 levels. Dursun and Tutus (1999) measured serum FT3, TT3, FT4, TT4, and TSH in a group of metal powder manufacture workers (n = 27) and a reference group (n = 30). Mean blood lead concentration in the workers was 17 μg/dL (range 9–36 μg/dL). A linear regression model that included age, blood lead concentration, and exposure duration, indicated a significant association between increasing exposure duration and increasing

serum TT4 levels ($r^2 = 0.3$, $p = 0.03$). The Gustafson et al. (1989) study examined a group of male secondary smelter workers (n = 21) and reference subjects, individually matched to the lead workers by age, sex, and work shift. Mean blood lead concentration in the workers was 39 µg/dL (SD 2). Serum TT4 levels were significantly higher ($p < 0.02$) in the lead workers compared to the reference group. The difference strengthened when the analysis was restricted to the age range <40 years ($p = 0.01$).

6.9.3.3 Reproductive Endocrine Function

6.9.3.3.1 Male Reproductive Endocrine Function

Low testosterone (TES) levels, blunted sex hormone secretion in response to gonadotropin releasing hormone (GNRH), and defects in spermatogenesis have been observed in humans exhibiting clinical neurological symptoms of lead poisoning (Braunstein et al., 1978; Cullen et al., 1984). However, the effects of lower exposure levels on reproductive endocrine status are less clear. Possible associations between lead exposure and changes in male reproductive hormone levels have been examined in studies of lead workers. Of these, five studies attempted to control for effects of age, an important determinant of testosterone levels (Alexander et al., 1998; Erfurth et al., 2001; Gustafson et al., 1989; McGregor and Mason, 1990; Ng et al., 1991). The outcomes from these studies are qualitatively summarized in Table 6-9.5. Blood lead ranges in the latter studies were similar (4–90 µg/dL), yet outcomes were mixed, with no change (Erfurth et al., 2001; Gustafson et al., 1989; McGregor and Mason, 1990) or subclinical decrease (Alexander et al., 1998, 1996; Ng et al., 1991) in serum testosterone (TES) in association with lead exposure. Mixed effects were observed for the effect of lead exposure on serum follicle stimulating hormone (FSH) and luteinizing hormone (LH), increases (McGregor and Mason, 1990; Ng et al., 1991), decreases (Gustafson et al., 1989), and with no change (Alexander et al., 1998, 1996; Erfurth et al., 2001) in hormone levels observed. The inconsistency in the direction of effects on TES and the two androgen regulating pituitary hormones, FSH and LH, is particularly noteworthy. In the absence of an abnormality in the hypothalamic-pituitary regulation of testosterone levels, an association between declining serum TES (or free TES) and increasing FSH and LH levels would be expected. Erfurth et al. (2001) observed a suppressed FSH response to GNRH in a group of lead workers compared to an

Table 6-9.5. Summary of Results of Selected Studies of Associations Between Lead Exposure and Male Sex Hormone Levels in Adults

Study	Subjects	n[a]	Blood Lead (µg/dL)		FSH	LH	PRL	TES
			Mean (SD)	Range				
Alexander et al. (1998, 1996)	primary smelter workers	152	NR	5–58	o	o	NR	–[b]
Erfurth et al. (2001)	secondary smelter workers	88	31.1[c]	4–93	o/-[d,e]	o/o[d]	o/o[d]	o[d]
Gustafson et al. (1989)	secondary smelter workers	42	39.4 (2.1)	NR	–	–	o	o
McGregor and Mason (1990)	lead workers	176	NR	17–77	+	+	NR	o
Ng et al. (1991)	battery manufacture workers	171	35 (13)	10–72	+	+	o	–

–, decrease; +, increase; o, no effect; NR, not reported, FSH, follicle stimulating hormone, LH, luteinizing hormone; PRL, prolactin; TES, testosterone

[a] total number of subjects (including reference group)
[b] in association with increasing semen lead levels, not with blood lead
[c] median
[d] basal/gonadotropin releasing hormone-stimulated
[e] effect was evident in comparison between groups, but not in multivariate regression that adjusted for age

age-matched reference group; however, the magnitude of the response was not significantly associated with lead exposure indices in a multivariate regression analysis that accounted for age.

Alexander et al. (1998, 1996) examined serum FSH, LH, and TES in males (n = 152) who worked at the Trail British Columbia smelter complex. Covariate-adjusted hormone levels and prevalence of clinically abnormal values were unrelated ($p \geq 0.05$) to blood lead concentration (range 5–58 µg/dL); however, increasing semen lead concentration (range 0.3-17 µg/dL) was significantly associated with decreasing semen testosterone levels ($p = 0.004$). Erfurth et al. (2001) measured serum TES, sex hormone binging globulin (SHBG), and GNRH-stimulated changes in serum FS, LH, and PRL in male secondary smelter workers (n = 62) and in a reference group (n = 26). Mean blood lead in the lead workers was 31 µg/dL (range 8-93 µg/dL). Age-adjusted basal hormone levels were unrelated to blood, plasma, or urine lead concentrations. In an age-matched subset of the cohorts (n = 9 lead workers, n = 11 reference), median GNRH-stimulated serum FSH was significantly lower in lead workers than in the reference group; however, GNRH-stimulated LH, FSH, and PRL were not significantly associated with any of the lead measures in a multivariate regression analysis. Gustafson et al. (1989) measured serum FSH, LH, and TES (total and free) in a group of male secondary smelter workers (n = 21) and in a group of reference subjects individually matched to the lead workers by age, sex, and work shift. Mean blood lead concentrations were 39 µg/dL (SD 2) in the lead workers and 5.0 µg/dL (SD 0.2) in the reference group. Serum FSH levels were significantly lower ($p = 0.009$) in lead workers compared to reference group. When the analysis was restricted to the age range <40 years, lead workers had significantly lower FSH and LH compared to the reference group. McGregor and Mason (1990) measured serum FSH, LH, TES, and SHBG in a group of male lead workers (n = 90) and in a reference group (n = 86). Blood lead range in the lead workers was 17–77 µg/dL; blood lead concentrations in the reference subjects were <12 µg/dL. Prevalences of abnormal hormone levels in the lead workers and reference group were not different; however, age-adjusted serum FSH was significantly higher in lead workers compared to reference group and increasing FSH levels were significantly associated with increasing blood lead concentrations. Increasing serum LH was significantly associated with increasing exposure duration but not with blood lead concentration or age. Serum TES or SHBG levels were unrelated to blood lead concentration or exposure duration. Ng et al. (1991) measured serum FSH, LH, PRL, and TES in a group of male battery

manufacture workers (n = 122) and a reference group (n = 49). Mean blood lead concentrations were 35 µg/dL (range 10–77 µg/dL) in the lead workers and 8 µg/dL (range 3-15 µg/dL) in the reference group. When cohorts were stratified by age, serum FSH and LH levels were significantly higher in lead workers <40 years of age compared to corresponding age stratum of the reference group; serum TES was significantly lower in lead workers ≥40 years of age, compared to the same age stratum in the reference group. Covariate-adjusted (age, tobacco smoking) serum TES levels were significantly lower in lead workers in the 10-year exposure duration stratum, compared to the reference group. Covariate-adjusted serum FSH and LH were significantly higher in lead workers in the <10-year exposure duration stratum, compared to the reference group.

6.9.3.3.2 Female Reproductive Endocrine Function

Although delays in sexual maturation in humans have been associated with blood lead concentrations (Selevan et al., 2003; Wu et al., 2003), and lead has been shown to alter levels of female sex hormones and the menstrual cycle in nonhuman primates (Foster, 1992; Franks et al., 1989; Laughlin et al., 1987), epidemiologic studies of interactions between lead exposure and reproductive endocrinology in females have not been reported. Lead introduced into cultures of human ovarian granulosa cells suppresses progesterone production (Paksy et al., 2001) and suppresses expression of aromatase and estrogen receptor β (Taupeau et al., 2003).

6.9.3.4 Pituitary and Adrenal Endocrine Function

Several studies of possible associations between lead exposure and levels of pituitary hormones that regulate production and secretion of thyroid hormones (see Section 6.9.3.2) and reproductive hormones (see Section 6.9.3.3) have been reported. In addition to the above studies, Gustafson et al. (1989) found that serum cortisol levels were lower in a group of male secondary smelter workers (n = 21) compared to a reference group individually matched to the lead workers by age, sex, and work shift. Mean blood lead concentration were 39 µg/dL (SD 2) in the workers and 5.0 µg/dL (SD 0.2) in the reference group. Campbell et al. (1985) measured various biomarkers of status of the renin-angiotensin-aldosterone system in male welders (n = 5) and reference subjects (n = 8). Mean blood lead concentration was 35 µg/dL (range 8-62 µg/dL). Significant positive correlations were observed between blood lead concentration and plasma

aldosterone ($r = 0.53$, $p < 0.002$), which may have been, at least in part, secondary to a lead effect on plasma renin activity ($r = -0.76$, $p < 0.001$) and angiotensin I levels ($r = 0.68$, $p < 0.002$). Saenger et al. (1984) found lower urinary levels of 6-β-OH-cortisol, but not cortisol, in children who had elevated urinary lead in an EDTA provocation test (>500 μg/24 h), compared to children who did not have elevated urinary lead levels, or whose blood lead concentrations were <30 μg/dL. The change in urinary excretion of 6-β-OH-cortisol in the absence of a change in cortisol levels may reflect an effect of lead on liver cytochrome P450 activity, rather than an effect on the adrenal gland (see Section 6.9.4).

6.9.3.5 Calcitropic Endocrine Function

Children exposed to relatively high level of lead >30 μg/dL may exhibit depressed levels of circulating 1,25-OH-D (Mahaffey et al., 1982; Rosen et al., 1980). These effects were not detected in a study of calcium-replete children with average lifetime blood lead levels below 25 μg/dL (Koo et al., 1991). In adults, lead exposures that result in blood lead concentrations >40–60 μg/dL may increase, rather than decrease, circulating levels of 1,25-OH-D and PTH. These studies also are summarized in Annex Tables AX6-9.5 and AX6-9.6. Outcomes from the more pertinent studies are qualitatively summarized in Table 6-9.6 and are discussed in greater detail below.

Epidemiologic studies of possible associations between lead exposure and vitamin D status in children have yielded mixed results. Mahaffey et al. (1982) and Rosen et al. (1980) observed lower 1,25-OH-D in association with increasing blood lead concentration. Koo et al. (1991) found no association between 1,25-OH-D and blood lead concentration. The Koo et al. (1991) study was a longitudinal analysis of a subset of a prospective study of pregnancy outcomes. Serum calcium magnesium, phosphorus, PTH, CAL, 25-OH-D, 1,25-OH-D, and bone mineral content were measured in children ($n = 105$) at ages 21, 27, and 33 months. Mean lifetime average blood lead concentrations (based on quarterly assessments) was 9.7 μg/dL (range 4.8–23.6 μg/dL). The range of highest values observed was 6–63 μg/dL. A structural equation model was developed that initially considered age, sex, race, sampling season, and dietary intake of calcium, phosphorus, and vitamin D as covariables; the final model retained age, sex, race, and sampling season. Decreasing blood lead (ln-transformed) was significantly associated with covariate-adjusted decreasing serum phosphorus. No other covariate-adjusted

Table 6-9.6. Summary of Results of Selected Studies of Associations Between Lead Exposure and Calcitropic Hormones

Study	Subjects	n[a]	Blood Lead (µg/dL)		PTH	CAL	1,25D	25D
			Mean (SD)	Range				
Children								
Koo et al. (1991)	ages: 21, 27, 33 mo	105	9.7	5–24	o	o	o	o
Mahaffey et al. (1982)	ages: 1–16 yr	177	NR	12–120	o	o	–	o
Rosen et al. (1980)	ages: 1–5 yr	45	18, 47, 74[b]	10–120	+	o	–	–
Adults								
Chalkley et al. (1998)	smelter workers[c]	19	47	21–76	NR	NR	+[c]	o
Kristal-Boneh et al. (1998)	battery manufacture workers	140	43	1–77	+	NR	+	NR
Mason et al. (1990)	lead workers	138	NR	15–95	o	NR	+	NR

–, decrease; +, increase; o, no effect; NR, not reported, PTH, parathyroid hormone; CAL, calcitonin; 1,25D, 1,25-dihydroxyvitamin D; 25D, 25-hydroxyvitamin D

[a] total number of subjects (including reference group)
[b] group means: low, moderate, high
[c] cadmium, lead, zinc smelter workers, effect on 1,24D in association with high blood cadmium and lead and high urinary cadmium

outcomes were significantly associated with blood lead. The distribution of dietary calcium intakes was 4% for ≤600 mg/day, 55% for 600–1200 mg/day, and 41% for >1200 mg/day. Intakes of phosphorous were similar, suggesting that the subjects were nutritionally replete with respect to these two nutrients.

The different outcomes in Koo et al. (1991) compared to the Mahaffey et al. (1982) and Rosen et al. (1980) studies may reflect, in part, the lower blood lead range in the subjects in Koo et al. (1991) (range of lifetime average 5–24 µg/dL, range of observed highest values 6–63 µg/dL) compared to the Mahaffey et al. (1982) and Rosen et al. (1980) studies (10–120 µg/dL). Subjects in the Koo et al. (1991) study also had higher calcium intakes (4% with ≤600 mg/day, 43% with >1200 mg/day) than in the Rosen et al. (1980) study (mean 580 mg/day [SE 15] in high blood lead group). Calcium intake (and/or related nutritional factors) may also have been an uncontrolled confounder in the Rosen et al. (1980) study, as higher blood lead concentration appeared to be associated with lower calcium intakes (Sorrell et al., 1977). Mahaffey et al. (1982) did not report calcium intakes. Thus, the effect of lead exposure on vitamin D status may be more pronounced at higher blood lead concentrations (i.e., >60 µg/dL) and in combination with lower intakes of calcium (or other nutritional limitations).

Studies of lead workers have found evidence for higher serum levels of 1,25-OH-D and PTH in association with increasing blood lead concentration (Chalkley et al., 1998; Kristal-Boneh et al., 1998; Mason et al., 1990). The Chalkey et al. (1998) study was a small study (n = 19) of subjects exposed to both cadmium and lead, and effects of lead and cadmium on 1,25-OH-D could not be isolated. The Kristal-Boneh et al. (1998) and Mason et al. (1990) studies included larger samples of subjects whose exposure was primarily, but not exclusively, to lead. Attempts were made to control for effects of age and, in the Kristal-Boneh et al. (1998) study, other potential covariables. Kristal-Boneh et al. (1998) measured serum calcium, magnesium, phosphorus, PTH, 25-OH-D, and 1,25-OH-D in a group of male battery manufacture workers (n = 56) and a reference group (n = 90). Mean blood lead concentrations were 43 µg/dL (SD 14, range 1-77 µg/dL) in the lead worker group and 4.5 µg/dL (SD 2.6, range 1.4–19 µg/dL) in the reference group. Serum 1,25-OH-D and PTH, but not 25-OH-D, were significantly higher in lead workers compared to the reference group. Increasing blood lead concentration (ln-transformed) was significantly associated with covariate-adjusted increasing serum PTH and 1,25-OH-D levels. No effects on serum calcium were apparent. Occupational

lead exposure was also significantly associated with increasing PTH and 1,25-OH-D level. Covariates retained in the multivariate model were age, alcohol consumption, smoking; calcium intake, magnesium intake, and calorie intake. Mason et al. (1990) measured serum calcium, phosphate, PTH, and 1,25-OH-D in male lead workers (n = 63) and in a reference group (n = 75) and found significantly higher prevalence of elevated 1,25-OH-D (defined as >2 SD higher than reference mean) in lead workers (13%) compared to the reference group (1.3%). Serum levels of 1,25-OH-D were also significantly higher in lead workers compared to the reference group. After stratification of the lead workers into exposure categories (high exposure: blood lead ≥40 μg/dL and bone lead ≥40 μg/g; low exposure: blood lead ≤40 μg/dL and bone lead ≤40 μg/g), serum 1,25-OH-D levels were significantly higher in the high lead group. Serum calcium levels were not different in the two groups. Increasing blood lead was significantly associated with increasing 1,25-OH-D levels ($r^2 = 0.206$; with age and bone lead included, $r^2 = 0.218$). After excluding 12 subjects whose blood lead concentrations >60 μg/dL, the regression coefficient was no longer significant ($r^2 = 0.162$, $p = 0.26$).

6.9.4 Effects of Lead on the Hepatic System

6.9.4.1 Summary of Key Findings of the Effects of Lead on the Hepatic System from the 1986 Lead AQCD

The 1986 Lead AQCD noted that effects of lead on liver function in humans had not been extensively studied. Possible association between lead exposures (blood lead concentrations >70 μg/dL) and nonspecific liver injury (i.e., increases in liver enzymes in serum) were noted based on studies of workers (e.g., Cooper et al., 1973; Hammond et al., 1980). Also noted was evidence for possible association of suppression of hepatic cytochrome P450 activity with high blood lead concentrations (>70 μg/dL) (Meredith et al., 1977).

Few studies of hepatic effects of lead on humans have been reported since the 1986 Lead AQCD. Studies of hepatic enzyme levels in serum suggest that liver injury may be present in lead workers; however, associations specifically with lead exposures are not evident (Al-Neamy et al., 2001; Hsiao et al., 2001). Studies of urinary metabolites of cytochrome P450 phenotypes CYP2A6 and CYP3A4 suggest possible associations between lead exposure and suppression of hepatic enzyme activity. The effect on CYP2A6 activity was observed in children with high lead burdens (i.e., blood lead concentration >40 μg/dL, EDTA-provoked urinary lead >500 μg/dL).

The effect on CYP3A4 was observed in association with blood lead ranges of approximately 30-112 μg/dL (based on reported serum lead concentrations). These studies are summarized in Annex Table AX6-9.7 and the most pertinent findings are discussed below.

6.9.4.2 Non-specific Hepatic Injury

Possible association between occupational lead exposure and liver injury has been assessed from measurements of serum enzymes (Al-Neamy et al., 2001; Hsiao et al., 2001). Al-Neamy et al. (2001) found significantly higher serum activity of alkaline phosphatase (AP) and lactate dehydrogenase (LDH), both within clinically normal ranges, in a group (n = 100) of male lead workers (e.g., gas pump attendants, garage workers, printing workers, construction workers), compared to an age-matched reference group (n = 100). Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (γ-GT) were not different in the two groups. The mean lead concentrations were 78 μg/dL (SD 43) in the lead workers and 20 μg/dL (SD 12) in the reference group. Hsiao et al. (2001) found no association between blood lead concentration and ALT activity, in a longitudinal study of a group of battery manufactory workers (n = 30). Mean blood lead concentrations ranged from 60 μg/dL (approximate range 25–100 μg/dL) at the start of the study (1989) and 30 μg/dL (approximate range 10–60 μg/dL) in the final year of the study (1999).

6.9.4.3 Hepatic Cytochrome P-450 Function

Urinary excretion of 6-β-hydroxycortisol (6-β-OH-cortisol) derives primarily from oxidation of cortisol through the hepatic cytochrome P450 phenotype CYP3A4. A lower urinary 6-β-OH-cortisol:cortisol ratio is indicative of possible suppression of hepatic CYP3A4 activity. Saenger et al. (1984) found significantly lower (~45% lower) urinary excretion of 6-β-OH-cortisol and lower urinary 6-β-OH-cortisol:cortisol ratio in 2–9 year-old children (n = 26) who qualified for chelation (EDTA-provoked urinary lead >500 μg/24 h) than in children who did not qualify, and significantly lower than in an age-matched reference group. Urinary 6-β-OH-cortisol:cortisol ratio was significantly correlated with blood lead ($r = -0.514$, $p < 0.001$), urinary lead, and EDTA-provoked urinary lead ($r = -0.593$, $p < 0.001$). Mean blood lead concentrations were 46 μg/dL (range 33–60 μg/dL), prior to chelation, and 42 μg/dL (range 32-60 μg/dL) in the children who did not qualify for chelation.

Satarug et al. (2004) measured urinary excretion of 7-hydroxy-coumarin (7-OH-coumarin) following a single oral dose of coumarin to assess effects of cadmium and lead exposure on cytochrome P450 phenotype CYP2A6. The rationale for this approach is that 7-hydroxylation of coumarin occurs solely through the CYP2A6 pathway. Coumarin-induced urinary 7-OH-coumarin was measured in a group (n = 118) selected from the general population in Bangkok, Thailand. All subjects were nonsmokers. The study found a significant association between increasing urinary lead and decreasing covariate-adjusted urinary 7-OH-coumarin in males, but not in females. Covariates retained included age and zinc excretion. A significant association, in opposite direction, was found between urinary cadmium and urinary 7-OH-coumarin. Mean urinary lead levels (blood lead concentrations were not reported) were 1.3 μg/g creatinine (range 0.1–1.2 μg/dL) in males, and 2.4 μg/g creatinine (range 0.6–6.8 μg/dL) in females. Mean serum lead concentrations were 4 μg/L (range 1–28 μg/dL) in males and 3 μg/dL (range 1–12 μg/dL) in females. The range 1–28 μg/L serum would correspond to a blood lead concentration range of approximately 30–112 μg/dL (U.S. Environmental Protection Agency, 2003). These results are consistent with observations of depressed excretion of metabolites of the CYP2A6 substrate, phenazone, in association with overt clinical lead toxicity in lead workers (Fischbein et al., 1977; Meredith et al., 1977).

6.9.5 Effects of Lead on the Gastrointestinal System

6.9.5.1 Summary of Key Findings of the Effects of Lead on the Gastrointestinal System from the 1986 Lead AQCD

The 1986 Lead AQCD described gastrointestinal colic (abdominal pain, constipation, intestinal paralysis) as a consistent early symptom of lead poisoning in humans and noted that such symptoms may be present in association with blood lead concentrations in the range of 30-80 μg/dL. The 1986 Lead AQCD concluded that information was insufficient to establish clear concentration (i.e., blood concentration)-response relationships in the general population in association with environmental exposure. Subsequent to the 1986 AQCD several studies of prevalence of symptoms of gastrointestinal colic in lead workers have been reported that provide evidence for symptoms in association with blood lead concentrations >50–80 μg/dL (Awad el Karim et al., 1986; Holness and Nethercott, 1988; Lee et al., 2000; Matte et al., 1989).

Summaries of these studies are presented in Annex Table AX6-9.8. Similar types of studies of children have not been reported.

6.9.5.2 Gastrointestinal Colic

Lee et al. (2000) collected data on symptoms (self-reported questionnaire) in male lead workers (n = 95) who worked in secondary smelters, PVC-stabilizer manufacture facilities, or battery manufacture facilities. A logistic regression model was applied to the prevalence data for gastrointestinal symptoms (loss of appetite, constipation or diarrhea, abdominal pain). The covariate-adjusted odds ratio for symptoms, in association with blood lead concentration (≥versus <the group median, 45.7 μg/dL), was not significant (1.8, [95% CI: 0.7, 4.5]). The corresponding odds ratio for DMSA-provoked urinary lead (≥versus <260.5 μg/4 h, the group median) was also not significant (1.1, [95% CI: 0.4, 2.5]). However, the odds ratio for neuromuscular symptoms in association with DMSA-provoked urinary lead was significant (7.8, [95% CI: 2.8, 24.5]), suggesting that neuromuscular symptoms may occur in association with exposures that are insufficient to result in detectable gastrointestinal symptoms. Covariates retained in the final regression models were age, tobacco smoking, and alcohol consumption.

Three other studies have attempted to quantify associations between lead exposure and gastrointestinal symptoms in lead workers (Awad el Karim et al., 1986; Holness and Nethercott, 1988; Matte et al., 1989). Holness and Nethercott (1988) found a significantly ($p < 0.05$) higher prevalence of symptoms in a group of demolition workers (n = 119) in association with a blood lead concentration range 50–70 μg/dL (n = 87), 37% for abdominal cramps and 42% for constipation, or >70 μg/dL (n = 19) 77% for abdominal cramps and 62% for constipation compared to a group of workers in which the blood lead concentration range was <50 μg/dL (n = 13), prevalences of 8% and 6%. Awad el Karim et al. (1986) found higher prevalence of gastrointestinal symptoms, for abdominal colic and constipation, respectively, in male battery manufacture workers, 41.3% for abdominal colic and 41.4% for constipation, compared to a reference group of workers, n = 40 prevalences of 7.5% and 10% for abdominal colic and constipation, respectively. The blood lead ranges were 55–81 μg/dL in the lead workers and 7-33 μg/dL in the reference group. Matte et al. (1989) did not find a significant difference in prevalence of gastrointestinal symptoms (decreased appetite, nausea, abdominal pain) among a group of battery manufacture and repair workers (n = 63) when stratified by blood lead

concentration (60 µg/dL, ≥60 µg/dL). The prevalence ratio (high/low blood lead strata) for abdominal pain was 1.5 (95% CI: 0.5, 4.6).

In a small study of environmentally-exposed adults, Bercovitz and Laufer (1991) found that the lead level in the dentine of patients with gastrointestinal ulcers (n = 11), even long after recovery, were significantly higher (mean lead 75.02 µg/g [SE 8.15]) than that in healthy subjects (mean lead 25.62 µg/g [SE 10.15]). Ten of the 11 peptic ulcer patients had a higher lead level than the healthy subjects. In these 10 patients, increased severity of the ulcer and longevity of suffering was associated with increased tooth lead levels. The authors suggested that increased absorption of lead was associated with damage to the epithelial mucosal cells of the gastrointestinal tract.

6.9.6 Effects of Lead on the Respiratory System

6.9.6.1 Summary of Key Findings of the Effects of Lead on the Respiratory System from the 1986 Lead AQCD

The 1986 Lead AQCD did not discuss effects of lead on the respiratory tract on humans. Only one study since the 1986 document has examined the association between lead and respiratory health outcomes.

6.9.6.2 Pulmonary Function

Bagci et al. (2004) conducted pulmonary function tests on a group of male battery manufacture workers (n = 22), automobile exhaust repair workers (n = 40), and a group of hospital workers (n = 24). Mean blood lead concentrations were 37 µg/dL (SD 8) in the battery manufacture group, 27 µg/dL (SD 9) in the exhaust repair group, and 15 µg/dL (SD 3) in the hospital workers. Lead workers and the reference group had similar tobacco smoking prevalences (51–56%). Battery manufacture workers had significantly lower forced expiratory volume in one second (FEV_1), FEV_1:vital capacity (VC) ratio, FEV_1/forced vital capacity (FVC) ratio, forced expiration flow (FEF), and maximum voluntary ventilation (MVV) compared to the hospital workers. Blood lead concentration was significantly negatively correlated with FEV_1/FVC ($r = -0.31$, $p = 0.006$) and FEF ($r = -0.30$, $p = 0.009$) after adjusting for age, cigarette smoking, and exposure duration. Results from this study are further summarized in Annex Table AX6-9.9.

6.9.7 Effects of Lead on Bone and Teeth

6.9.7.1 Summary of Key Findings of the Effects of Lead on Bone and Teeth from the 1986 Lead AQCD

The 1986 Lead AQCD did not discuss the effects of lead on bone and teeth. Since completion of the 1986 AQCD, an additional development in lead epidemiology has been studies that have explored possible associations between lead exposure and risk of dental caries (Campbell et al., 2000; Dye et al., 2002; Gemmel et al., 2002; Moss et al., 1999). In addition, a limited number of studies also examined the toxic effect of lead on bone. These studies are summarized in Annex Table AX6-9.10.

6.9.7.2 Bone Toxicity

The number of papers dealing with direct toxicity of lead on bone is limited. Most papers are reviews (Hu et al., 1991; Puzas, 2000; Puzas et al., 1992; Rabinowitz, 1991; Silbergeld, 1991; Silbergeld et al., 1993; Vig and Hu, 2000) or based on cellular studies (e.g., Pounds et al., 1991) or animals.

Various authors have suggested that lead is a potential risk factor for osteoporosis because of the pivotal role of the skeleton in lead toxicokinetics (Goyer et al., 1994). Bone cells accumulate lead actively and earlier ideas suggested that lead was incorporated into the mineral matrix of the bone (Wittmers et al., 1988). However, in an in vivo iliac bone biopsy using laser microbeam mass analysis on a lead-intoxicated adult female following chelation therapy, Flood et al. (1988) found the extracellular lead was concentrated in the superficial 3 to 6 μm of the osteoid zone of bony trabeculae. As lead was absent from the deeper parts of the mineralized matrix, the authors suggested that lead binds more strongly to the organic matrix than to bone mineral.

There is increasing evidence from cell culture experiments, animal studies, and from measurements in humans that lead may exert detrimental effects on bone mineral metabolism. In humans this evidence comes from several studies. Following on from the earlier observations of Rosen et al. (1980) that 1,25 $(OH)_2$ vitamin D levels are reduced in lead poisoned children, Markowitz et al. (1988) found that osteocalcin levels were inversely related to lead body burden in moderately lead poisoned children. During chelation treatment for lead, the osteocalcin levels were shown to increase.

An inverse relationship between blood lead and stature and chest circumference has been observed in children from the NHANES II study (Schwartz et al., 1986). There are several explanations for the inverse correlation between blood lead and growth in children. First, blood lead level may be a composite factor for genetic, ethnic, nutritional, environmental, and sociocultural factors. Second, nutritional deficits that retard growth also enhance lead absorption. Finally, there may be a direct effect of low level lead on growth in children. This condition was explained by Dowd et al. (1994) as resulting from the inhibition by Pb^{2+} of binding of osteocalcin to hydroxyapatite. Effects similar to those described by Schwartz et al. (1986) were reported by Angle and Kuntzelman (1989), Lauwers et al. (1986), and Shukla et al. (1989).

Puzas et al. (1992) suggested lead could upset the very sensitive interactive metabolic activity of osteoblasts and chondrocytes and thereby affect bone growth. In a later review, Puzas (2000) enlarged upon his earlier paper and described in more detail the potential mechanism of lead on growth plate cartilage metabolism and effects of lead on osteoclasts and osteoblasts, especially associated with osteoporosis.

Observational studies by Spencer et al. (1992, 1994) suggested a link between occupational exposure to lead and Paget's disease in both males and females but the authors declined to advocate a causal effect. Later Spencer et al. (1995) found that 92% of a group of 48 patients with Paget's disease were exposed to lead either from occupational or environmental sources. Adachi et al. (1998) explored a possible association between lead and bone disease from XRF analyses of cortical and trabecular bone lead content in 117 patients who attended a metabolic bone disease clinic (n = 92) or were undergoing dialysis for renal failure (n = 25). In patients suffering from Paget's disease, cortical bone lead content was higher than it was in controls, patients with osteoporosis, and patients on dialysis. Trabecular bone lead content was lowest in patients with Paget's disease or osteitis fibrosa. However, the authors could not distinguish between two alternatives, the first being that increased bone turnover due to Paget's disease releases lead from trabecular bone that is then available for deposition into cortical bone, or secondly, that an increased lead content in cortical bone may cause increased turnover with release of lead from trabecular bone.

In another facet of the Normative Aging Study, Shadick et al. (2000) investigated a possible association between long-term lead accumulation and hyperuricemia and gouty arthritis

in 777 male subjects. They found a positive association between patella bone lead and uric acid levels ($p = 0.022$) but no association between bone or blood lead and gout in this environmentally-exposed group.

6.9.7.3 Dental Health

Caries is considered an infectious disease arising from a multifactorial process involving particular flora, dietary exposures, and a susceptible host (Schafer and Adair, 2000). Increased caries risk has been detected in association with increasing blood lead concentrations in populations whose mean blood lead concentrations are approximately 2–3 µg/dL (Dye et al., 2002; Gemmel et al., 2002; Moss et al., 1999).

Several studies have examined relationships between lead exposure and the occurrence of dental caries in children and adults. The two largest studies were analyses of data collected in the NHANES III; both found significant associations between increasing caries prevalence and increasing blood lead concentrations in children and adolescent (Moss et al., 1999) and the adult (Dye et al., 2002) populations, whose geometric mean blood lead concentration was ~2.5 µg/dL. In the Moss et al. (1999) study, the odds ratios for caries in association with a 5 µg/dL increase in blood lead concentration (i.e., from <2 µg/dL) was 1.8 (95% CI: 1.3, 2.5). Outcomes of two smaller studies were mixed, with one study finding no significant association between blood lead and caries prevalence (Campbell et al., 2000) and one study finding significant associations (Gemmel et al., 2002); the latter, in children whose mean blood lead concentration was 2.9 µg/dL (maximum 13 µg/dL).

The Moss et al. (1999) NHANES III analysis included the results of coronal caries examinations on 24,901 subjects, stratified by age: 2–5 years (n = 3,547), 6–11 years (n = 2,894), and ≥12 years (n = 18,460). Specific outcomes assessed varied by age group: for children 2–11 years who had at least one deciduous tooth, the number of deciduous teeth displaying decayed or filled surfaces (DFS); for subjects ≥6 years and who had at least one permanent tooth, the number of permanent teeth displaying decayed or filled surfaces; and for subjects ≥12 years, the sum of decayed, missing, and filled surfaces on permanent teeth (DMFS). In a multivariate linear regression model, increasing blood lead concentration (log-transformed) was significantly associated with covariate-adjusted increases in dfs in the 2–5 year age group ($\beta = 1.78$ [SE 0.59], $p = 0.004$) and in the 6–11 year age group ($\beta = 1.42$ [SE 0.51], $p = 0.007$). Log-transformed

blood lead also was associated with increases in DFS in the 6-11 years age group (β = 0.48 [SE 0.22], p = 0.03) and in the ≥12 years age group (β = 2.50 [SE 0.69], p<0.001), and increases in DMFS in the ≥12 years age group (β = 5.48 [SE 1.44], p = 0.01). The odds ratios (compared to 1st tertile, ≤1.66 μg/dL) for the binomial outcome, 0 or ≥1 DMFS, were 1.36 (95% CI: 1.01, 2.83) for the blood lead concentration range 1.66-3.52 μg/dL, and 1.66 (95% CI: 1.12, 2.48) for the range >3.52 μg/dL. Corresponding population risks attributable to blood lead concentration were 9.6% and 13.5% in the blood lead strata, respectively. An increase in blood lead of 5 μg/dL was associated with an odds ratio of 1.8 (95% CI: 1.3, 2.5). Covariates included in the models were age, gender, race/ethnicity, poverty income ratio, exposure to cigarette smoke, geographic region, educational level of head of household, carbohydrate and calcium intakes, and frequency of dental visits.

Gemmel et al. (2002) conducted a cross-sectional study of associations between blood lead concentration and dental caries in children, 6-10 years of age (n = 543), who resided either in an urban (n = 290) or rural (n = 253) setting. Mean blood lead concentrations were 2.9 μg/dL (SD 2.0, maximum 13 μg/dL) in the urban group and 1.7 μg/dL (SD 1.0, maximum 7 μg/dL) in the rural group. Increasing blood lead concentration (ln-transformed) was significantly associated with covariate-adjusted number of caries (dfs + DFS) (ln-transformed) in the urban group (β = 0.22 [SE 0.08], p = 0.005), but not in the rural group (β = –0.15 [SE 0.09], p = 0.09). When dfs counts were stratified by permanent or deciduous teeth, the blood lead association in the urban group was significant for deciduous teeth (β = 0.28 [SE 0.09], p = 0.002), but not for permanent teeth (β = 0.02 [SE 0.07], p = 0.8). Covariates retained in the linear regression model were age, sex, ethnicity, family income, education of female guardian, maternal smoking, frequency of tooth brushing, firmness of toothbrush bristles, and frequency of chewing gum.

Campbell et al. (2000) was a retrospective cohort study in which dfs were assessed in children 7-12 years of age (n = 248) from Rochester, NY. Mean blood lead concentration, measured at ages 18 and 37 months of age, was 10.7 μg/dL (range 18.0-36.8 μg/dL). The covariate-adjusted odds ratios for caries associated with a blood lead concentration >10 μg/dL compared to ≤10 μg/dL were 0.95 μg/dL (95% CI: 0.43, 2.09) for permanent teeth and 1.77 μg/dL (95% CI: 0.97, 3.24) for deciduous teeth. Covariates retained in the logistic model were age, grade in school, number of tooth surfaces at risk. Other covariates examined in the models, all of which had no significant effect on the outcome, were gender, race/ethnicity, SES,

parental education, residence in community supplied with fluoridated drinking water, and various dental hygiene variables. This study did not demonstrate that lead exposure >10 μg/dL as a toddler was a strong predictor of caries among school-age children, but the authors noted that this might be due to limited statistical power.

Dye et al. (2002) analyzed data collected in NHANES III on indices of periodontal bone loss. The analysis was confined to subjects 20-69 years of age (n = 10,033). The geometric mean blood lead concentration of the study group was 2.5 μg/dL (SE 0.08), with 2.4% of the group having blood lead levels >10 μg/dL. Increasing log-transformed blood lead was significantly associated with increasing prevalence of covariate-adjusted dental furcation (β = 0.13 [SE 0.05], p = 0.005). Dental furcation is indicative of severe periodontal disease. Covariates retained in the linear regression model were age, sex, race/ethnicity, education, smoking, and age of home. Smoking status was a significant interaction term when included in the model (β = 0.10 [SE 0.05], p=0.034). When stratified by smoking status, the association between dental furcation and blood lead concentration was significant for current smokers (β = 0.21 [SE 0.07], p = 0.004) and former smokers (β = 0.17 [SE 0.07], p=0.015), but not for nonsmokers (β = –0.02 [SE 0.07], p = 0.747).

Some studies examined the relationship between tooth lead concentrations and dental caries. In their compilation of metal concentrations in 1,200 deciduous teeth from a Norwegian population, Tvinnereim et al. (2000) found that carious teeth had higher lead concentrations than noncarious teeth. Gil et al. (1994) measured lead concentrations from 220 whole deciduous and permanent teeth from Coruna, Spain. The geometric mean lead level was 10.36 μg/g of tooth. There was a significant increase in teeth lead levels with advancing age. Permanent teeth showed higher mean lead values (13.09 μg/g [SEM 1.07]) than deciduous teeth (3.96 μg/g [SEM 1.07]). The authors reported a possible relationship between increased lead content and periodontal pathology but did not observe any relationship between caries and lead concentrations.

6.9.8 Effects of Lead on Ocular Health

6.9.8.1 Summary of Key Findings of the Effects of Lead on Ocular Health from the 1986 Lead AQCD

The 1986 Lead AQCD did not address effects of lead on ocular health in humans. Various disturbances of the visual system have been observed in association with overt clinical lead poisoning, including retinal stippling and edema, cataracts, ocular muscle paralysis, and impaired vision (see Otto and Fox, 1993 for review). Two longitudinal studies completed since 1986 provide evidence for possible associations between lead exposure and visual evoked retinal responses in children of mothers whose blood lead concentrations in mid-pregnancy were in the range of 10–32 μg/dL (Rothenberg et al., 2002), and evidence for a possible association between lead exposure and risk of cataracts in middle-aged males whose tibia bone lead levels were in the range 31–126 μg/g (Schaumberg et al., 2004). These studies are summarized in Annex Table AX6-9.11.

6.9.8.2 Ocular Effects

In the Mexico City prospective lead study, Rothenberg et al. (2002) measured flash-evoked electroretinograms (ERG) in a subset of the study group (n = 45) at ages 7–10 years. As part of the prospective study, blood lead concentrations had been measured during pregnancy and in the children, at birth and every 6 months, thereafter. Increasing maternal blood lead, measured at 12 weeks of gestation, was significantly associated with increasing ERG a-wave and b-wave amplitude, with significant increases in a-wave in the second maternal blood lead tertile (range 6.0–10.0 μg/dL), and a-wave and b-wave in the third maternal blood lead tertile (range 10.5–32.5 μg/dL), compared to the first blood lead tertile (range 2.0–5.5 μg/dL). No other blood lead measurements were significantly associated with any ERG outcomes.

As part of the longitudinal Normative Aging Study, Schaumberg et al. (2004) analyzed prevalence of cataracts in adult males (n = 642), mean age 69 years (range 60–93). Subjects were stratified by blood lead, patella bone lead, or tibia bone lead quintiles for a logistic regression analysis of the odds ratios for cataracts (first quintile as reference). Covariate adjusted odds ratio for cataracts in the fifth tibia bone lead quintile was significant (3.19 [95% CI: 1.48, .90]). Odds ratios for cataracts were not significantly associated with patella bone lead (1.88 [95% CI: 0.88, 4.02]) or blood lead (0.89 [95% CI: 0.46, 1.72]). The first and fifth

quintile lead levels were 0–11 μg/g and 31–126 μg/g for tibia bone; 1–16 μg/g and 43–165 μg/g for patella bone; and 1.0–3.0 μg/g and 8–35 μg/g for blood. Covariates retained in the regression model were age, smoking, history of diabetes; and daily intake of vitamin C, vitamin E, and carotenoids.

Cavalleri et al. (1982) measured visual fields of male workers in a polyvinyl pipe manufacturing facility (n = 35) who were exposed to lead stearate. Workers in a reference group (n = 350) were individually matched for age, smoking, and alcohol consumption. Visual sensitivity was significantly lower in lead workers compared to the reference group; however, visual sensitivity index was not significantly associated with blood or urine lead. Prevalence of scotoma in the mesopic field was 28.5% in the lead workers and 0% in the reference group. Mean blood lead levels were 46 μg/dL (range 21–82 μg/dL) in the lead workers and 30 μg/dL (range 21-42 μg/dL) in the reference group.

6.9.9 Summary of the Epidemiologic Evidence for the Effects of Lead on Other Organ Systems

Biochemical Effects of Lead

Evidence for disruption of heme synthesis derives from numerous studies in which lead exposure has been associated with decreased activities of enzymes in the heme synthesis pathway (i.e., ALAS, ferrochelatase) and increased levels of substrates for heme synthesis (i.e., ALA, coproporphyrin, erythrocyte protoporphrin) in both children and adults. Quantitative relationships between blood lead concentration and the above biomarkers of impaired heme synthesis are highly consistent across studies (e.g., Alessio et al., 1977, 1976; Gennart et al., 1992; Hernberg et al., 1970; Morita et al., 1997; Oishi et al., 1996; Piomelli et al., 1982; Roels and Lauwerys, 1987; Selander and Cramer, 1970; Soldin et al., 2003; Wildt et al., 1987). Increases in blood lead concentration of approximately 20–30 μg/dL are sufficient to halve erythrocyte ALAD activity and sufficiently inhibit ferrochelatase to double erythrocyte protoporphyrin levels.

Associations between occupational exposure to lead and changes in blood lipid composition have been observed. These include increased levels of lipid peroxides in blood and/or serum (Jiun and Hsien, 1994; Sugawara et al., 1991; Ito et al., 1985) and increased serum levels of total and HDL cholesterol (Kristal-Boneh et al., 1999). Effects on serum cholesterol

levels were evident in association with a mean blood lead concentration of 42 μg/dL (Kristal-Boneh et al., 1999) or a range of 5–62 μg/dL (approximated mean 14 μg/dL) (Ito et al., 1985). Oxidative changes in blood lipids (e.g., increased levels of lipid peroxides and malondialdehyde levels) as well as decreased levels of erythrocyte superoxide dismutase, catalase, G6PD, and GSH peroxidase; and increased lymphocyte reactive oxygen species and depleted GSH levels, indicative of increased oxidative stress, have been observed in lead workers in association with blood lead concentrations >30 μg/dL (Fracasso et al., 2002; Ito et al., 1985; Jiun and Hsien, 1994; Solliway et al., 1996; Sugawara et al., 1991).

Disruption of Hemoglobin Synthesis and Declines in Erythrocyte Numbers

Exposures that result in blood lead concentrations below 40 μg/dL appear to be tolerated without a decline in blood hemoglobin levels or hematocrit. However, perturbation of erythropoiesis, indicated by changes in serum erythropoietin and progenitor cells, occurs in association with blood lead concentrations below 40 μg/dL and in the absence of detectable changes in blood hemoglobin levels or hematocrit in children (Graziano et al., 2004; Liebelt et al., 1999) and adults (Graziano et al., 1990; Osterode et al., 1999; Romeo et al., 1996). Risk of clinical anemia in children becomes appreciable at much higher blood lead concentrations; a 10% decrease in hematocrit has been estimated to occur in association with blood lead concentrations ≥85 μg/dL; a 10% probability of anemia (hematocrit <35%) was estimated to be associated with a blood lead concentration of approximately 20 μg/dL at age 1 year, 50 μg/dL at age 3 years, and 75 μg/dL at age 5 years. (Schwartz et al., 1990). In adults, with blood lead levels below 25 μg/dL, increasing patella bone lead, but not blood lead, was associated with a significant decrease in hematocrit.

Effects on the Endocrine System

Several studies have examined possible associations between lead exposures in children and adults and various biomarkers of endocrine function, including the thyroid, male reproductive, and calcitropic endocrine systems. The strongest study designs have yielded no associations, or weak associations, between lead exposure and thyroid hormone status (Erfurth et al., 2001; Schumacher et al., 1998; Tuppurainen et al., 1988; Zheng et al., 2001). Studies of occupational exposures which included subjects having blood lead concentrations exceeding

100 µg/dL have found depression of serum T3 and/or T4 levels, without a detectable increase in serum TSH; however, studies in which the blood lead distribution was dominated by levels well below 100 µg/dL, have found either no effects or subclinical increases in serum T3, T4, with no change in TSH levels.

Studies of the male reproductive system that attempted to control for confounding effects of age have yielded mixed outcomes (Alexander et al., 1998, 1996; Erfurth et al., 2001; Gustafson et al., 1989; McGregor and Mason, 1990; Ng et al., 1991). Blood lead ranges in these studies were similar (4–90 g/dL), yet outcomes were mixed, with no change (Erfurth et al., 2001; Gustafson et al., 1989; McGregor and Mason, 1990), or subclinical decrease (Alexander et al., 1998, 1996; Ng et al., 1991) in serum testosterone (TES) in association with lead exposure. There are also mixed effects on serum follicle stimulating hormone (FSH) and luteinizing hormone (LH) with increases (McGregor and Mason, 1990; Ng et al., 1991), decreases (Gustafson et al., 1989), and with no change (Alexander et al., 1998, 1996; Erfurth et al., 2001) in hormone levels observed. The inconsistency in the direction of effects on TES and the two androgen-regulating pituitary hormones, FSH and LH, is particularly noteworthy, in the absence of evidence for effects of lead exposure on GNRH-induced FSH (Erfurth et al. 2001).

Children exposed to relatively a high level of lead >30 µg/dL may exhibit depressed levels of circulating 1,25-OH-D (Mahaffey et al., 1982; Rosen et al., 1980). However, associations between serum vitamin D status and blood lead may not be present in calcium-replete children who have average lifetime blood lead concentrations below 25 µg/dL (Koo et al., 1991). In adults, exposures to lead that result in blood lead concentrations >40–60 µg/dL may increase, rather than decrease, circulating levels of 1,25-OH-D and PTH (Kristal-Boneh et al., 1999; Mason et al., 1990).

Effects on the Hepatic System

Few studies of hepatic effects of lead on humans have been reported since the 1986 Lead AQCD. Studies of hepatic enzyme levels in serum suggest that liver injury may be present in lead workers; however, associations specifically with lead exposures are not evident (Al-Neamy et al., 2001; Hsiao et al., 2001). Studies of urinary metabolites of cytochrome P450 phenotypes CYP2A6 and CYP3A4 suggest possible associations between lead exposure and suppression of hepatic enzyme activity. The effect on CYP2A6 activity was observed in children with high lead

burdens (i.e., blood lead concentration >40 µg/dL, EDTA-provoked urinary lead >500 µg/dL). The effect on CYP3A4 was observed in association with blood lead ranges of approximately 30-112 µg/dL (based on reported serum lead concentrations).

Effects on the Gastrointestinal System

Several studies of prevalence of symptoms of gastrointestinal colic in lead workers provide evidence for symptoms in association with blood lead concentrations >50–80 µg/dL (Awad el Karim et al., 1986; Holness and Nethercott, 1988; Lee et al., 2000; Matte et al., 1989). Similar types of studies of children have not been reported.

Effect on Bone and Teeth

There is limited, but suggestive evidence of an association between lead exposure and bone toxicity. However, in most studies, it is difficult to assess the direct contribution of lead on bone diseases or reduced growth. Several studies that have explored possible associations between lead exposure and risk of dental caries (Campbell et al., 2000; Dye et al., 2002; Gemmel et al., 2002; Moss et al., 1999). Increased caries risk has been detected in association with increasing blood lead concentrations in populations whose mean blood lead concentrations are approximately 2-3 µg/dL (Dye et al., 2002; Gemmel et al., 2002; Moss et al., 1999).

Ocular Health

Various disturbances of the visual system have been observed in association with overt clinical lead poisoning, including retinal stippling and edema, cataracts, ocular muscle paralysis, and impaired vision (Otto and Fox, 1993). Two longitudinal studies completed since the 1986 Lead AQCD provide evidence for possible associations (a) between lead exposure and visual evoked retinal responses in children of mothers whose blood lead concentrations in mid-pregnancy was 10.5–32.5 µg/dL (Rothenberg et al., 2002) and (b) between lead exposure and risk of cataracts in middle-aged males whose tibia bone lead levels were 31-126 µg/g (Schaumberg et al., 2004).

6.10 INTERPRETIVE ASSESSMENT OF THE EVIDENCE IN EPIDEMIOLOGIC STUDIES OF LEAD HEALTH EFFECTS

6.10.1 Introduction

A remarkable expansion has occurred since the 1990 Lead Supplement in the extent of the database available for drawing inferences about the various expressions of lead toxicity. Moreover, the nature of the evidence available has changed as well. Many of the studies conducted prior to 1990 focused on the issue of whether an observed observation was likely to be real or the result of chance, selection bias, residual confounding, or some other methodological error. The validity of any association still needs to be assured. The studies since 1990 mainly focus on characteristics of the pertinent concentration-response relationships, including the functional forms of the relationships, the slopes of the relationships, the natural histories of adverse effects, and the effect modifying influences of various co-exposures and host characteristics.

6.10.2 Exposure and Outcome Assessment in Lead Epidemiologic Studies

6.10.2.1 Assessment of Lead Exposure and Body Burdens Using Biomarkers

For any health endpoint of interest, the most useful biomarker of exposure is one that provides information about the lead dose at the critical target organ and, moreover, reflects the exposure averaging time that is appropriate to the underlying pathogenetic processes (e.g., cumulative over lifetime, cumulative over a circumscribed age range, concurrent, etc.). In recent studies of lead and health, the exposure biomarkers most frequently used are blood lead and bone lead. For outcomes other than those relating to hematopoeisis and bone health, these biomarkers provide information about lead dose that is some distance from the target organ. For example, given that the central nervous system is considered the critical target organ for childhood lead toxicity, it would be most helpful to be able to measure, in vivo, the concentration of lead at the cellular site(s) of action in the brain. Because such measurements are not currently feasible, however, investigators must rely on measurements of lead in the more readily accessible but peripheral tissues. The relationship between brain lead and lead in each of these surrogate tissues is still poorly understood, although the pharmacokinetics clearly differs among these compartments. In both rodents and nonhuman primates, brain lead level falls much more slowly than blood lead level following chelation with succimer and, in the rodent, in nonchelated

animals after cessation of exposure. These observations suggest that using blood lead as an index of lead in the brain will result in exposure misclassification, although the magnitude of this bias in any specific setting will be difficult to characterize. The most likely direction, however, would be underestimation of the amount of lead in the brain, at least under scenarios involving chronic exposure.

As an exposure biomarker, blood lead level has other limitations. Only about 5% of an individual's total body lead burden resides in blood. Furthermore, blood consists of several sub-compartments. More than 90% of lead in whole blood is bound to red cell proteins such as hemoglobin, with the balance in plasma. From a toxicological perspective, this unbound fraction is likely to be the most important sub-compartment of blood lead because of the ease with which it diffuses into soft tissues. The concentration of lead in plasma is much lower than in whole blood, however. For example, in a group of pregnant women with blood lead levels below 10 μg/dL, plasma lead levels were less than 0.3% of the whole blood lead level. The greater relative abundance of lead in whole blood makes its measurement much easier (and more affordable) than the measurement of lead in plasma. The use of whole blood lead as a surrogate for plasma lead could be justified if the ratio of whole blood lead to plasma lead were well characterized, but this is not so. At least some studies suggest that it varies several-fold among individuals with the same blood lead level. Moreover, the ability of red cells to bind lead is limited, so the ratio of blood lead to plasma lead would be expected to be nonlinear. Thus, interpreting whole blood lead level as a proxy for plasma lead level, which, itself, is a proxy for brain lead level, will result in some exposure misclassification.

Another limitation in the use of blood lead as the exposure biomarker is that its residence time in blood is closely linked to red cell lifetime, with a half-time on the order of 30 days. Thus, a high blood lead level does not necessarily indicate a high body lead burden. Similarly, individuals who have the same blood lead level will not necessarily have similar body burdens or exposure histories. The rate at which blood lead level changes with time/age depends on exposure history due to re-equilibration of lead stored in the various body pools. In nonchelated children, the time for blood lead to decline to a value less than 10 μg/dL was linearly related to baseline blood lead level. A single blood lead measurement might therefore provide limited information about an individual's lead exposure history, a difficulty frequently cited with respect to the interpretation of cross-sectional studies of pediatric lead toxicity, in which children's blood

lead level is often measured only once, and sometimes only well after the period when levels typically peak (18-30 months). If it is exposures to lead in the early postnatal years that are most detrimental to children's development, categorizing a child's exposure status based on the blood lead level that is contemporaneous with the measurement of neurodevelopment at school-age could result in exposure misclassification. Unless intra-individual stability of serial blood lead levels is very high within a study cohort, misclassification would probably be non-differential, more likely resulting in an underestimate rather than an overestimate of the effect of lead on child neurodevelopment (Jurek et al., 2005). This concern must be qualified, however, by recent data from some longitudinal studies indicating that concurrent blood lead level, even at ages well beyond 18 to 30 months, is sometimes the strongest predictor of late outcomes (Dietrich et al., 1993a,b; Canfield et al., 2003a; Tong et al., 1996; Wasserman et al., 2000b). Age-related changes in vulnerability, and the reasons why it might differ across studies, remain uncertain. It might be that among children with chronically elevated exposure, but not in children with relatively low lifetime exposure, blood lead level measured at school-age is a reasonably good marker of cumulative exposure. That concurrent blood lead level is, under some circumstances, a stronger predictor of school-age outcomes than is blood lead level in the early postnatal years does not necessarily imply greater vulnerability of the brain to ongoing than to past exposure.

The development of X-ray-fluorescence (XRF) methods for measuring lead in mineralized tissues offers another approach for characterization and reconstruction of exposure history. Such tissues are long-term lead storage sites, with a half-life measured in decades and contain approximately 90% of the total body lead burden in adults and 70% in children. Thus, bone lead is an index with a long exposure averaging time. XRF methods have proven useful in studying individuals with occupational lead exposure, those living in highly polluted environments, and those for whom community lead exposures are or, in the past, were relatively high (e.g., Korrick et al., 1999; Schwartz et al., 2000a,b,c,d). In a relatively highly exposed cohort of pregnant women in Mexico City, higher bone lead levels at one month postpartum were associated with reduced birth weight, less infant weight gain, smaller head circumference and birth length, and slower infant development (Gomaa et al., 2002; Gonzalez-Cossio et al., 1997; Hernandez-Avila et al., 2002; Sanin et al., 2001). Among children living near a large lead smelter in Yugoslavia, IQ at age 10-12 years was more strongly associated, inversely, with tibia lead level than with blood lead level (Wasserman et al., 2003).

Current XRF methods for measuring bone lead levels have limitations, however. Temporal features of exposure history cannot readily be discerned. Some progress has been made toward this goal by examining the spatial distribution of lead in teeth in relation to the relative abundance of stable lead isotopes, but the specialized technologies needed to carry out these analyses are unlikely ever to be widely available, and the unpredictability of tooth exfoliation makes this tissue difficult to collect unless the study design involves contact with (and the cooperation of) participants at the appropriate ages. Current XRF methods might not be sufficiently sensitive for studies of the health effects of low-dose community exposures. The bone lead levels of a large percentage of subjects might be below the detection limit, e.g., 80% in a case-control study of bone lead levels and juvenile delinquency in which the minimum detection limit was 21.5 μg/g bone mineral (Needleman et al., 2002). Even among individuals known to have histories of substantial lead exposures, such as adolescents and young adults who grew up near the Bunker Hill smelter in Idaho (McNeill et al., 2000), bone lead levels tend to be low. Lead appears to be deposited at sites of most active calcification. In children, this is trabecular bone, in which the rate of fractional resorption in early childhood is high. Depending on the amount of the child's ongoing exposure, lead deposited in bone might not remain there for decades, making bone lead level an imprecise index of lifetime lead exposure. This concern also exists in the use of tooth lead to represent cumulative lead exposure in children. Rabinowitz et al. (1993) observed that a child's tooth lead level was more strongly related to blood lead level around the time of tooth exfoliation than to an integrated index of blood lead level prior to exfoliation. Finally, it is difficult to compare the performance of different laboratories using XRF methods to measure bone lead because of the absence of standard reference materials. Nevertheless, efforts continue to modify the instrumentation or measurement protocols to reduce the detection limit.

A major research need is the development and validation of biomarkers of critical dose that, compared to blood lead or bone lead, are fewer toxicokinetic steps removed from the sites of lead's actions in the brain. One promising front in the effort to deduce the contents of the "black box" separating external dose and clinical disease is the measurement of processes and products that potentially mediate the association between them. For example, magnetic resonance spectroscopy (MRS) has been used in small case series to measure the ratio of N-acetylaspartate (NAA) to creatine, which are a marker of neuronal and axonal damage and

thus, an early biological effect rather than a biomarker of exposure. In children, higher lead exposures are associated with lower NAA to creatine ratios in the frontal gray matter and, to a lesser extent, in frontal white matter (Trope et al., 1998, 2001). Similarly, an adult who had higher bone and blood lead levels than did his monozygotic twin had both greater neuropsychological deficits and lower NAA to creatine ratios in the hippocampus, frontal lobe, and midbrain (Weisskopf et al., 2004). While much remains uncertain about the interpretation of MRS, the use of this and other biochemical imaging methods, in combination with more conventional structural and functional imaging methods, might bring us closer to understanding the mechanisms of lead neurotoxicity. With the number of toxicokinetic steps separating lead levels at the critical target organs from the usual exposure biomarkers, the progress made in characterizing the concentration-response relationships is remarkable.

6.10.2.2 Assessment of Health Outcomes

Outcome measurement and outcome classification have generally received less attention from investigators than have exposure measurement and misclassification. The specific problems are, to some extent, endpoint domain-specific. With regard to neurodevelopmental toxicities, critical issues are whether the assessment instruments used are psychometrically sound and appropriate for the study cohort, the data generated will support adequate tests of the study hypotheses, and whether the instruments have been administered and scored consistently and correctly. With regard to the cardiovascular toxicities of increased blood pressure/prevalence of hypertension, the critical issue is whether the blood pressure value recorded for a participant is an accurate estimate. Multiple measurements of blood pressure are frequently made in a study but investigators usually have not taken advantage of the collected information to quantify the amount of error in the measurements. This information can be used to improve the reliability of the measurements, which would be expected to improve the precision of the associations estimated. Similarly, aggregating scores to estimate latent variables representing, for instance, "language skills" or "visual-spatial skills" is an approach that might take advantage of the overlapping information provided by the multiple tests included in neurobehavioral test batteries, producing more reliable endpoint variables. This approach, however, has not been widely applied in lead studies.

6.10.3 Concentration-Response Relationship of Lead Health Effects

Recent studies have not altered the consensus that the developing nervous system is the organ system that is most sensitive to lead toxicity in children and adults. Neurobehavioral deficits appear to occur at lower levels of exposure than do other adverse health effects, although adverse effects in other organ systems have been observed in some susceptible populations at similarly low levels (e.g., adverse renal outcomes in individuals with hypertension or chronic renal insufficiency). Effects have been reported at blood lead levels as low as 1 to 2 µg/dL in the case of neurobehavioral toxicity. Accumulating data appear to validate well the statement made in the 1996 AQCD and Addendum, and 1990 Supplement that adverse effects occur at blood lead levels of 10 to 15 µg/dL or "possibly lower." In a recent study of 6 to 16 year old children in the NHANES III survey, concentration-related deficits in reading and arithmetic scores were found even when analyses were restricted to children with concurrent blood lead levels below 5 µg/dL (Lanphear et al., 2000).

Canfield et al. (2003a) applied semi-parametric models with penalized splines to their data, essentially allowing the data to reveal the functional form that best described them. These analyses showed that the IQ decline per µg/dL increase in blood lead was greater below 10 µg/dL than it was above 10 µg/dL. The estimated slope of the IQ decline per µg/dL was greatest among children for whom the maximum blood lead level measured over the course of the study never exceeded 10 µg/dL. A similarly steeper slope at lower than at higher blood lead levels was found in a re-analysis of the Boston prospective study (Bellinger and Needleman, 2003).

Identifying the functional form that best fits a particular set of data and that presumably serves as the best description of the pertinent underlying concentration-response relationship is clearly important. The linear model (Figure 6-10.1) is, as the name implies, linear over the entire range of the exposure data. For certain tests, the assumption is made that the residuals (observed – predicted response) are normally distributed with constant variance, but violations of this assumption (heteroscedasticity) have no real effect on the estimation and minimal effect on the tests of significance (see Annex Section AX6.10). If heteroscedasticity is present but all other conditions are met, regression still yields unbiased estimators, but the standard errors can be larger than when remedial efforts such as using weighted regression are employed. The use of regression requires no assumption concerning the distribution of the independent variable

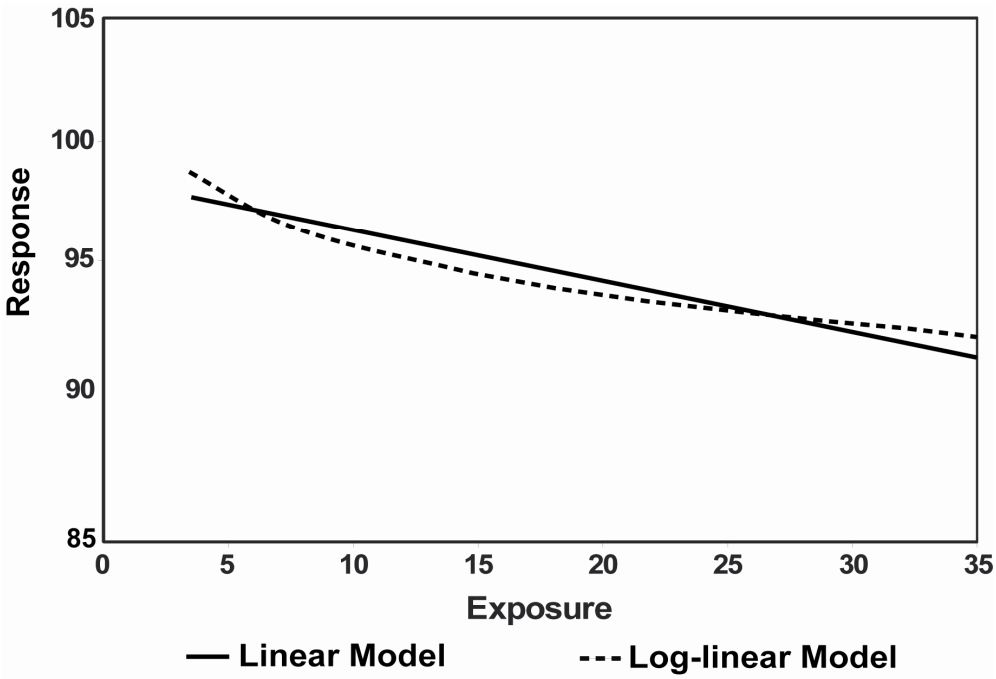


Figure 6-10.1. Comparison of a linear and log-linear model to describe the relationship between exposure and response.

(lead exposure marker). However, when the form of the heteroscedasticity is an increase in variance with level of blood lead and when the data are lognormally distributed or otherwise skewed, there are possibly a large number of influential data points at high blood lead where the data is least reliable. In this case, a log transformation of blood leads may result in more precise estimation of the slope parameter. The presence of heteroscedasticity and other departures from assumptions forming the basis for regression analysis can be detected by using diagnostic tests or graphics. These are rarely used in epidemiologic studies of lead health effects.

The log-linear model (see Figure 6-10.1) is written as:

$$\text{Response} = \alpha + \beta \, \text{Ln}(\text{lead exposure marker}),$$

where Ln is the natural logarithmic function. The log-linear model is concave upwards (assuming that the estimated coefficient is negative). It approaches a linear function for very high exposure values, but approaches infinity at very low exposure values. In other words, it is assumed that the adverse effect of lead is greater at lower than at higher blood lead levels.

Blood lead levels have been shown repeatedly to follow a lognormal distribution (Azar et al., 1975; Billick et al., 1979; Hasselblad and Nelson, 1975; Yankel et al., 1977; Hasselblad et al., 1980; U.S. Environmental Protection Agency, 1986), but this fact is not an argument for choosing the log-linear model. The choice of either log-linear or linear may be based on the Akaike's Information Criteria (Akaike, 1973), J-test (Davidson and MacKinnon, 1981), or other statistical tests if the choice is to be based on the best fitting model. Rothenberg and Rothenberg (2005) compared the linear lead model with the log-linear lead model for the pooled data from Lanphear et al. (2005) using the J-test. The J-test showed that the log lead specification was still significant ($p = 0.009$) in a model that also included the linear lead specification, indicating that the log lead specification described the data significantly better than did the linear lead specification. Other models have been used, such as nonparametric models, spline functions, and polynomial models, but the vast majority of the analyses have used either a linear model or a log-linear model.

Nonlinear concentration-response relationships are not uncommon in toxicology, although many of these are claimed to be examples of hormesis, with the lowest doses of a toxicant being associated with a beneficial effect rather than a greater adverse effect. A biological mechanism for a steeper slope at lower than at higher blood lead levels has not been identified. Perhaps the predominant mechanism at very low blood lead levels is rapidly saturated, and that a different, less rapidly saturated process becomes predominant at blood lead levels greater than 10 μg/dL. This ad hoc explanation is more descriptive than explanatory, however, and the specific processes that would produce this result have not yet been identified. Nevertheless, relationships of this apparent form have been observed in several data sets, indicating the need to determine whether such a relationship is real or a statistical artifact.

An important caveat regarding efforts to specify the functional form of the concentration-response relationship is that the accuracy that can be achieved is constrained by the extent to which the biomarker of lead concentration does, in fact, reflect the concentration at the critical target organ, the brain. The greater the misclassification, the more uncertain will be the biological relevance of the best statistical description of the concentration-response relationship.

6.10.4 Interindividual Variability in Susceptibility to Lead Toxicity

Although increased lead exposure has been linked to adverse health effects in many different organ systems, scatterplots reveal tremendous variability of observed points about the best fit lines representing the concentration-response relationships. In other words, individuals for whom the lead biomarker measured has the same value can have markedly different values on the health indicator measured. Even for neurobehavioral deficits in children, the correlation between biomarker level and test score rarely exceeds −0.2, indicating that the explained variance in the test score generally does not exceed 5%. A major challenge is therefore to decompose this variability, to distinguish components of it that reflect error from components that reflect biological processes that determine an individual's response to lead.

Deviation of the observed points from the fitted point can have many sources. Exposure misclassification is one source. The lead biomarker measured might not adequately capture the lead dose delivered to the target organ and at the time that is most appropriate biologically. In general, the error would be expected to be non-differential, i.e., it would not introduce a systematic bias in estimation of the concentration-response relationship. On average, such misclassification would be expected to result both in an attenuation of the slope of the concentration-response relationship and an increase in the scatter of the observations. As focus shifts to the risks associated with lower and lower levels of lead exposure, the importance of errors introduced by poor dosimetry will assume greater importance insofar as the effects at such levels will presumably be more subtle and increasingly difficult to detect amid the noise contributed by exposure misclassification. Outcome misclassification is another source of error that is likely to contribute to apparent interindividual variability in response. This results if the indicator of the critical health effect that is measured is fallible, i.e., an imperfect measure of the target function. Such misclassification would generally be expected to be non-differential, introducing random noise rather than a systematic bias.

Another likely source of scatter in observed points is true interindividual variability in response to a given lead dose. That is, the magnitude of individual response to lead might depend on other characteristics of that individual. Three major categories of such effect modifying factors that might influence susceptibility to lead toxicity are genetic polymorphisms, nutritional status, and social environmental factors. Adequate data are not available to provide a quantitative estimate of the amount of interindividual variability in susceptibility to lead.

6.10.4.1 Influence of Genetic Polymorphisms on Risk

Genetic polymorphisms that are presumed to influence lead toxicokinetics and/or toxicodynamics have been identified, mostly in studies of adults who were occupationally exposed to lead. Compared to workers with the wild type allele of amino levulinic acid dehydratase, workers with the variant allele had a higher mean blood lead level, greater lead-associated renal dysfunction, and an increased risk of amyotrophic lateral sclerosis (Kamel et al., 2003). Lead workers with the ATP1A2(3′) polymorphism appear to be at increased risk of lead-associated effects on blood pressure (Glenn et al., 2001). The slope of the association between floor dust lead and blood lead is steeper among children with the less common variant of the vitamin D receptor (Fox 1 or B) than among children with the wild-type allele (Haynes et al., 2003). In adults, these same alleles are associated with higher blood lead levels and increased blood pressure (Schwartz et al., 2000c; Lee et al., 2001). Greater lead-associated reductions in renal function have been observed in adults with a variant allele of nitric acid synthetase, although cardiovascular outcomes, such as blood pressure and hypertension do not appear to depend on eNOS (endogenous nitric oxide synthase) allele (Weaver et al., 2003). Adults with variants of the hemochromatosis gene (C282Y and/or H63D) have higher patella lead levels (Wright et al., 2004). Only one polymorphism has been shown to modify lead neurotoxicity. Lead workers with the apolipoprotein E4 allele showed greater lead-associated decreases in neurobehavioral function than did workers with the E1, E2, or E3 alleles (Stewart et al., 2002). This work is in its early stages, and while it promises to shed light on bases of susceptibility to lead toxicity, firm conclusions cannot yet be drawn.

6.10.4.2 Influence of Nutritional Status on Risk

Only limited epidemiologic data are available on the role of nutritional status in modifying an individual's risk of lead toxicity. Adjusting for severity of environmental lead contamination, iron-deficient children appear to have higher blood lead levels than iron-replete children (Bradman et al., 2001). One interpretation of these data is that children experiencing the same external lead dose can experience different internal doses. In another study of iron status, a decline in blood lead level was associated with improved cognitive performance in iron-sufficient but not in iron-deficient children (Ruff et al., 1996). Among the possible explanations for this finding is that iron deficiency contributes to pharmacodynamic variability, increasing the

toxicity of a given lead dose. Some evidence suggests that the intellectual deficit associated with an elevated blood lead level is greater among undernourished children than well-nourished children (Gardner et al., 1998).

Several studies have suggested that dietary calcium may have a protective role by decreasing absorption of lead in the gastrointestinal tract and decreasing the mobilization of lead from bone stores to blood, especially during periods of high metabolic activity of the bone such as pregnancy and lactation. Lower calcium intake during pregnancy, especially the second half, appears to increase the mobilization of lead from bone compartments (Hernandez-Avila et al., 1996). However, in other studies, calcium supplementation had no effect on bone lead levels pregnant and lactating women (Rothenberg et al., 2000; Téllez-Rojo et al., 2002).

6.10.4.3 Influence of Health Status on Risk

The influence of an individual's health status on susceptibility to lead toxicity has been demonstrated most clearly for renal outcomes. Individuals with diabetes, hypertension, and chronic renal insufficiency are at increased risk of lead-associated declines in renal function and adverse effects have been demonstrated at blood lead levels below 5 µg/dL (Lin et al., 2001, 2003; Muntner et al., 2003; Tsaih et al., 2004). As discussed in an earlier section, children with nutritional deficiencies also appear to be more vulnerable to lead-associated neurobehavioral deficits.

6.10.4.4 Influence of Co-Exposures on Risk

Epidemiologic studies do not provide an adequate basis for determining whether cigarette smoking and/or alcohol affect the nature or severity of the health effects associated with lead exposure. Both factors have often been included in models of both child and adult health outcomes in order to adjust for potential confounding. In addition, both have been evaluated as pertinent pathways of adult exposure. However, their possible roles as effect modifiers have not been well studied.

Although most individuals are not exposed to lead in isolation but to lead in combination with other toxicants including cadmium, arsenic, mercury, and polychlorinated biphenyls, epidemiologic studies generally have focused solely on lead. Other toxicant exposures have sometimes been measured but are usually treated as potential confounders in the statistical

analyses, with their status as potential modifiers of lead toxicity left unexplored (Bellinger, 2000). As a result, epidemiologic studies do not provide an adequate basis for determining whether co-exposure to other toxicants affects the nature or severity of the health effects associated with lead exposure.

6.10.4.5 Influence of Timing of Exposure on Risk

6.10.4.5.1 Children

Studies do not provide a definitive answer to the question of whether lead-associated neurodevelopmental deficits are the result of exposure during a circumscribed critical period or of cumulative exposure. Although support can be cited for the conclusion that it is exposure within the first few postnatal years that is most important in determining long-term outcomes (Bellinger et al., 1992), other studies suggest that concurrent blood lead level is as predictive, and perhaps more predictive, of long-term outcomes than are early blood lead levels (Canfield et al., 2003a; Dietrich et al., 1993a,b; Tong et al., 1996; Wasserman et al., 2000b). Because of the complex kinetics of lead, an accumulative toxicant, it is extremely difficult to draw strong conclusions from these observational studies about windows of heightened vulnerability in children. The high degree of intraindividual "tracking" of blood lead levels over time, especially among children in environments providing substantial, chronic exposure opportunities (e.g., residence near a smelter or in older urban dwellings in poor repair), poses formidable obstacles to identifying the time interval during which exposure to lead caused the health effects measured in a study. It could be that damage occurred during a circumscribed period when the critical substrate was undergoing rapid development, but that the high correlation between serial blood lead levels impeded identification of the special significance of exposure at that time. Under such circumstances, an index of cumulative blood lead level or concurrent blood lead level, which might be a good marker of overall body burden under conditions of relatively steady-state exposure, might bear the strongest association with the adverse effect.

6.10.4.5.2 Aging Population

Increases in blood lead for postmenopausal women have been attributed to release of lead from the skeleton associated with increased bone remodeling during menopause in both occupationally- and environmentally-exposed women (Garrido-Latorre et al., 2003; Popovic et al., 2005). In middle-aged to elderly males from the Normative Aging Study, patella lead

accounted for the dominant portion of variance in blood lead (Hu et al., 1996). These findings provide evidence that the skeleton may serve as a potential endogenous source of lead in the aging population.

Considerable evidence also suggests that indicators of cumulative or long-term lead exposure are associated with adverse effects in several organ systems, including the central nervous, renal, and cardiovascular systems. Among occupationally-exposed men, higher tibia lead levels have been associated with increased cognitive decline over repeated assessments (Schwartz et al., 2005). With regard to the renal system, increased lead exposure may accelerate the effects of normal aging, producing a steeper age-related decline in function. Weaver et al. (2003) observed that higher lead exposure and dose were associated with worse renal function in older workers, but with lower blood urea nitrogen and serum creatinine in young workers.

6.10.4.5.3 Pregnancy

Potential mobilization of lead from the skeleton also occurs during pregnancy and lactation due to increased bone remodeling (Hertz-Picciotto et al., 2000; Manton, 1985; Silbergeld, 1991). In women who have been exposed to lead in childhood and have accumulated large stores in their bones, there may be significant mobilization of lead from bone to blood during late pregnancy and lactation. The greatest probability of lead toxicity for the mothers will be in postpartum while they are lactating; the infants will be particularly vulnerable during the prenatal period, especially in the last weeks of pregnancy (Manton et al., 2003).

A variety of adverse reproductive outcomes have been associated with higher paternal or maternal lead exposures, including reduced fertility, spontaneous abortion, gestational hypertension, congenital malformations, fetal growth deficits, and neurobehavioral deficits in offspring. The levels of exposure at which different adverse outcomes occur vary. Increased risks of spontaneous abortion, neurobehavioral deficits in offspring and, in some studies, gestational hypertension, have been reported at pregnancy blood lead levels below 10 μg/dL (Bellinger, 2005).

6.10.5 Reversibility of Lead Health Effects

6.10.5.1 Natural History of Effects

The absence of a clear operational definition of "reversibility" is a major impediment to drawing inferences about the natural history of any adverse effect associated with an accumulative neurotoxicant such as lead. Rather than indicating irreversibility, a performance deficit that remains detectable after external exposure has ended could reflect ongoing toxicity due to lead remaining at the critical target organ or lead deposited at the organ post-exposure as the result of redistribution of lead among body pools. As noted earlier, brain lead levels can remain elevated long after blood lead levels fall. A rigorous test of reversibility would require that every lead atom has been cleared from the body. This being unattainable, investigators must exploit opportunities that permit only weaker tests of hypotheses about reversibility. These include assessing the persistence of deficits previously associated with lead biomarkers and evaluating performance changes associated with natural experiments, i.e., events such as chelation or a change in external exposure that would be expected to perturb the equilibrium of lead among different body pools.

The likelihood of reversibility, as defined above, appears to be related, at least for the adverse effects observed in certain organ systems, to both the age-at-exposure and the age-at-assessment. In occupationally-exposed adults, the central and peripheral nervous system correlates of higher lead burdens appear to attenuate if exposure is reduced.

The prospective studies of childhood lead exposure, involving serial measurements of lead biomarkers and health outcomes, provide the best opportunities available to assess the natural history of adversities associated with low-level lead exposures. In some prospective studies, associations observed in infancy between biomarkers of prenatal exposure and neurodevelopment attenuated by the time children reached preschool age. It can be difficult to determine, however, whether this reflects actual disappearance of the effect or an increased difficulty in detecting it due to the emergence of associations between neurodevelopment and lead biomarkers measured postnatally. It is notable, however, that in some prospective studies of children, associations between biomarkers of prenatal lead exposure and various outcomes in middle adolescence have been reported, suggesting that the persistence of the associations might be endpoint-specific**.** For example, among children in Kosovo, Yugoslavia, IQ scores at the age of 8 years were inversely associated with a composite index of prenatal lead exposure (average

of mothers' blood lead levels at midpregnancy and at delivery) (Wasserman et al., 2000). This association was independent of changes in postnatal blood lead levels. Among 15 to 17 year old inner-city children in Cincinnati, OH, maternal blood lead levels in the 1st trimester (ranging from 1 to ~30 μg/dL) were inversely related to attention and visuoconstruction (Ris et al., 2004) and positively related to the frequency of self-reported delinquent behaviors (Dietrich et al., 2001).

The results of the prospective studies are more consistent in showing that higher postnatal lead biomarkers are associated with neurocognitive deficits that persist, in some studies, into early adulthood when the concurrent lead exposures are generally much lower. Ongoing external exposure does not appear to be necessary to maintain the deficits, although, as noted previously, it is not possible to exclude entirely a role for ongoing endogenous exposures of the target organs resulting from the redistribution, over time, of lead stores among different compartments. These data are consistent with those from experimental nonhuman primate studies, in which the temporal characteristics of exposure are manipulated as opposed to merely observed as in the human studies.

In most epidemiologic studies, the potential for true longitudinal analysis of the data has not been fully exploited, with the data evaluated in what is effectively a series of cross-sectional analyses.

6.10.5.2 Medical Interventions

Data from the Treatment of Lead Poisoned Children (TLC) study, a randomized controlled trial of the late outcomes of children treated for lead poisoning, support the hypothesis that the deficits associated with exposures of such magnitude are persistent and, possibly, permanent (Dietrich et al., 2004; Rogan et al., 2001). At 36-months post-treatment and at age 7 years, no significant differences in cognition or behavior were noted between the succimer and placebo groups. Current blood lead levels were significantly associated with cognitive performance at baseline, 36-months post-treatment, and at 7 years of age, and the regression coefficients were similar in magnitude to those estimated in observational studies (i.e., ~3 point IQ decline per 10 μg/dL increase in blood lead), providing a linkage between the results of the observational studies and those of this experimental study. However, within-child analyses

indicated that changes in developmental test scores over time were not consistently associated with changes over time in blood lead level.

6.10.6 Confounding of Lead Health Effects

6.10.6.1 Adjustment for Confounding in Epidemiologic Studies of Lead

The possibility that the adverse health effects associated with increased lead exposure in epidemiologic studies are, in fact, due to risk factors with which increased lead exposure is associated remains the most important impediment to drawing causal inferences. Various approaches have been taken to reduce the uncertainty this creates. Some investigators have specified the sampling frame or the eligibility criteria so as to increase the homogeneity of the study participants on factors known to be strong risk factors for the outcome of interest, thereby reducing the correlation between them and lead, and their potential to confound any association observed between increased lead exposure and poor outcome. Reducing confounding by means of design decisions has the disadvantage that an investigator cannot determine whether the impact of lead on the outcome varies depending on the factor whose range of potential values has been restricted. More frequently, however, investigators have relied on statistical procedures, applied post data collection, to identify and control for potential confounding. Unlike sample restriction, this approach preserves the opportunity to explore possible modification of the lead effect by cofactors.

Adjustment for confounding has been performed primarily using multiple regression analyses and data stratification. For multiple regression modeling, stepwise regression has been frequently used for covariate selection. Stepwise regression has many faults and is often less acceptable then the use of a few well-chosen covariates. However, the stepwise regression methodology may be considered less bias as it selects from a class of variables that represent a wide scientific viewpoint rather than the narrower one of the investigator. One problem with stepwise regression pointed out by Bellinger (2004) is that the usual adjustment strategy assumes that all the variance in the response shared by the exposure and the confounder belongs to the confounder. In some settings, this is likely to be excessively conservative, because confounders can, to some extent, also be proxies for exposure. This is further discussed in the next section.

Splitting the data set into smaller data sets (partitioning or stratification) and analyzing those data sets separately was used in some of the studies examining the relationship between

blood pressure and lead. This practice also has some advantages and disadvantages. An advanced statistical method could be used to determine how the partitioning should be done (Young and Hawkins, 1998), which could reveal relationships that would not be possible to detect using the usual regression techniques. A disadvantage of partitioning a small data set is that the smaller sample size may lack the power to detect otherwise detectable associations and to yield reliable estimates.

The segmented line model consists of joined straight line segments where the joined points are chosen to best fit the data (Quandt, 1958). The log-linear and the quadratic models have shown in several cases to better fit the biomarker-response relationship than the linear model. However, these models are not considered practicable for extrapolation outside the range of the biomarker variable. The segmented line model is suggested as a more reasonable model for extrapolation into the low-concentration sparse-data region.

6.10.6.2 Confounding Adjustment on Lead Health Effect Estimates

The ability of the investigator to determine how much of the apparent association between a lead biomarker and an outcome reflects residual confounding by a cofactor depends on the characteristics of the joint distribution of lead and the cofactor. Co-factors for lead health effects include maternal IQ, maternal smoking, alcohol use, birth weight, and many others depending on the health outcome of interest. Some of these cofactors are truly independent predictors and can be adjusted for using multiple regression analyses. Under some circumstances, however, lead and the cofactor may be so highly related that one cannot be confident that their associations with the outcome have been disentangled by the statistical methods applied. Moreover, the true causal relationships among lead, the cofactors, and the outcome might not be sufficiently well understood that the outcome variance shared by lead and the cofactors can be characterized appropriately in the analyses.

In studies of lead and neurodevelopment, the magnitude of the lead coefficient, reflecting the decline in test score per unit increase in the lead biomarker, is substantially reduced, often by half or more, by adjusting for markers of the social environment. During the 1980s, adjustment for parental IQ and quality of the home environment (e.g., HOME scores) became almost mandatory if the findings of a study of lead and children's cognitive outcomes were to be considered credible. While both factors surely strongly influence child outcomes in ways that

are independent of lead, a case can also be made that lead might contribute to the associations. A parent's IQ presumably reflects the parent's early lead exposure and, assuming that the physical environments in which a parent and child grow up are not completely unrelated to one another, provide similar lead exposure opportunities. Adjusting for parent IQ in evaluating the association between a child's lead exposure and his or her IQ, therefore, will result in an underestimate of the contribution of the child's lead exposure to his or her IQ. Similarly, if early lead exposure alters child behavior, the transactional model of child development would generate the prediction that the changes will elicit different behaviors from parents, altering the characteristics of the child rearing environment. For instance, increased lead exposure might result in an infant being more irritable, less soothable, and the parent less nurturing. In so far as measurement of the quality of the rearing environment in studies occurs after the children have experienced some lead exposure, the hypothesis that lead is responsible for shaping some aspects of that environment cannot be entirely dismissed, and control for HOME scores might be excessively conservative. For example, in the pooled analysis by Lanphear et al. (2005) that included seven prospective studies, the crude coefficient for concurrent lead and childhood IQ score was −4.66 (95% CI: −5.72, −3.60), but the coefficient adjusted for study site, HOME score, birth weight, maternal IQ, and maternal education was −2.70 (95% CI: −3.74, −1.66).

Other aspects of model building in assessing the association of lead with health outcomes also warrant comment. In many studies of lead and cognitive outcomes in children, investigators have adjusted for factors such as birth weight or length of gestation that might, themselves, reflect adverse effects of lead, i.e., mediating factors that lie between lead and condition on the causal pathway. The coefficient estimated for lead in a model that contained such factors would be smaller in magnitude than it would be if terms for such mediating factors had not been included.

Recognizing imperfections in the ability to measure such factors well, a concern is expressed that the lead coefficient could be reduced further, perhaps all the way to the null, if better, more comprehensive methods of measurement were applied. On the other hand, the methods used to adjust for such factors may be excessively conservative insofar as they attribute to a factor all of the outcome variance that it shares with lead, despite the likelihood that the true relationships among lead, social factors, and outcome are unlikely to be as simple as this model assumes. Some factors might, in part, be markers of lead exposure opportunities. For example,

both lead biomarker levels and lower cognitive function in children are associated with lower social class standing. Social class is a complex construct that conveys information about a multitude of factors that might influence children's health, including the amount of lead in environmental media. Thus, some of the association between lower social class and poorer health might reflect the effect of higher lead exposure. If so, routine adjustment of health outcome for social class in assessing the association between increased lead exposure and poorer health in children will fail to distinguish these lead-related and non-lead-related components of the association between social class and health, and, in fact, will assume that all of it is non-lead-associated. It is nearly impossible to actually determine if the problem of overadjustment exists in a particular data set. There are several statistical methods which attempt to address this problem. These include using partial F tests, ridge regression, path analysis, and structural equations. None of these methods are completely satisfactory.

6.10.7 Inferences of Causality

Even with more sophisticated and nuanced models, however, any conclusions about the causal forces generating the results of any observational epidemiologic study are necessarily uncertain. In the absence of random assignment to exposure group, residual confounding will always be a possible explanation of an observed association. As in other areas of epidemiology, a weight-of-evidence approach remains the best option available as a basis for drawing of causal inferences. If the association between a lead biomarker and a health outcome of interest is observed in settings that vary widely in terms of the characteristics of the social environment including sociodemographic and cultural characteristics, characteristics of the study participants, including nutritional status, genetic factors, and lifestyle factors, the likelihood that the association is attributable, in its entirety, to residual confounding is reduced. For instance, the pooled analyses of data contributed by many of the international prospective studies provide a compelling demonstration that the association between blood lead level and child IQ is remarkably robust across disparate socio-cultural settings (Lanphear et al., 2005). Even such consistency in the effect estimate across diverse settings is only indirect and weak evidence of causality, however. In general, epidemiologic studies rarely provide data that enhance our understanding of the “black box” between biomarkers of lead burden and indicators of health status. Epidemiologic data identify associations between exposure biomarkers and health

indicators, but are not highly informative regarding possible mechanisms of lead toxicity that underlie the associations. A critical stage in applying the overall weight-of-evidence approach is the examination of the epidemiologic data in the context of data from experimental animal behavioral and mechanistic studies. Although such data have their own limitations, they are not subject to many of the most important potential biases that can becloud the interpretation of the epidemiologic data.

6.10.8 Effects on the Individual Versus Effects on the Population

The critical distinction between population and individual risk, an issue pertinent to many questions in chronic disease epidemiology, has frequently been blurred in discussions of the public health implications of lead-associated decrements in health. With respect to neurodevelopment, while it may be true that a two- or three-point decline in IQ may not be consequential for an individual, the same level of decline observed in a population mean is of great importance. Similarly, although an increase of a few mm Hg in blood pressure may generally not be of concern for an individual's well-being, a very modest increase in the population mean is associated with substantial increases in the percentages of individuals with values that are sufficiently extreme that they exceed the criteria used to diagnose illness (Rose and Day, 1990). In other words, the mean value conveys substantial information about the percentage of individuals with clinically relevant, extreme values of the indicator. Moreover, interventions that shift the population mean by an amount that is without clinical consequence for an individual have been shown to produce substantial changes in the percentage of individuals with indicator values that are clinically significant (Bellinger, 2004). The following subsections will discuss quantitatively lead-related effects of a population level change in IQ and blood pressure.

6.10.8.1 Effects of Lead on Intelligence

The outcome most often examined to investigate neurotoxic effects of lead is IQ. Although the definition of "intelligence" is quite abstract, IQ remains a useful outcome measure as it is correlated with important measures of life success, such as academic achievement, earnings, and social status (Bellinger, 2003; Weiss, 2000). Several studies reported quantitative relationships between full scale IQ and current blood lead levels for children aged 5 to 11 years

old, and these are summarized in Table 6-10.1. The estimated relationships as reported by the authors are used.

Table 6-10.1. Summary of Studies with Quantitative Relationships for IQ and Blood Lead

Reference	Study Location	n	Estimated Slope (IQ points/µg/dL) – Blood Lead 10th to 90th Percentile	Estimated Slope (IQ points/µg/dL) – Blood Lead Under 10 µg/dL
Bellinger et al. (1992)	Boston, Massachusetts	116	−0.5	NA
Canfield et al. (2003a)	Rochester, New York	182	−0.7	−0.8
Dietrich et al. (1993a)	Cincinnati, Ohio	221	−0.3	−0.3
Ernhart et al. (1989)	Cleveland, Ohio	160	−0.1	NA
Wasserman et al. (1997)	Kosovo, Yugoslavia	231	−0.2	NA
Baghurst et al. (1992)	Port Pirie, South Australia	324	−0.2	−0.4
Silva et al. (1988)	Dunedin, New Zealand	579	−0.3	−0.3
Lanphear et al. (2005)	International Pooled Analysis	1,333	−0.5	−0.2

The curves over a range of blood lead levels from the 10th percentile to the 90th percentile are shown in Figure 6-10.2. The curves are restricted to that range because log-linear curves become very steep at the lower end of the blood lead levels, and this may be an artifact of the model chosen. The percentiles are estimated using various methods and are only approximate values. Studies which estimated a linear relationship are shown as reported, and similarly for the log-linear relationships. Note that these are not forest plots of slopes or hazard ratios – they are the actual estimated relationships.

The analysis by Lanphear et al. included the studies of Baghurst et al. (1992), Bellinger et al. (1992), Canfield et al. (2003a), Dietrich et al. (1993a), Ernhart et al. (1989) and Wasserman et al. (1997). The pooled analysis also included the Mexico City study of Schnaas et al. (2000). The results from Schnaas et al. are not included in Table 6-10.1 or Figure 6-10.2 because the

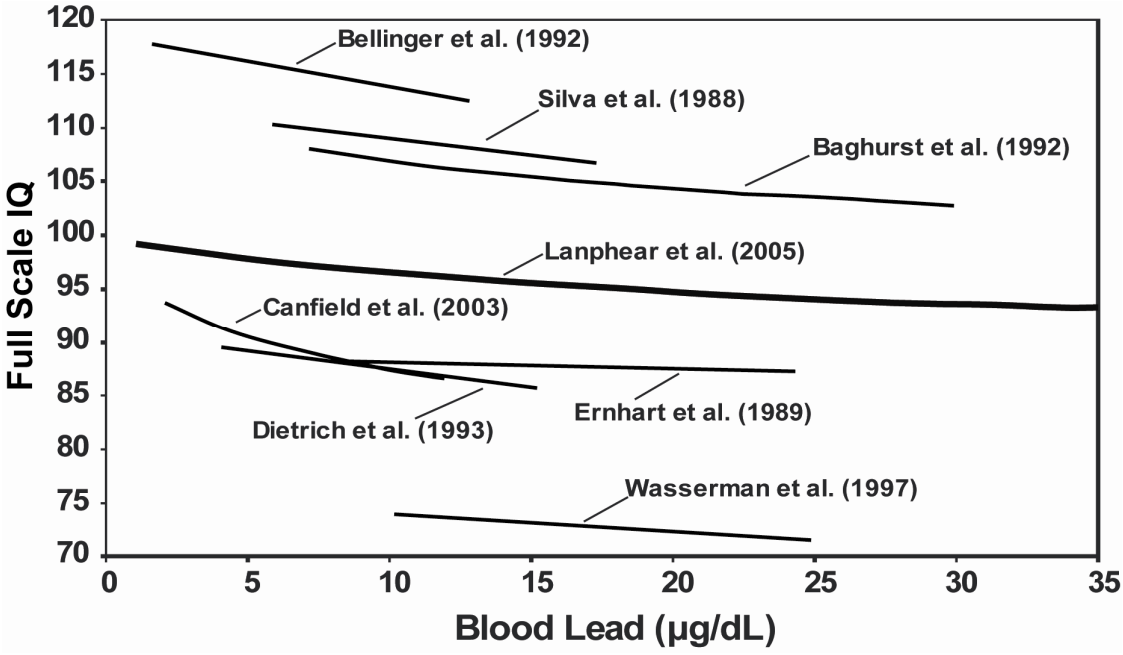


Figure 6-10.2. Concentration-response relationships of IQ to blood lead for the individual studies and the pooled analysis by Lanphear et al. (2005).

authors did not provide regression coefficients in their paper, thus concentration-response relationship were not estimable. The study by Silva et al. (1988) is not included in the pooled analysis of Lanphear et al., but is included in this section as its results are comparable and informative.

Several conclusions can be drawn from these graphs. First, note that the overall IQ levels are quite different. This results from different populations and from different applications of the IQ tests. Second, all studies showed a decreasing IQ score as the blood lead level increased. It is the slope of the studies that is relevant, not the actual IQ scores. Third, for studies with lower blood lead levels, the slopes appear to be steeper. This is the reason that many authors choose to use the log-linear model. However, for those studies where the blood leads were generally high, the log-linear and linear models are almost identical. Thus it is not surprising that some authors chose a linear model instead of a log-linear model. The curves in Figure 6-10.2 do not show evidence of a no-effect threshold because the slopes increase as the blood lead levels become smaller. The observed mean adjusted IQ levels (for blood lead <5, 5 to 10,

10 to 15, 15 to 20, and >20 µg/dL) reported by Lanphear et al. (2005) also show no evidence of a threshold, as seen in Figure 6-10.3.

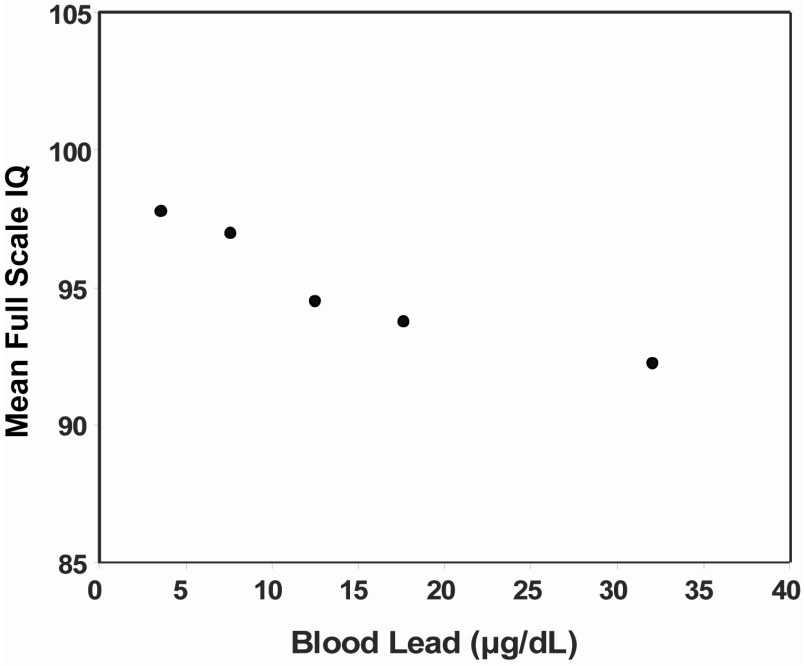


Figure 6-10.3. Mean blood lead levels adjusted for HOME Score, maternal education, maternal IQ, and birth weight from the pooled analysis of seven studies by Lanphear et al. (2005). Mean adjusted IQ levels at blood lead levels of <5, 5 to 10, 10 to 15, 15 to 20, and >20 µg/dL are shown.

Weiss (1990) predicted, on purely statistical grounds, that a downward shift of five points in mean IQ, if the amount of dispersion in the distribution remained the same, should be accompanied by a doubling of the numbers of individuals with scores two or more standard deviations below the mean and a reduction by half of the number of individuals with scores two or more standard deviations above the mean. With respect to lead, the general accuracy of this prediction has been empirically demonstrated in two different datasets by Needleman et al. (1982) and Bellinger (2004). The example below provides further evidence of the change in percentages of individuals with IQ <70 or <50 points after restricting the analysis to those with blood lead levels less than 10 µg/dL.

The average slope was estimated for those studies with a significant portion of the subjects with blood lead levels less than 10 µg/dL. These average slopes are given in Table 6-10.1. In addition, the results of Lanphear et al. (2005) were considered. The average slope at blood lead levels less than 10 µg/dL from that pooled analysis was −0.5 IQ points per µg/dL. Based on the individual studies and the pooled analysis it appears that the average slope is between −0.3 and −0.5 points per µg/dL, with the exception of the large negative slope of −0.8 points per 10 µg/dL from the study by Canfield et al. (2003a). The value of −0.4 points per µg/dL will be used in calculations of the implications of the slope at blood lead levels less than 10 µg/dL.

A nonexposed population was assumed to have a standard mean IQ of 100 and standard deviation of 15 at a blood lead exposure of 0 µg/dL. The fraction of the population that would have an IQ <70 or <50 as a function of blood lead level was then calculated. The results are shown in Figure 6-10.4. Note that the fraction with an IQ level below 70, a level often requiring community support to live (World Health Organization, 1992) increases from a little over 2 percent for no lead exposure to about 4 percent with a blood lead level of 10 µg/dL. In addition, the fraction with an IQ level below 50, a level often requiring continuous support to live (World Health Organization, 1992) increases from a little over 4 per 100,000 for no lead exposure to about 11 per 100,000 with a blood lead level of 10 µg/dL.

A shift in the mean value of a health indicator has substantial importance for both extremes of the distribution. In the case of lead, a downward shift in the mean IQ value is associated not only with a substantial increase in the percentage of individuals achieving very low scores, it is associated as well with a substantial decrease in the percentage achieving very high scores. Based on the study by Bellinger et al. (1987) examining intelligence test scores of lead-exposed children, Weiss (1988) discussed the shift of the population distribution of IQ from a mean of 100 and a standard deviation of 15 to a mean of 95, a 5% reduction. When the mean IQ level is 100, 2.3% of the individuals in a given population would score above 130. However, with the population distribution shift and the resulting mean decline in IQ, only 0.99% of the individuals would score above 130. Weiss states that the implication of such as loss transcends the current circumscribed definitions of risk.

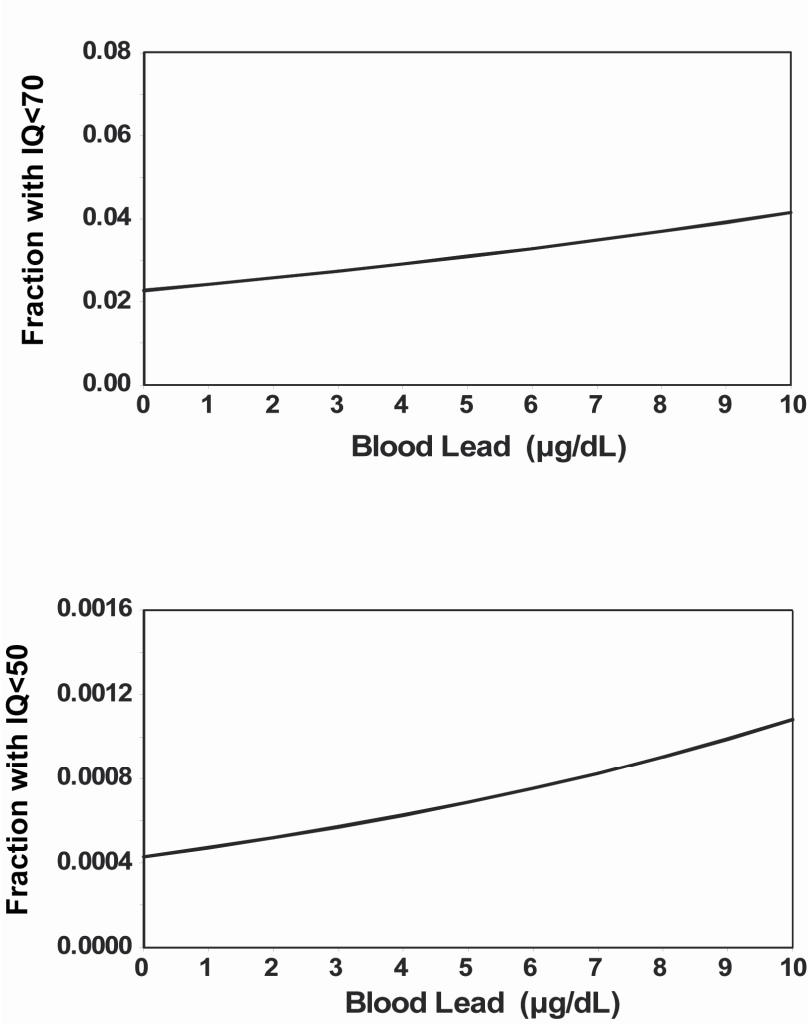


Figure 6-10.4. Effect of blood lead on fraction of population with IQ level <70 or <50 points.

6.10.8.2 Cardiovascular Effects of Lead

In studies investigating the cardiovascular effects of lead, blood pressure has been examined most frequently. Results from the Framingham Heart Study show that higher levels of blood pressure, even within the nonhypertensive range, impose increased rates of cardiovascular disease (Kannel, 2000a,b). A continuous graded increase in cardiovascular risk is observed as blood pressure increases, with no evidence of a threshold value. Most events arise not in the most severe cases, but mainly in those with high normal blood pressure (i.e., mild hypertension). This view is further supported by the Seventh Report of the Joint National Committee on

Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003). Kannel (2000b) states that reducing even moderate elevation in blood pressure is likely to be beneficial.

Kannel (2000a) states that systolic blood pressure exerts a strong, influence on cardiovascular events, as it is the prime causal function of hypertension and its adverse cardiovascular sequelae. Cardiovascular events include coronary disease, stroke, peripheral artery disease, and cardiac failure. Risk ratios are larger for cardiac failure and stroke, but coronary disease (i.e., myocardial infarction, angina pectonis, sudden death) is the most common and most lethal sequela of hypertension (Kannel, 1996). Kannel (2000a) notes that the Framingham Heart Study has recognized that elevated blood pressure tends to occur alongside other major risk factors of cardiovascular disease such as glucose intolerance, dyslipidemia, abdominal obesity, and left ventricular hypertrophy, among others. If a cluster of multiple risk factors is present, the hazard is formidable for coronary disease and stroke.

No critical level of blood pressure is evident. The risk appears to be simply proportional from the lowest to the highest level recorded. In the Multiple Risk Factor Intervention Trial (MRFIT), Neaton et al. (1995) confirmed a continuing and graded influence of systolic blood pressure on cardiovascular disease mortality extending down into the range of <140 mm Hg. The Prospective Studies Collaboration (2002) meta-analysis of 61 prospective studies relates blood pressure to vascular mortality without indication of a threshold down to 115/75 mm Hg. The absence of a demonstrable safe or critical level of blood pressure suggests using the range of blood pressure rather than discrete categories such as hypertension.

Many studies have suggested a relationship between blood lead and systolic blood pressure. In particular, the meta-analysis of Nawrot et al. (2002) indicated that a doubling of the blood lead corresponded to a 1 mm Hg increase in systolic blood pressure. Although this magnitude of increase is not clinically meaningful for an individual, a population shift of 1 mm Hg is important.

The Framingham Heart Study results (Kannel, 2000a) were used to estimate a typical population distribution of systolic blood pressure values (Figure 6-10.5). The distribution of systolic blood pressure values was approximated well by a lognormal distribution for both women and men ($p \geq 0.4$). The relationship between systolic blood pressure and the risk of

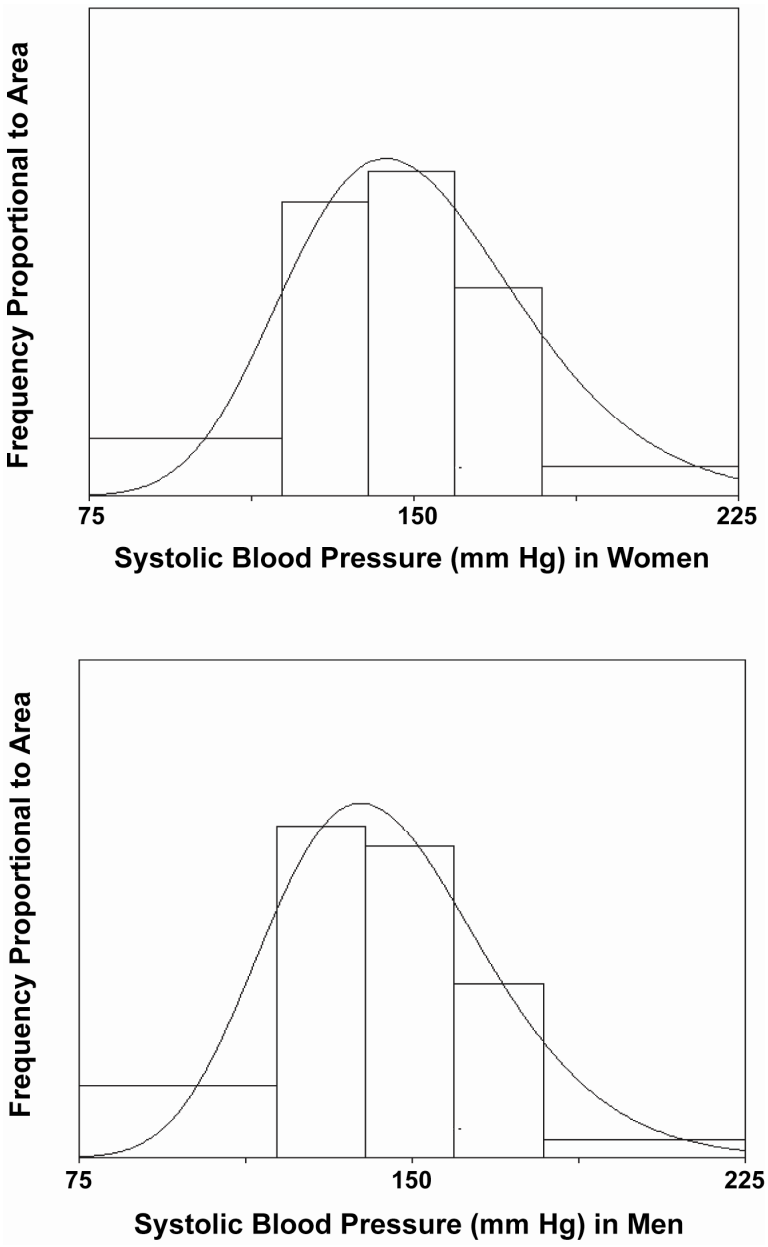


Figure 6-10.5. Distribution of systolic blood pressure in women and men aged 35 to 64 years from the Framingham Heart Study (Kannel, 2000a).

cardiovascular events was also given by Kannel (2000a). The relationships are shown in Figure 6-10.6.

To estimate population risk, it was assumed that the effect of blood lead on blood pressure was to shift the entire distribution by the amount given by Nawrot et al. (2002). For each shift in

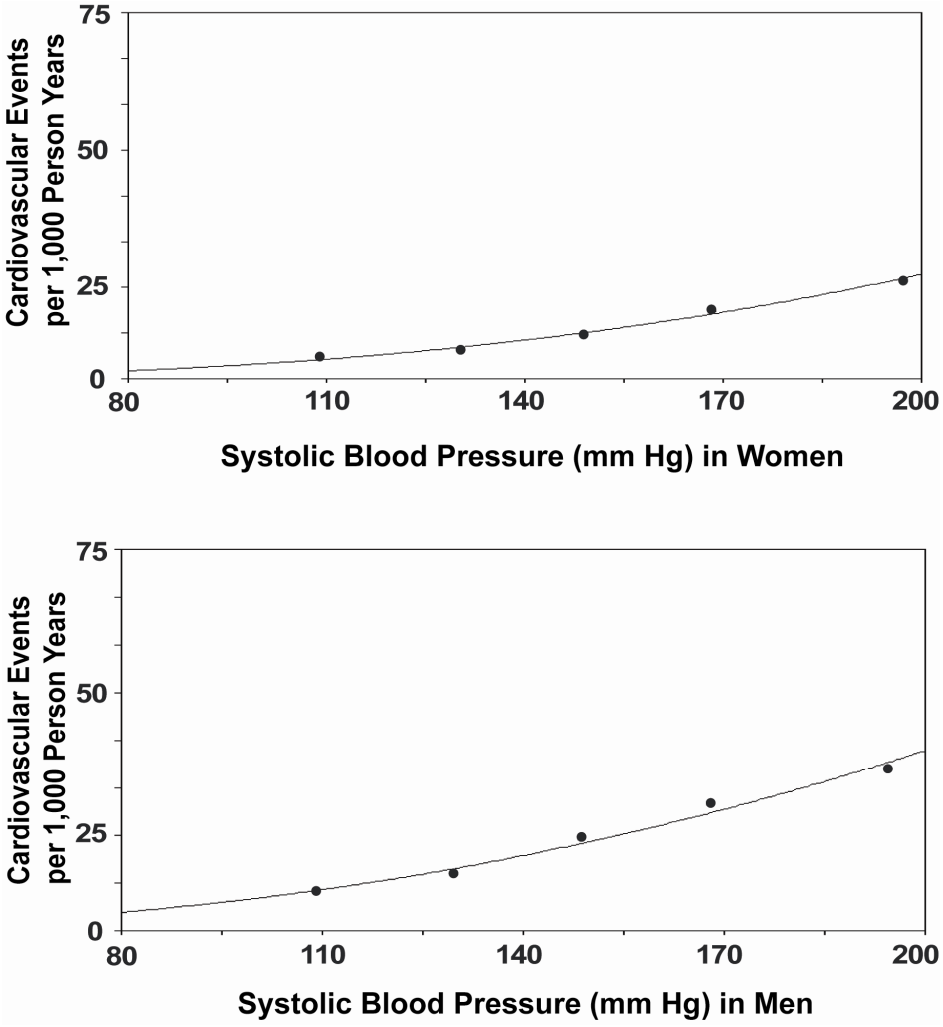


Figure 6-10.6. Relationship of cardiovascular events (coronary disease, stroke, peripheral artery disease, cardiac failure) to systolic blood pressure in women and men aged 35 to 64 years from the Framingham Heart Study (Kannel, 2000a).

the distribution, the entire distribution was integrated out over the risk given in Figure 6-10.6. The result estimated was expected number of cardiovascular events per 1,000 person years, and this was plotted for blood lead levels ranging from 5 to 15 µg/dL for both women and men. The results are shown in Figure 6-10.7. Although the effects are modest, they translate into a large number of events for a moderate population size. For example, a decrease in blood lead from 10 to 5 µg/dL results in an annual decrease of 27 events per 100,000 women and 39 events per 100,000 men.

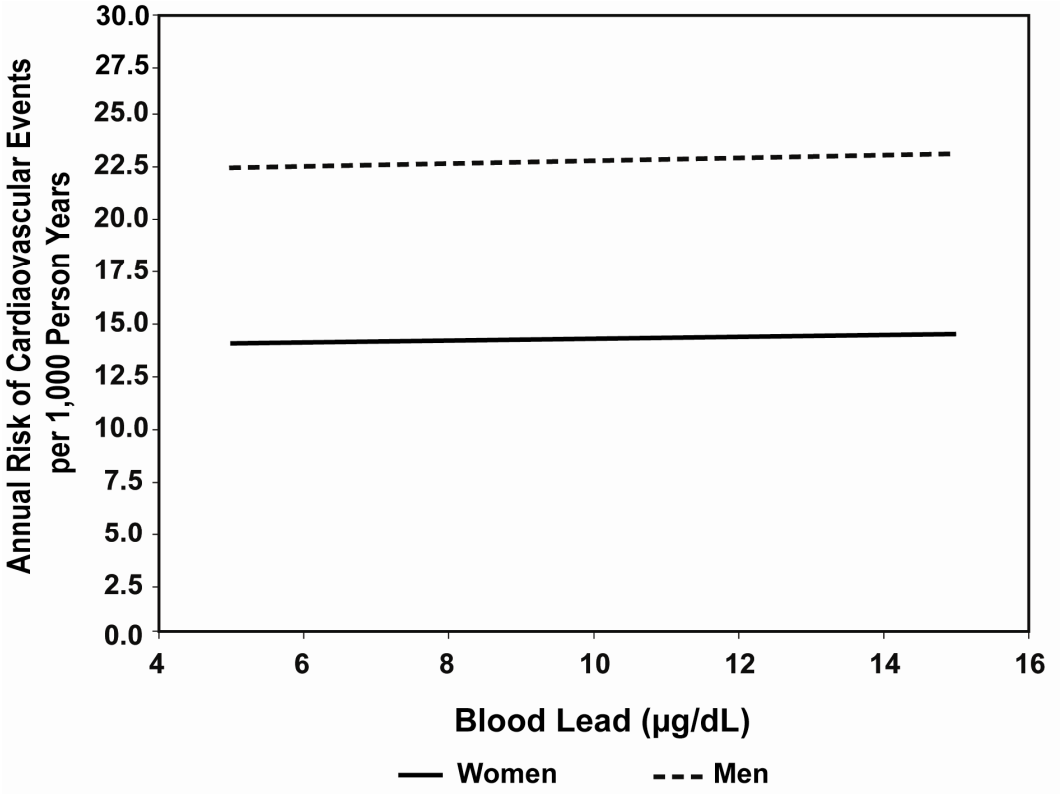


Figure 6-10.7. Effect of blood lead on expected annual risk of cardiovascular events per 1,000 person years.

6.10.9 Summary of Key Findings and Conclusions Derived from Lead Epidemiology Studies

The remarkable progress that has been made since the mid-1980s in understanding the effects of lead on health can be gauged by noting the changes that have occurred over time in the questions investigators have addressed. In the 1980s, the question of interest was often, "Does low-level lead exposure affect health?" The questions asked in recent studies have more often focused on details of the associations, including the shapes of concentration-response relationships, especially at levels well within the range of general population exposures, biological and socio-environmental factors that either increase or decrease an individual's risk, the prognoses associated with lead-associated effects, the efficacy of interventions to reduce adverse effects, and so on. In fact, "low-level," a term long-used to describe exposures that are not sufficiently high to produce clinical signs and symptoms, is increasingly being recognized as

a descriptor that has little biological meaning and is interpretable only in a specific historical context. What was considered "low" in the 1980s is an order of magnitude higher than the current mean level in the U.S. population, and the current mean remains perhaps as much as two orders of magnitude above "natural" background levels in humans. The current CDC screening guideline for children of 10 µg/dL is not a "bright line" separating toxicity from safety, but merely a risk management tool. There is no level of lead exposure that can be clearly identified, with confidence, as "safe." Recent studies of lead neurotoxicity in infants have observed adverse effects at blood lead levels of only 1 or 2 µg/dL and adverse renal outcomes have been reported at blood lead levels below 5 µg/dL. Public health interventions have resulted in declines, over the last 25 years, of more than 90% in the mean blood lead level within all age and gender subgroups of the U.S. population, substantially decreasing the numbers of individuals at risk of lead toxicities.

The following are a listing of key health outcomes discussed earlier in the epidemiology chapter:

- **Neurotoxic effects of lead in children.** The effects of lead on neurobehavior in children have been observed with remarkable consistency across numerous studies of various designs, populations, and developmental assessment protocols. The negative impact of lead on neurocognitive ability and other neurobehavioral outcomes persist in most recent studies even after adjustment for numerous confounding factors including social class, quality of caregiving, and parental intelligence. An international pooled analysis of seven prospective cohort studies offers evidence that exposure to lead has an effect on the intellectual attainment of preschool and school age children even at blood lead levels below 10 µg/dL.

  Epidemiologic studies have demonstrated that lead also may be associated with increased risk for antisocial and delinquent behavior, which may be a consequence of attention problems and academic underachievement among children who have suffered higher exposures to lead during their formative years. Direct measures of brain damage using Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) also are suggesting evidence of harm due to lead exposure. Pharmacological or nutritional intervention strategies generally have not shown to eliminate or reduce lead-associated neurodevelopmental morbidities.

- **Neurotoxic effects of lead in adults.** Environmental lead exposure has not been found to be associated with impaired cognitive performance in the elderly if competing risk factors are considered. In adults, the effect of lead on the nervous system may not be detected through neurobehavioral testing due to cognitive reserve, the ability to compensate for brain impairment.

  Numerous studies of occupational lead exposure observed associations of blood lead with peripheral sensory nerve impairment, visuomotor and memory impairment, and postural sway abnormalities. Past occupational exposure to lead also was associated with increased risk of developing Amyotrophic Lateral Sclerosis (ALS), motor neuron disease, and essential tremor. The odds of developing ALS and essential tremor were significantly increased in individuals with the ALAD2 allele. These neurobehavioral impairments in occupationally-exposed individuals were typically associated with higher blood lead levels (approximately 30-40 μg/dL); however, essential tremor was found to be associated with much lower blood lead levels (mean 3 μg/dL).

- **Renal effects of lead.** In the general population, both cumulative and circulating lead was found to be associated with longitudinal decline in renal functions. In the large NHANES III study, renal dysfunction was observed in hypertensives at a mean blood lead of only 4.2 μg/dL. These results provide strong evidence that the kidney is a target organ for adverse effects from lead in adults at current U.S. environmental exposure levels. The renal impact in children environmental lead exposure is difficult to assess since the most studies have measured early biological effect markers and their prognostic value is uncertain.

  Studies involving the longitudinal assessment of renal function decline in susceptible patient populations observed that low levels of blood lead (<5 μg/dL) and chelatable lead levels were associated with decline in glomerular filtration rate over a 4 year follow-up period in patients with chronic renal insufficiency. Renal function in these patients was found to stabilize and, in some cases, improve after therapeutic chelation.

- **Cardiovascular effects of lead.** Epidemiologic studies support the relationship between increased lead exposure and increased adverse cardiovascular outcome, including increased blood pressure and increased incidence of hypertension. A recent meta-analysis reported that a doubling of blood lead level was associated with a 1.0 mm Hg increase in systolic blood pressure and a 0.6 mm Hg increase in diastolic pressure. Studies also have found that cumulative past lead exposure (e.g., bone lead) may be as important, if not more, than present exposure in assessing cardiovascular effects. The evidence for an association of lead with cardiovascular morbidity and mortality is limited but supportive.

- **Reproductive and developmental effects of lead.** The epidemiologic evidence suggests small associations between exposure to lead and male reproductive outcomes, including perturbed semen quality and increased time to pregnancy. These associations appear at blood lead levels greater the 45 μg/dL, as most studies only considered exposure in the occupational setting. There are no adequate data to evaluate associations between lead exposure and female fertility. For many other outcomes, the observed associations are fairly small, especially at the levels of exposure that are currently of interest. However, there may be populations that are highly susceptible to lead-related reproductive effects, especially if they have additional risk factors for these outcomes.

- **Genotoxic and carcinogenic effects of lead.** Studies of genotoxicity consistently find associations of lead exposure with DNA damage and micronuclei formation; however, the associations with the more established indicator of cancer risk, chromosomal aberrations, are inconsistent. Epidemiologic studies of highly-exposed occupational populations suggest a relationship between lead and cancers of the lung and the stomach; however the evidence is limited by the presence of various potential confounders, including coexposures (e.g., arsenic, cadmium), smoking, and dietary habits. The 2004 IARC review concluded that lead was a probable carcinogen based on limited evidence in humans and sufficient evidence in animals.

- **Effects of lead on the immune system.** Several studies have examined possible associations between lead exposures and biomarkers of immune function. Findings from recent epidemiologic studies suggest that lead exposure may be associated with effects on

cellular and humoral immunity. These effects include changes in serum immunoglobulin levels; perturbation of peripheral lymphocyte phenotype profiles, including decreases in peripheral blood T-cell abundance and changes in T-cell to B-cell abundance ratios; suppression of lymphocyte activation; and suppression of neutrophil chemotaxis and phagocytosis. Studies of biomarkers of humoral immunity in children have consistently found significant associations between increasing blood lead concentrations and serum IgE levels at blood lead levels below 10 µg/dL.

- **Effects of lead on the hematopoietic system.** Lead exposure has been associated with disruption of heme synthesis in both children and adults. Increases in blood lead concentration of approximately 20–30 µg/dL are sufficient to halve erythrocyte ALAD activity and sufficiently inhibit ferrochelatase to double erythrocyte protoporphyrin levels. Perturbation of erythropoiesis, indicated by changes in serum erythropoietin and progenitor cells, occurs in the absence of detectable changes in blood hemoglobin levels or hematocrit in children and adults at blood lead levels below 40 µg/dL. Risk of clinical anemia in children becomes appreciable at much higher blood lead concentrations.

- **Effects of lead on the hepatic and gastrointestinal system.** Studies of hepatic enzyme levels in serum suggest that liver injury may be present in lead workers; however, associations specifically with lead exposures are not evident. Studies of urinary metabolites of cytochrome P450 phenotypes CYP2A6 and CYP3A4 suggest possible associations between lead exposure and suppression of hepatic enzyme activity in adults and children. Several studies observed an association between occupational lead exposure and prevalence of symptoms of gastrointestinal colic. These hepatic and gastrointestinal effects are largely observed only at blood lead concentrations (>40 µg/dL).

- **Effects of lead on the endocrine system.** Most studies have yielded no associations, or weak associations, of lead exposure with thyroid hormone status and male reproductive endocrine status in highly-exposed occupational populations. Children exposed to relatively high levels of lead (blood lead >30 µg/dL) exhibit depressed levels of circulating 1,25-dihydroxy vitamin D (1,25-OH-D). However, associations between serum vitamin D

status and blood lead were not evident in a study of calcium-replete children who had average lifetime blood lead concentrations below 25 μg/dL.

- **Effects of lead on bone and teeth.** The epidemiologic evidence is limited, but suggestive of an association between lead exposure and bone toxicity. Studies have found an association between occupational exposure to lead and Paget's disease. However, it is difficult to assess whether increased lead results from bone diseases or the bone disease is a result of increase lead exposure. Increased risk of dental caries has been associated with lead exposure in children and adults. Lead effects on caries were observed in populations whose mean blood lead levels were less than 10 μg/dL.

- **Effects of lead on ocular health.** Recent longitudinal studies provide evidence for possible associations between lead exposure and adverse ocular health outcomes in low- to moderately-exposed populations. In children whose mothers had blood lead levels of 10.5–32.5 μg/dL in mid-pregnancy, an association was observed between lead exposure and visual evoked retinal responses. Middle-aged males whose tibia bone lead levels were 31–126 μg/g had increased risk of cataracts.

6.11 REFERENCES

Abadin, H. G.; Wheeler, J. S. (1993) Guidance for risk assessment of exposure to lead: a site-specific, multi-media approach. In: Andrews, J. S.; Frumkin, H.; Johnson, B. L.; Mehlman, M. A.; Xintaras, C.; Bucsela, J. A., eds. Hazardous waste and public health: International Congress on the health effects of hazardous waste. Princeton, NJ: Princeton Scientific Publishing Company, Inc.; pp. 477-485.

Abbate, C.; Buceti, R.; Munao, F. (1995) Neurotixicity induced by lead levels: an electrophysiological study. Int. Arch. Occup. Environ. Health 66: 389-392.

Aberg, G.; Fosse, G.; Stray, H. (1998) Man, nutrition and mobility: a comparison of teeth and bone from the Medieval era and the present from Pb and Sr isotopes. Sci. Total Environ. 224: 109-119.

Abudhaise, B. A.; Alzoubi, M. A.; Rabi, A. Z.; Alwash, R. M. (1996) Lead exposure in indoor firing ranges: environmental impact and health risk to the range users. Int. J. Occup. Med. Environ. Health 9: 323-329.

Adachi, J. D.; Arlen, D.; Webber, C. E.; Chettle, D. R.; Beaumont, L. F.; Gordon, C. L. (1998) Is there any association between the presence of bone disease and cumulative exposure to lead? Calcif. Tissue Int. 63: 429-432.

Ades, A. E.; Kazantzis, G. (1988) Lung cancer in a non-ferrous smelter: the role of cadmium. Br. J. Ind. Med. 45: 435-442.

Agency for Toxic Substances and Disease Registry. (1993) Toxicological profile for cadmium. Atlanta, GA: U.S. Department of Health & Human Services, Public Health Service; report no. ATSDR/TP-92/06. Available from: NTIS, Springfield, VA; PB93-182418.

Agency for Toxic Substances and Disease Registry. (1995) Multisite lead and cadmium exposure study with biological markers incorporated. Final report. Atlanta, GA: U.S. Department of Health and Human Services.

Aguilera de Benzo, Z.; Fraile, R.; Carrion, N.; Loreto, D. (1989) Determination of lead in whole blood by electrothermal atomisation atomic absorption spectrometry using tube and platform atomisers and dilution with triton X-100. J. Anal. At. Spectrom. 4: 397-400.

Ahlgren, L.; Liden, K.; Mattsson, S.; Tejning, S. (1976) X-ray fluorescence analysis of lead in human skeleton in vivo. Scand. J. Work Environ. Health 2: 82-86.

Akaike, H. (1973) Information theory and an extension of the maximum likelihood principle. In: Petrov, B. N.; Csaki, F., eds. 2nd International symposium on information theory; September 1971; Tsahkadsor, Armenia, USSR. Budapest, Hungary: Akademiai Kiado; pp. 267-281.

Al-Ashban, R. M.; Aslam, M.; Shah, A. H. (2004) Kohl (surma): a toxic traditional eye cosmetic study in Saudi Arabia. Public Health. 118: 292-298.

Al-Hakkak, Z. S.; Hamamy, H. A.; Murad, A. M.; Hussain, A. F. (1986) Chromosome aberrations in workers at a storage battery plant in Iraq. Mutat. Res. 171: 53-60.

Al-Neamy, F. R.; Almehdi, A. M.; Alwash, R.; Pasha, M. A. H.; Ibrahim, A.; Bener, A. (2001) Occupational lead exposure and amino acid profiles and liver function tests in industrial workers. Int. J. Environ. Health Res. 11: 181-188.

Al-Saleh, I. A. (1995) Lead exposure in Saudi Arabia and its relationship to smoking. BioMetals 8: 243-245.

Al-Saleh, I.; Khalil, M. A.; Taylor, A. (1995) Lead, erythrocyte protoporphyrin, and hematological parameters in normal maternal and umbilical cord blood from subjects of the Riyadh region, Saudi Arabia. Arch. Environ. Health 50: 66-73.

Alessio, L.; Bertazzi, P. A.; Monelli, O.; Toffoletto, F. (1976) Free erythrocyte protoporphyrin as an indicator of the biological effect of lead in adult males. III. Behavior of free erythrocyte protoporphyrin in workers with past lead exposure. Int. Arch. Occup. Environ. Health 38: 77-86.

Alessio, L.; Castoldi, M. R.; Buratti, M.; Maroni, M.; Bertazzi, P. A. (1977) Behaviour of some indicators of biological effect in female lead workers. Int. Arch. Occup. Environ. Health 40: 283-292.

Alexander, B. H.; Checkoway, H.; Van Netten, C.; Muller, C. H.; Ewers, T. G.; Kaufman, J. D.; Mueller, B. A.; Vaughan, T. L.; Faustman, E. M. (1996a) Semen quality of men employed at a lead smelter. Occup. Environ. Med. 53: 411-416.

Alexander, B. H.; Checkoway, H.; Van Netten, C.; Kaufman, J. D.; Vaughan, T. L.; Mueller, B. A.; Faustman, E. M. (1996b) Paternal Occupational Lead Exposure and Pregnancy Outcome. Int. J. Occup. Environ. Health 2: 280-285.

Alexander, B. H.; Checkoway, H.; Faustman, E. M.; Van Netten C.; Muller, C. H.; Ewers, T. G. (1998) Contrasting associations of blood and semen lead concentrations with semen quality among lead smelter workers. Am. J. Ind. Med. 34: 464-469.

Alfven, T.; Jarup, L.; Elinder, C.-G. (2002) Cadmium and lead in blood in relation to low bone mineral density and tubular proteinuria. Environ. Health Perspect. 110: 699-702.

Alomran, A. H.; Shleamoon, M. N. (1988) The influence of chronic lead exposure on lymphocyte proliferative response and immunoglobulin levels in storage battery workers. J. BioI. Sci. Res. 19: 575-585.

Altmann, L.; Weinsberg, F.; Sveinsson, K.; Lilienthal, H.; Wiegand, H.; Winneke, G. (1993) Impairment of long-term potentiation and learning following chronic lead exposure. Toxicol. Lett. 66: 105-112.

Altmann, L.; Sveinsson, K.; Kramer, U.; Winneke, G.; Wiegand, H. (1997) Assessment of neurophysiologic and neurobehavioral effects of environmental pollutants in 5- and 6-year-old children. Environ. Res. 73: 125-131.

Altmann, L.; Sveinsson, K.; Kramer, U.; Weishoff-Houben, M.; Turfeld, M.; Winneke, G.; Wiegand, H. (1998) Visual functions in 6-year-old children in relation to lead and mercury levels. Neurotoxicol. Teratol. 20: 9-17.

American Educational Research Association, American Psychological Association, National Council on Measurement in Education (1999). Standards for Educational and Psychological Testing. Washington, DC: American Psychological Association.

Anderson, L. A., Jr. (1995) A review of blood lead results from the third National Health and Nutrition Examination Survey (NHANES III). Am. Ind. Hyg. Assoc. J. 56: 7-8.

Anderson et al. (1991)

Anetor, J. I.; Adeniyi, F. A. A. (1998) Decreased immune status in Nigerian workers occupationally exposed to lead. Afr. J. Med. Med. Sci. 28: 169-172.

Angell, N. F.; Lavery, J. P. (1982) The relationship of blood levels to obstetric outcome. Am. J. Obstet. Gynecol. 142: 40-46.

Angle, C. R.; Kuntselman, D. R. (1989) Increased erythrocyte protoporphyrins and blood lead--a pilot study of childhood growth patterns. J. Toxicol. Environ. Health. 26: 149-156.

Annesi-Maesano, I.; Pollitt, R.; King, G.; Bousquet, J.; Hellier, G.; Sahuquillo, J.; Huel, G. (2003) In utero exposure to lead and cord blood total IgE. Is there a connection? Allergy 58: 589-594.

Anttila, A.; Heikkila, P.; Pukkala, E.; Nykyri, E.; Kauppinen, T.; Hernberg, S; Hemminki, K. (1995) Excess lung cancer among workers exposed to lead. Scand. J. Work Environ. Health. 21: 460-469.

Anttila, A.; Heikkila, P.; Nykyri, E.; Kauppinen, T.; Pukkala, E.; Hernberg, S.; Hemminki, K. (1996) Risk of nervous system cancer among workers exposed to lead. J. Occup. Environ. Med. 38: 131-136.

Apostoli, P.; Maranelli, G.; Dei Cas, L.; Micciolo, R. (1990) Blood lead and blood pressure: a cross sectional study in a general population group. Cardiologia 35: 597-603.

Apostoli, P.; Maranelli, G.; Micciolo, R. (1992) Is hypertension a confounding factor in the assessment of blood lead reference values? Sci. Total Environ. 120: 127-134.

Apostoli, P.; Kiss, P.; Porru, S.; Bonde, J. P.; Vanhoorne, M.; the ASCLEPIOS study group. (1998) Male reproductive toxicity of lead in animals and humans. Occup. Environ. Med. 55: 364-374.

Apostoli, P.; Corulli, A.; Metra, M.; Dei Cas, L. (2004) Piombo e cardiopatie [Lead and cardiopathy]. Med. Lav. 95: 124-132.

Araki, S.; Aono, H.; Yokoyama, K.; Murata, K. (1986) Filterable plasma concentration, glomerular filtration, tubular balance, and renal clearance of heavy metals and organic substances in metal workers. Arch. Environ. Health 41: 216-221.

Araki, S.; Sata, F.; Murata, K. (1990) Adjustment for urinary flow rate: an improved approach to biological monitoring. Int. Arch. Occup. Environ. Health 62: 471 477.

Armon, C.; Kurland, L. T.; Daube, J. R.; Obrien, P. C. (1991) Epidemiologic correlates of sporadic amyotrophic lateral sclerosis. Neurology 41: 1077-1084.

Arnvig, E.; Grandjean, P.; Beckmann, J. (1980) Neurotoxic effects of heavy lead exposure determined with psychological tests. Toxicol. Lett. 5: 399-404.

Aro, A. C.; Todd, A. C.; Amarasiriwardena, C.; Hu, H. (1994) Improvements in the calibration of 109Cd K x-ray fluorescence systems for measuring bone lead in vivo. Phys. Med. Biol. 39: 2263-2271.

Aro, A.; Amarasiriwardena, C.; Lee, M. L.; Kim, R.; Hu, H. (2000) Validation of K x-ray fluorescence bone lead measurements by inductively coupled plasma mass spectrometry in cadaver legs. Med. Phys. 27: 119-123.

Arriada-Mendioca, N.; Rios-Castaneda, C.; Otero-Siliceo, E.; Corona-Vazquez, T. (2000) Amyotrophic lateral sclerosis in a secluded region in Mexico possibly related to lead toxicity. Arch. Neurocien. 5: 2-5.

Aschengrau, A.; Zierler, S.; Cohen, A. (1993) Quality of community drinking water and the occurrence of late adverse pregnancy outcomes. Arch. Environ. Health 48: 105-113.

Assennato, G.; Paci, C.; Baser, M. E.; Molinini, R.; Candela, R. G.; Altamura, B. M.; Giorgino, R. (1986) Sperm count suppression without endocrine dysfunction in lead-exposed men. Arch. Environ. Health 41: 387-390.

Assennato, G.; Baser, M.; Molinini, R.; Candela, R. G.; Altamura, B. M.; Giorgino, R.; Abbaticchio, G.; Paci, C. (1987) Sperm count suppression without endocrine dysfunction in lead-exposed men. Arch. Environ. Health 42: 124-127.

Audesirk, G. (1985) Effects of lead exposure on the physiology of neurons. Prog. Neurobiol. 24: 199-231.

Audesirk, G.; Shugarts, D.; Nelson, G.; Przekwas, J. (1989) Organic and inorganic lead inhibit neurite growth in vertebrate and invertebrate neurons in culture. In Vitro Cell Dev. Biol. 25: 1121-1128.

Auger, J; Kunstmann, J. M.; Czyglik, F.; Jouannet, P. (1995) Decline in semen quality among fertile men in Paris during the past 20 years. N. Engl. J. Med. 332: 281-285.

Awad El Karim, M. A.; Hamed, A. S.; Elhaimi, Y. A.; Osman, Y. (1986) Effects of exposure to lead among lead-acid battery factory workers in Sudan. Arch. Environ. Health 41: 261-265.

Axelson, O.; Steenland, K. (1988) Indirect methods of assessing the effects of tobacco use in occupational studies. Am. J. Ind. Med. 13: 105-118.

Ayatollahi, M. (2002) Study of the impact of blood lead level on humoral immunity in humans. Toxicol. Ind. Health 18: 39-44.

Azar, A.; Snee, R. D.; Habibi, K. (1975) An epidemiologic approach to community air lead exposure using personal samplers. In: Griffin, T. B.; Knelson, J. H., eds. Lead. Stuttgart, Federal Republic of Germany: Georg Thieme Publishers; pp. 254-290. (Coulston, F.; Korte, F., eds. Environmental quality and safety: supplement v. 2).

Azcona-Cruz, M. I.; Rothenberg, S. J.; Schnaas-Arrieta, L.; Romero-Placeres, M.; Perroni-Hernandez, E. (2000) [Levels of plasmatic lead in children 8-10 years of age and its relation to changes in visual-motor system and balance]. Salud Publica Mex. 42: 279-287.

Baer, R. D.; Garcia de Alba, J.; Mares Leal, R.; Plascencia Campos, A. R.; Goslin, N. (1998) Mexican use of lead in the treatment of empacho: community, clinic, and longitudinal patterns. Soc. Sci. Med. 47: 1263-1266.

Bagci, C.; Bozkurt, A. I.; Cakmak, E. A.; Can, S.; Cengiz, B. (2004) Blood lead levels of the battery and exhaust workers and their pulmonary function tests. Int. J. Clin. Pract. 58: 568-572.

Baghurst, P. A. (1995) Getting the lead out . . . Neurotoxicol. Teratol. 17: 213-214.

Baghurst, P. A.; McMichael, A. J.; Wigg, N. R.; Vimpani, G. V.; Robertson, E. F.; Roberts, R. J.; Tong, S.-L. (1992) Environmental exposure to lead and children's intelligence at the age of seven years: the Port Pirie cohort study. N. Engl. J. Med. 327: 1279-1284.

Baghurst, P. A.; McMichael, A. J.; Tong, S.; Wigg, N. R.; Vimpani, G. V.; Robertson, E. F. (1995) Exposure to environmental lead and visual-motor integration at age 7 years: the Port Pirie cohort study. Epidemiology 6: 104-109.

Baghurst, P. A.; Tong, S.; Sawyer, M. G.; Burns, J.; McMichael, A. J. (1999) Sociodemographic and behavioural determinants of blood lead concentrations in children aged 11-13 years. The Port Pirie Cohort Study. Med. J. Aust. 170: 63-67.

Bairati, C.; Goi, G.; Bollini, D.; Roggi, C.; Luca, M.; Apostoli, P.; Lombardo, A. (1997) Effects of lead and manganese on the release of lysosomal enzymes in vitro and in vivo. Clin. Chim. Acta 261: 91-101.

Baird, D. D.; Wilcox, A. J.; Weinberg, C. R. (1986) Use of time to pregnancy to study environmental exposures. Am. J. Epidemiol. 124: 470-480.

Baker, E. L., Jr.; Landrigan, P. J.; Barbour, A. G.; Cox, D. H.; Folland, D. S.; Ligo, R. N.; Throckmorton, J. (1979) Occupational lead poisoning in the United States: clinical and biochemical findings related to blood lead levels. Br. J. Ind. Med. 36: 314-322.

Balbus, J. M.; Stewart, W.; Bolla, K. I.; Schwartz, B. S. (1997) Simple visual reaction time in organolead manufacturing workers: comparison of different methods of modeling lead exposure and reaction time. Am. J. Ind. Med. 32: 544-549.

Balbus, J. Stewart, W.; Bolla, K. I.; Schwartz, B. S. (1998) Simple visual reaction time in organolead manufacturing workers: influence of the interstimulus interval. Arch. Environ. Health 53: 264-270.

Balbus-Kornfeld, J. M.; Stewart, W.; Bolla, K. I.; Schwartz, B. S. (1995) Cumulative exposure to inorganic lead and neurobehavioural test performance in adults: an epidemiological review. Occup. Environ. Med. 52: 2-12.

Ball, G. V.; Sorensen, L. B. (1969) Pathogenesis of hyperuricemia in saturnine gout. N. Engl. J. Med. 280: 1199-1202.

Ballard, J. L.; Novak, K. K.; Driver, M. (1979) A simplified score for assessment of fetal maturation of newly born infants. J. Pediatr. 95: 769-774.

Baloh, R. W.; Spivey, G. H.; Brown, C. P.; Morgan, D.; Campion, D. S.; Browdy, B. L.; Valentine, J. L. (1979) Subclinical effects of chronic increased lead absorption - a prospective study. II. Results of baseline neurologic testing. J. Occup. Med. 21: 490-496.

Banks, E. C.; Ferretti, L. E.; Shucard, D. W. (1997) Effects of low level lead exposure on cognitive function in children: a review of behavioral, neuropsychological and biological evidence. Neurotoxicology 18: 237-281.

Barltrop, D. (1968) Lead poisoning in childhood. Postgrad. Med. J. 44: 537-542.

Barry, P. S. I. (1975) A comparison of concentrations of lead in human tissues. Br. J. Ind. Med. 32: 119-139.

Basaran, N.; Undeger, U. (2000) Effects of lead on immune parameters in occupationally exposed workers. Am. J. Ind. Med. 38: 349-354.

Bates, M.; Malcolm, M.; Wyatt, R.; Garrett, N.; Galloway, Y.; Speir, T.; Read, D. (1995) Lead in children from older housing areas in the Wellington region. N. Z. Med. J. 108: 400-404.

Battistuzzi, G.; Petrucci, R.; Silvagni, L.; Urbani, F. R.; Caiola, S. (1981) "Delta"-aminolevulinate dehydrase: a new genetic polymorphism in man. Ann. Hum. Genet. 45: 233-229.

Batuman, V. (1993) Lead nephropathy, gout, and hypertension. Am. J. Med. Sci. 305: 241-247.

Batuman, V.; Maesaka, J. K.; Haddad, B.; Tepper, E.; Landry, E.; Wedeen, R. P. (1981) The role of lead in gout nephropathy. N. Engl. J. Med. 304: 520-523.

Batuman, V.; Landy, E.; Maesaka, J. K.; Wedeen, R. P. (1983) Contribution of lead to hypertension with renal impairment. N. Engl. J. Med. 309: 17-21.

Bauchinger, M.; Dresp, J.; Schmid, E.; Englert, N.; Krause, Chr. (1977) Chromosome analyses of children after ecological lead exposure. Mutat. Res. 56: 75-80.

Begerow, J.; Freier, I.; Turfeld, M.; Kramer, U.; Dunemann, L. (1994) Internal lead and cadmium exposure in 6-year-old children from western and eastern Germany. Int. Arch. Occup. Environ. Health 66: 243-248.

Behringer, D.; Craswell, P.; Mohl, C.; Stoeppler, M.; Ritz, E. (1986) Urinary lead excretion in uremic patients. Nephron 42: 323-329.

Bekkelman, I.; Pfister, E. (2001) Neirotoksicheskie effekty mnogoletnei ekspozitsii svintsom [Neurotoxicity due to long-standing exposure to lead]. Med. Tr. Prom. Ekol. (5): 22-26.

Bellinger, D. (1995) Neuropsychologic function in children exposed to environmental lead (comment). Epidemiology 6: 101-103.

Bellinger, D. C. (1995) Interpreting the literature on lead and child development: the neglected role of the "experimental system." Neurotoxicol. Teratol. 17: 201-212.

Bellinger, D. C. (2000) Effect modification in epidemiologic studies of low-level neurotoxicant exposures and health outcomes. Neurotoxicol. Teratol. 22: 133-140.

Bellinger, D. (2002) Perspectives on incorporating human neurobehavioral end points in risk assessments. Risk Anal. 22: 487-498.

Bellinger, D. C. (2003) Perspectives on incorporating human neurobehavioral end points in risk assessments. Risk Anal. 23: 163-174.

Bellinger, D. C. (2004) Confounded by confounding. Epidemiology 15: 383-384.

Bellinger, D. C. (2005) Teratogen update: lead and pregnancy. Birth Defects Res. Part A 73: 409-420.

Bellinger, D.; Dietrich, K. N. (1994) Low-level lead exposure and cognitive function in children. Pediatr. Ann. 23: 600-605.

Bellinger, D. C.; Needleman, H. L. (2003) Intellectual impairment and blood lead levels [letter]. N. Engl. J. Med. 349: 500.

Bellinger, D.; Rappaport, L. (2002) Developmental assessment and interventions. In: Managing elevated blood lead levels among young children: recommendations from the Advisory Committee on Childhood Lead Poisoning Prevention. Atlanta, GA: Centers for Disease Control; pp. 79-95.

Bellinger, D.; Needleman, H. L.; Bromfield, R.; Mintz, M. (1984) A followup study of the academic attainment and classroom behavior of children with elevated dentine lead levels. Biol. Trace Elem. Res. 6: 207-223.

Bellinger, D.; Leviton, A.; Waternaux, C.; Allred, E. (1985) Methodological issues in modelling the relationship between low-level lead exposure and infant development: examples from the Boston lead study. In: Bornschein, R. L.; Rabinowitz, M. B., eds. The second international conference on prospective studies of lead; April 1984; Cincinnati, OH. Environ. Res. 38: 119-129.

Bellinger, D.; Leviton, A.; Needleman, H. L.; Waternaux, C.; Rabinowitz, M. (1986) Low-level lead exposure and infant development in the first year. Neurobehav. Toxicol. Teratol. 8: 151-161.

Bellinger, D.; Leviton, A.; Rabinowitz, M.; Needleman, H.; Waternaux, C. (1986) Correlates of low-level lead exposure in urban children at 2 years of age. Pediatrics 77: 826-833.

Bellinger, D.; Leviton, A.; Waternaux, C.; Needleman, H.; Rabinowitz, M. (1987) Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. N. Engl. J. Med. 316: 1037-1043.

Bellinger, D.; Leviton, A.; Waternaux, C.; Needleman, H.; Rabinowitz, M. (1988) Low-level lead exposure, social class, and infant development. Neurotoxicol. Teratol. 10: 497-503.

Bellinger, D.; Leviton, A.; Waternaux, C. (1989) Lead, IQ and social class. Int. J. Epidemiol. 18: 180-185.

Bellinger, D.; Leviton, A.; Waternaux, C.; Needleman, H.; Rabinowitz, M. (1989) Low-level lead exposure, social class, and infant development. Neurotoxicol. Teratol. 10: 497-503.

Bellinger, D.; Leviton, A.; Sloman, J. (1990) Antecedents and correlates of improved cognitive performance in children exposed in utero to low levels of lead. Environ. Health Perspect. 89: 5-11.

Bellinger, D.; Leviton, A.; Rabinowitz, M.; Allred, E.; Needleman, H.; Schoenbaum, S. (1991) Weight gain and maturity in fetuses exposed to low levels of lead. Environ. Res. 54: 151-158.

Bellinger, D.; Sloman, J.; Leviton, A.; Rabinowitz, M.; Needleman, H. L.; Waternaux, C. (1991) Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics 87: 219-227.

Bellinger, D. C.; Stiles, K. M.; Needleman, H. L. (1992) Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics 90: 855-861.

Bellinger, D.; Hu, H.; Titlebaum, L.; Needleman, H. L. (1994) Attentional correlates of dentin and bone lead levels in adolescents. Arch. Environ. Health 49: 98-105.

Bellinger, D.; Leviton, A.; Allred, E.; Rabinowitz, M. (1994) Pre- and postnatal lead exposure and behavior problems in school-aged children. Environ. Res. 66: 12-30.

Bellinger et al. (2003)

Bellinger, D. C.; Hu, H.; Kalaniti, K.; Thomas, N.; Rajan, P.; Sambandam, S.; Ramaswamy, P.; Balakrishnan, K. (2005) A pilot study of blood lead levels and neurobehavioral function in children living in Chennai, India. Int. J. Occup. Environ. Health 11: 138-143.

Benetou-Marantidou, A.; Nakou, S.; Micheloyannis, J. (1988) Neurobehavioral estimation of children with life-long increased lead exposure. Arch. Environ. Health 43: 392-395.

Benoff, S.; Hurley, I. R.; Millan, C.; Napolitano, B.; Centola, G. M. (2003a) Seminal lead concentrations negatively affect outcomes of artificial insemination. Fertil. Steril. 80: 517-525.

Benoff, S.; Centola, G. M. (2003b) Increased seminal plasma lead levels adversely affect the fertility potential of sperm in IVF. Hum. Reprod. 18: 374-383.

Bercovitz, K.; Laufer, D. (1991) Age and gender influence on lead accumulation in root dentine of human permanent teeth. Arch. Oral Biol. 36: 671-673.

Bercovitz, K.; Laufer, D. (1993) Carious teeth as indicators to lead exposure. Bull. Environ. Contam. Toxicol. 50: 724-729.

Bergdahl, I. A.; Skerfving, S. (1997) Partition of circulating lead between plasma and red cells does not seem to be different for internal and external sources of lead [letter]. Am. J. Ind. Med. 32: 317-318.

Bergdahl, I. A.; Gerhardsson, L.; Schutz, A.; Desnick, R. J.; Wetmur, J. G.; Skerfving, S. (1997) Delta-aminolevulinic acid dehydratase polymorphism: influence on lead levels and kidney function in humans. Arch. Environ. Health 52: 91-96.

Bergdahl, I. A.; Schutz, A.; Gerhardsson, L.; Jensen, A.; Skerfving, S. (1997) Lead concentrations in human plasma, urine and whole blood. Scand. J. Work Environ. Health 23: 359-363.

Bergdahl, I. A.; Sheveleva, M.; Schutz, A.; Artamonova, V. G.; Skerfving, S. (1998) Plasma and blood lead in humans: capacity-limited binding to "delta"-aminolevulinic acid dehydratase and other lead-binding components. Toxicol. Sci. 46: 247-253.

Bergdahl, I. A.; Vahter, M.; Counter, S. A.; Schutz, A.; Buchanan, L. H.; Ortega, F.; Laurell, G.; Skerfving, S. (1999) Lead in plasma and whole blood from lead-exposed children. Environ. Res. 80: 25-33.

Berger, O. G.; Gregg, D. J.; Succop, P. A. (1990) Using unstimulated urinary lead excretion to assess the need for chelation in the treatment of lead poisoning. J. Pediatr. 116: 46-51.

Bergeret, A.; Pouget, E.; Tedone, R.; Meygert, T.; Cadot, R.; Descotes, J. (1990) Neutrophil functions in lead-exposed workers. Hum. Exp. Toxicol. 9: 231-233.

Berkowitz, G. S.; Wolff, M. S.; Lapinski, R. H.; Todd, A. C. (2004) Prospective study of blood and tibia lead in women undergoing surgical menopause. Environ. Health Perspect. 112: 1673-1678.

Bernard. (1999)

Bernard, A. (2004) Renal dysfunction induced by cadmium: biomarkers of critical effects. Biometals 17: 519-523.

Bernard, A. M.; Vyskocil, A.; Roels, H.; Kriz, J.; Kodl, M.; Lauwerys, R. (1995) Renal effects in children living in the vicinity of a lead smelter. Environ. Res. 68: 91-95.

Bernard, A.; Thielemans, N.; Roels, H.; Lauwerys, R. (1995) Association between NAG-B and cadmium in urine with no evidence of a threshold. Occup. Environ. Med. 52: 177-180.

Bhattacharya, A.; Shukla, R.; Bornschein, R.; Dietrich, K.; Kopke, J. E. (1988) Postural disequilibrium quantification in children with chronic lead exposure: a pilot study. Neurotoxicology 9: 327-340.

Bhattacharya, A.; Shukla, R.; Bornschein, R. L.; Dietrich, K. N.; Keith, R. (1990) Lead effects on postural balance of children. In: Conference on advances in lead research: implications for environmental health; January 1989; Research Triangle Park, NC. Environ. Health Perspect. 89: 35-42.

Bhattacharya, A.; Shukla, R.; Dietrich, K.; Bornschein, R.; Berger, O. (1995) Effect of early lead exposure on children's postural balance. Dev. Med. Child Neurol. 37: 861-878.

Bhattacharya, A.; Shukla, R.; Dietrich, K. N.; Miller, J.; Bagchee, A.; Bornschein, R. L.; Cox, C.; Mitchell, T. (1993) Functional implications of postural disequilibrium due to lead exposure. Neurotoxicology 14: 179-189.

Biagini, G.; Caudarella, R.; Vangelista, A. (1977) Renal morphological and functional modification in chronic lead poisoning. In: Brown, S. S., ed. Clinical chemistry and chemical toxicology of metals. New York, NY: Elsevier/North-Holland Biomedical Press; pp. 123-126.

Billick, I. H.; Curran, A. S.; Shier, D. R. (1979) Analysis of pediatric blood lead levels in New York City for 1970-1976. Environ. Health Perspect. 31: 183-190.

Binder, S.; Matte, T. (1993) Childhood lead poisoning: the impact of prevention. JAMA J. Am. Med. Assoc. 269: 1679-1681.

Bleecker, M.; Bolla-Wilson, K.; Kawas, C.; Agnew, J. (1988) Age-specific norms for the mini-mental state exam. Neurology 38: 1565-1568.

Bleecker, M. L.; Lindgren, K. N.; Ford, D. P. (1997a) Differential contribution of current and cumulative indices of lead dose to neuropsychological performance by age. Neurology 48: 639-645.

Bleecker, M. L.; Lindgren, K. N.; Tiburzi, M. J.; Ford, D. P. (1997b) Curvilinear relationship between blood lead level and reaction time. Differential association with blood lead fractions derived from exogenous and endogenous sources. J. Occup. Environ. Med. 39: 426-431.

Bleecker, M. L.; Lindgren, K. N.; Ford, D. P.; Tiburzi, M. J. (2002) The interaction of education and cumulative lead exposure on the mini-mental state examination. J. Occup. Environ. Med. 44: 574-578.

Bleecker, M. L.; Ford, D. P.; Lindgren, K. N.; Hoese, V. M.; Walsh, K. S.; Vaughan, C. G. (2005a) Differential effects of lead exposure on components of verbal memory. Occup. Environ. Med. 62: 181-187.

Bleecker, M. L.; Ford, D. P.; Baughan, C. G.; Lindgren, K. N.; Tiburzi, M. J.; Walsh, K. S. (2005b) Effect of lead exposure and ergonomic stressors on peripheral nerve function. Environ. Health Perspect. 113: 1730-1734.

Bogden, J. D.; Thind, I. S.; Louria, D. B.; Caterini, H. (1978) Maternal and cord blood metal concentrations and low birth weight--a case-control study. Am. J. Clin. Nutr. 31: 1181-1187.

Bogden, J. D.; Oleske, J. M.; Louria, D. B. (1997) Lead poisoning--one approach to a problem that won't go away. Environ. Health Perspect. 105: 1284-1287.

Boivin, M. J.; Giordani, B. (1995) A risk evaluation of the neuropsychological effects of childhood lead toxicity. Dev. Neuropsychol. 11: 157-180.

Bonde, J. P. E.; Kolstad, H. (1997) Fertility of Danish battery workers exposed to lead. Int. J. Epidemiol. 26: 1281-1288.

Bonde, J. P.; Joffe, M.; Apostoli, P.; Dale, A. Kiss, P.; Spano, M.; Caruso, F.; Giwercman, A.; Bisanti, L.; Porru, S.; Vanhoorne, M.; Comhaire, F.; Zschiesche, W. (2002) Sperm count and chromatin structure in men exposed to inorganic lead: lowest adverse effect levels. Occup. Environ. Med. 59: 243-242.

Borja-Aburto, V. H.; Hertz-Picciotto, I.; Lopez, M. R.; Farias, P.; Rios, C.; Blanco, J. (1999) Blood lead levels measured prospectively and risk of spontaneous abortion. Am. J. Epidemiol. 150: 590-597.

Bornschein, R. L.; Rabinowitz, M. B. (1985) The second international conference on prospective studies of lead – foreword. Environ. Res. 38: 1-2.

Bornschein, R. L.; Grote, J.; Mitchell, T., Succop. P. A.; Dietrich, K. N.; Krafft, K. M.; Hammond, P. B. (1989) Effects of prenatal lead exposure on infant size at birth. In: Smith, M. A.; Grant, L. D.; Sors, A. I., eds. Lead exposure and child development: an international assessment [workshop organized by the Commission of the European Communities and the U.S. Environmental Protection Agency]; September 1986; Edinburgh, United Kingdom. Dordrecht, The Netherlands: Kluwer Academic Publishers BV; pp. 307-319.

Bornschein et al. (1990)

Bos, A. J. J.; Van der Stap, C. C. A. H.; Valkovic, V.; Vis, R. D.; Verheul, H. (1985) Incorporation routes of elements into human hair: implications for hair analysis used for monitoring. Sci.Total Environ. 42: 157-169.

Boscolo, P.; De Gioacchino, M.; Sabbioni, E.; Di Giacomo, F.; Reale, M.; Volpe, A. R.; Di Sciascio, M. B.; Conti, P.; Giuliano, G. (2000) Lymphocyte subpopulations, cytokines and trace elements in asymptomatic atopic women exposed to an urban environment. Life Sci. 67: 1119-1126.

Bost, L.; Primatesta, P.; Dong, W.; Poulter, N. (1999) Blood lead and blood pressure: evidence from the Health Survey for England 1995. J. Hum. Hypertens. 13: 123-128.

Bound, J. P.; Harvey, P. W.; Francis, B. J.; Awwad, F.; Gatrell, A. C. (1997) Involvement of deprivation and environmental lead in neural tube defects: a matched case-control study. Arch. Dis. Child. 76: 107-112.

Bourgoin, B. P.; Evans, D. R.; Cornett, J. R.; Lingard, S. M.; Quattrone, A. J. (1993) Lead content in 70 brands of dietary calcium supplements. Am. J. Public Health 83: 1155-1160.

Bradbury, M. W. (1992) An approach to study of transport of trace metals at the blood-brain barrier. Prog. Brain Res. 91: 133-138.

Bradman, A.; Eskenazi, B.; Sutton, P.; Athanasoulis, M.; Goldman, L. R. (2001) Iron deficiency associated with higher blood lead in children living in contaminated environments. Environ. Health Perspect. 109: 1079-1084.

Braun, C. M. J.; Daigneault, S. (1991) Sparing of cognitive executive functions and impairment of motor functions after industrial exposure to lead: a field study with control group. Neuropsychology, 5: 179-193.

Braunstein, G. D.; Dahlgren, J.; Loriaux, D. L. (1978) Hypogonadism in chronically lead-poisoned men. Infertility 1: 33-51.

Bressler, J. P.; Goldstein, G. W. (1991) Mechanisms of lead neurotoxicity. Biochem. Pharmacol. 41: 479-484.

Brito, J. A. A.; McNeill, F. E.; Stronach, I.; Webber, C. E.; Wells, S.; Richard, N.; Chettle, D. R. (2001) Longitudinal changes in bone lead concentration: implications for modelling of human bone lead metabolism. J. Environ. Monit. 3: 343-351.

Brito, J. A. A.; McNeill, F. E.; Webber, C. E.; Wells, S.; Richard, N.; Carvalho, M. L.; Chettle, D. R. (2002) Evaluation of a novel structural model to describe the endogenous release of lead from bone. J. Environ. Monit. 4: 194-201.

Brockhaus, A.; Collet, W.; Dolgner, R.; Engelke, R.; Ewers, U.; Freier, I.; Jermann, E.; Kramer, U.; Manojlovic, N.; Turfeld, M.; Winneke, G. (1988) Exposure to lead and cadmium of children living in different areas of north-west Germany: results of biological monitoring studies 1982-1986. Int. Arch. Occup. Environ. Health 60: 211-222.

Brody, D. J.; Pirkle, J. L.; Kramer, R. A.; Flegal, K. M.; Matte, T. D.; Gunter, E. W.; Paschal, D. C. (1994) Blood lead levels in the US population: phase 1 of the third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991). JAMA J. Am. Med. Assoc. 272: 277-283.

Brown, A.; Tompsett, S. L. (1945) Poisoning due to mobilization of lead from the skeleton by leukaemic hyperplasia of bone marrow. Br. Med. J. 2: 764-765.

Brown, M. J.; Hu, H.; Gonzales-Cossio, T.; Peterson, K. E.; Sanin, L.-H.; de Luz Kageyama, M.; Palazuelos, E.; Aro, A.; Schnaas, L.; Hernandez-Avila, M. (2000) Determinants of bone and blood lead concentrations in the early postpartum period. Occup. Environ. Med. 57: 535-541.

Buchet, J. P.; Lauwerys, R.; Roels, H.; Bernard, A.; Bruaux, P.; Claeys, F.; Ducoffre, G.; De Plaen, P.; Staesen, J.; Amery, A.; Linjen, P.; Thijs, L.; Rondia, D.; Sartor, F.; Saint Remy, A.; Nick, L. (1990) Renal effects of cadmium body burden of the general population. Lancet 336: 699-702.

Budd, P.; Montgomery, J.; Evans, J.; Trickett, M. (2004) Human lead exposure in England from approximately 5500 BP to the 16th century AD. Sci. Total Environ. 318: 45-58.

Burgstahler, A. W. (2003) Influence of fluoride and lead on children's IQ: U.S. tolerance standards in question. Fluoride 36: 79-81.

Burns, J. M.; Baghurst, P. A.; Sawyer, M. G.; McMichael, A. J.; Tong, S.-L. (1999) Lifetime low-level exposure to environmental lead and children's emotional and behavioral development at ages 11-13 years. The Port Pirie cohort study. Am. J. Epidemiol. 149: 740-749.

Cake, K. M.; Bowins, R. J.; Vaillancourt, C.; Gordon, C. L.; McNutt, N. H., Laporte, R.; Webber, C. E.; Chettle, D. R. (1996) Partition of circulating lead between serum and red cells is different for internal and external sources of lead. Am. J. Ind. Med. 29: 440-445.

Calderon, J.; Navarro, M. E.; Jimenez-Capdeville, M. E.; Santos-Diaz, M. A.; Golden, A.; Rodriguez-Leyva, I.; Borja-Aburto, V.; Diaz-Barriga, F. (2001) Exposure to arsenic and lead and neuropsychological development in Mexican children. Environ. Res. 85: 69-76.

Calderon-Salinas, J. V.; Hernandez-Luna, C.; Valdez-Anaya, B.; Maldonado-Vega, M.; Lopez-Miranda, A. (1996) Evolution of lead toxicity in a population of children. Hum. Exp. Toxicol. 15: 376-382.

Campara, P.; D'Andrea, F.; Micciolo, R.; Savonitto, C.; Tansella, M.; Zimmermann-Tansella, C. (1984) Psychological performance of workers with blood-lead concentration below the current threshold limit value. Int. Arch. Occup. Environ. Health 53: 233-246.

Campbell, J. R.; Toribara, T. Y. (2001) Hair-root lead to screen for lead toxicity. J. Trace Elem. Exp. Med. 14: 69-72.

Campbell, B. C.; Meredith, P. A.; Scott, J. J. C. (1985) Lead exposure and changes in the renin-angiotensin-aldosterone system in man. Toxicol. Lett. 25: 25-32.

Campbell, J. R.; Moss, M. E.; Raubertas, R. F. (2000) The association between caries and childhood lead exposure. Environ. Health Perspect. 108: 1099-1102.

Campbell, T. F.; Needleman, H. L.; Riess, J. A.; Tobin, M. J. (2000) Bone lead levels and language processing performance. Dev. Neuropsychol. 18: 171-186.

Canfield, R. L.; Henderson, C. R., Jr.; Cory-Slechta, D. A.; Cox, C.; Jusko, T. A.; Lanphear, B. P. (2003a) Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. N. Engl. J. Med. 348: 1517-1526.

Canfield, R. L.; Kreher, D. A.; Cornwell, C.; Henderson, C. R., Jr. (2003b) Low-level lead exposure, executive functioning, and learning in early childhood. Child Neuropsychol. 9: 35-53.

Canfield, R. L.; Gendle, M. H.; Cory-Slechta, D. A. (2004) Impaired neuropsychological functioning in lead-exposed children. Dev. Neuropsychol. 26: 513-540.

Cantarow, A.; Trumper, M. (1944) Lead poisoning. Baltimore, MD: Williams & Wilkins Co.

Carbone, R.; Laforgia, N.; Crollo, E.; Mautone, A.; Iolascon, A. (1998) Maternal and neonatal lead exposure in southern Italy. Biol. Neonate 73: 362-366.

Cardenas, A.; Roels, H.; Bernard, A. M.; Barbon, R.; Buchet, J. P.; Lauwerys, R. R.; Rosello, J.; Hotter, G.; Mutti, A.; Franchini, I.; Fels, L. M.; Stolte, H.; De Broe, M. E.; Nuyts, G. D.; Taylor, S. A.; Price, R. G. (1993) Markers of early renal changes induced by industrial pollutants. I. Application to workers exposed to mercury vapor. Br. J. Ind. Med. 50: 17-27.

Cardenas, A.; Roels, H.; Bernard, A. M.; Barbon, R.; Buchet, J. P.; Lauwerys, R. R.; Rosello, J.; Ramis, I.; Mutti, A.; Franchini, I.; Fels, L. M.; Stolte, H.; De Broe, M. E.; Nuyts, G. D.; Taylor, S. A.; Price, R. G. (1993) Markers of early renal changes induced by industrial pollutants. II. Application to workers exposed to lead. Br. J. Ind. Med. 50: 28-36.

Cardozo dos Santos, A.; Colacciopo, S.; Bo, C. M. R. dal; Santos, N. A. G. dos. (1994) Occupational exposure to lead, kidney function tests, and blood pressure. Am. J. Ind. Med. 26: 635-643.

Carsia, R. V.; Forman, D.; Hock, C. E.; Nagele, R. G.; McIlroy, P. J. (1995) Lead alters growth and reduces angiotensin II receptor density of rat aortic smooth muscle cells. Proc. Soc. Exp. Biol. Med. 210: 180-190.

Carta, P.; Cocco, P.; Picchiri, G. (1994) Lung cancer mortality and airways obstruction among metal miners exposed to silica and low levels of radon daughters. Am. J. Ind. Med. 25: 489-506.

Carta, P.; Aru, G.; Cadeddu, C.; Nieddu, V.; Polizzi, M.; Nurchis, P.; Flore, C.; Salis, S.; Sanna, R. F. (2003) Mortalita per cancro polmonare in lavoratori di una fonderia di piombo della Sardegna [Mortality from lung cancer among workers of a Sardinian lead smelter [Follow-up: 1972-2001]]. G. Ital. Med. Lav. Ergon. 25(suppl. 3): 17-18.

Carta, P.; Aru, G.; Nurchis, P.; Cadeddu, C.; Polizzi, M.; Nieddu, V.; Sali, G.; Gaviano, L.; Flore, C.; Sanna, R. F. (2005) Studio di mortalita per cause specifiche in lavoratori di una fonderia di piombo e zinco della Sardegna. G. Ital. Med. Lav. Ergon. 27(suppl. 1): 43-45.

Casey, C. E.; Robinson, M. F. (1978) Copper, manganese, zinc, nickel, cadmium and lead in human foetal tissue. Br. J. Nutr. 39: 639-646.

Cavalleri, A.; Trimarchi, F.; Gelmi, C.; Baruffini, A.; Minoia, C.; Biscaldi, G.; Gallo, G. (1982) Effects of lead on the visual system of occupationally exposed subjects. Scand. J. Work Environ. Health 8(suppl. 1): 148-151.

Cecil, K. M.; Weihong, Y.; Holland, S.; Wessel, S.; Dietrich, K.; Ris, D.; Lanphear, B. (2005) The influence of childhood lead exposure on language function in young adults: an fMRI study. Presented at: International Society for Magnetic Resonance Imaging: 12th scientific meeting and exhibition; May; Miami, FL; A1443.

Centers for Disease Control and Prevention. (1991) Preventing lead poisoning in young children: a statement by the Centers for Disease Control. Atlanta, GA: U.S. Department of Health and Human Services; October.

Centers for Disease Control and Prevention. (1993) Lead poisoning associated with use of traditional ethnic remedies. Morb. Mortal. Wkly. Rep. 42: 521-524.

Centers for Disease Control and Prevention. (1995) Blood lead levels among children -- Rhode Island, 1993-1995. Morb. Mortal. Wkly. Rpt. MMWR 44: 788-791.

Centers for Disease Control and Prevention. (1995) Blood lead levels among children in a managed-care organization -- California, October 1992-March 1993. Morb. Mortal. Wkly. Rep. 44: 627-635.

Centers for Disease Control and Prevention. (1997) Adult blood lead epidemiology and surveillance - United States, third quarter, 1996. Morb. Mortal. Wkly Rpt. MMWR 46: 105-107.

Centers for Disease Control and Prevention. (1997) Blood lead levels - United States, 1991-1994. Morb. Mortal. Wkly. Rep. MMWR 46: 141-146.

Centers for Disease Control and Prevention. (2000) Blood lead levels in young children -- United States and selected states, 1996-1999. Morb. Mortal. Wkly. Rep. 49: 1133-1137.

Centers for Disease Control and Prevention. (2005) Third national report on human exposure to environmental chemicals. Atlanta, GA: U.S. Department of Health and Human Services, National Center for Environmental Health. NCEH Pub. No. 05-0570.

Chalkley, S. R.; Richmond, J.; Barltrop, D. (1998) Measurement of vitamin D3 metabolites in smelter workers exposed to lead and cadmium. Occup. Environ. Med. 55: 446-452.

Chamberlain, A. C.; Heard, M. J.; Little, P.; Newton, D.; Wells, A. C.; Wiffin, R. D. (1978) Investigations into lead from motor vehicles. Harwell, United Kingdom: United Kingdom Atomic Energy Authority; report no. AERE-R9198.

Chancellor, A. M.; Slattery, J. M.; Fraser, H.; Warlow, C. P. (1993) Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register. J. Neurol. Neurosurg. Psychiatry 56: 1200-1206.

Chaube, S.; Swinyard, C. A.; Nishimura, H. (1972) A quantitative study of human embryonic and fetal lead with considerations of maternal fetal lead gradients and the effect of lead on human reproduction. Teratology 5: 253.

Chen, A.; Dietrich, K. N.; Ware, J. H.; Radcliffe, J.; Rogan, W. J. (2005) IQ and blood lead from 2 to 7 years of age: are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environ. Health Perspect. 113: 597-601.

Cheng, Y.; Willett, W. C.; Schwartz, J.; Sparrow, D.; Weiss, S.; Hu, H. (1998a) Relation of nutrition to bone lead and blood lead levels in middle-aged to elderly men. The Normative Aging Study. Am. J. Epidemiol. 147: 1162-1174.

Cheng, Y.; Schwartz, J.; Vokonas, P. S.; Weiss, S. T.; Aro, A.; Hu, H. (1998b) Electrocardiographic conduction disturbances in association with low-level lead exposure (the Normative Aging Study). Am. J. Cardiol. 82: 594-599.

Cheng, Y.; Schwartz, J.; Sparrow, D.; Aro, A.; Weiss, S. T.; Hu, H. (2001) Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension: the Normative Aging Study. Am. J. Epidemiol. 153: 164-171.

Chettle, D. R.; Fleming, D. E. B.; McNeill, F. E.; Webber, C. E. (1997) Serum (plasma) lead, blood lead, and bone lead [letter]. Am. J. Ind. Med. 32: 319-320.

Cheung et al. (1998)

Chia, S. E.; Chua, L. H.; Ng, T. P.; Foo, S. C.; Jeyaratnam, J. (1994) Postural stability of workers exposed to lead. Occup. Environ. Med. 51: 768-771.

Chia, K. S.; Mutti, A.; Alinovi, R.; Jeyaratnam, J.; Tan, C.; Ong, C. N.; Lee, E. (1994) Urinary excretion of tubular brush-border antigens among lead exposed workers. Ann. Acad. Med. Singapore 23: 655-659.

Chia, K. S.; Mutti, A.; Tan, C.; Ong, H. Y.; Jeyaratnam, J.; Ong, C. N.; Lee, E. (1994) Urinary N-acetyl-"beta"-D-glucosaminidase activity in workers exposed to inorganic lead. Occup. Environ. Med. 51: 125-129.

Chia, K. S.; Jeyaratnam, J.; Lee, J.; Tan, C.; Ong, H. Y.; Ong, C. N.; Lee, E. (1995) Lead-induced nephropathy: relationship between various biological exposure indices and early markers of nephrotoxicity. Am. J. Ind. Med. 27: 883-895.

Chia, K. S.; Jeyaratnam, J.; Tan, C.; Ong, H. Y.; Ong, C. N.; Lee, E. (1995) Glomerular function of lead-exposed workers. Toxicol. Lett. 77: 319-328.

Chia, S.; Chia, K.; Chia, H.; Ong, C.; Jeyaratnam, J. (1996a) Three-year follow-up of serial nerve conduction among lead-exposed workers. Scand. J. Work Environ. Health 22: 374-380.

Chia, S.; Chia, H.; Ong, C.; Jeyaratnam, J. (1996b) Cumulative blood lead levels and nerve conduction parameters. Occup. Med. 46: 59-64.

Chia, S.; Chia, H.; Ong, C.; Jeyaratnam, J. (1996c) Cumulative concentrations of blood lead and postural stability. Occup. Environ. Med. 53: 264-268.

Chia, S.-E.; Chia, H.-P.; Ong, C.-N.; Jeyaratnam, J. (1997) Cumulative blood lead levels and neurobehavioral test performance. Neurotoxicology 18: 793-803.

Chiodo, L. M.; Jacobson, S. W.; Jacobson, J. L. (2004) Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol. Teratol. 26: 359-371.

Chisolm, J. J., Jr.; Mellits, E. D.; Barrett, M. B. (1976) Interrelationships among blood lead concentration, quantitative daily ALA-U and urinary lead output following calcium EDTA. In: Nordberg, G. F., ed. Proceedings of third meeting of the subcommittee on the toxicology of metals under the Permanent Commission and International Association on Occupational Health; November 1974; Toyko, Japan. Amsterdam, The Netherlands: Elsevier Publishing Co.; pp. 416-433.

Chobanian, A. V.; Bakris, G. L.; Black, H. R.; Cushman, W. C.; Green, L. A.; Izzo, J. L., Jr.; Jones, D. W.; Materson, B. J.; Oparil, S.; Wright, J. T., Jr.; Roccella, E. J.; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Institute; National High Blood Pressure Education Program Coordinating Committee. (2003) Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 42: 1206-1252.

Chow, B. J. W.; Hassan, A. H.; Chan, K. L.; Tang, A. S. L. (2003) Prevalence and significance of lead-related thrombi in patients with implantable cardioverter defibrillators. Am. J. Cardiol. 91: 88-90.

Chowdhury, A. R.; Rao, R. V.; Gautam, A. K. (1986) Histochemical changes in the testes of lead induced experimental rats. Folia Histochem. Cytobiol. 24: 233-237.

Christoffersson, J. O.; Schutz, A.; Ahlgren, L.; Haeger-Aronsen, B.; Mattsson, S.; Skerfving, S. (1984) Lead in finger-bone analysed in vivo in active and retired lead workers. Am. J. Ind. Med. 6: 447-457.

Christoffersson, J. O.; Ahlgren, L.; Schwartz, A.; Skerfving, S.; Mattsson, S. (1986) Decrease of skeletal lead levels in man after end of occupational exposure. Arch. Environ. Health 41: 312-318.

Christoffersson et al. (1994)

Chu, N.-F.; Liou, S.-H.; Wu, T.-N.; Chang, P.-Y. (1999) Reappraisal of the relation between blood lead concentration and blood pressure among the general population in Taiwan. Occup. Environ. Med. 56: 30-33.

Chuang, H.-Y.; Schwartz, J.; Tsai, S.-Y.; Lee, M.-L. T.; Wang, J.-D.; Hu, H. (2000) Vibration perception thresholds in workers with long term exposure to lead. Occup. Environ. Med. 57: 588-594.

Chuang, H. Y.; Schwartz, J.; Gonzales-Cossio, T.; Lugo, M. C.; Palazuelos, E.; Aro, A.; Hu, H.; Hernandez-Avila, M. (2001) Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. Environ. Health Perspect. 109: 527-532.

Chuang, H.-Y.; Yu, K.-T.; Ho, C.-K.; Wu, M.-T.; Lin, G.-T.; Wu, T.-N. (2004) Investigations of vitamin D receptor polymorphism affecting workers' susceptibility to lead. J. Occup. Health 46: 316-322.

Churchill, D.; Perry, I. J.; Beevers, D. G. (1997) Ambulatory blood pressure in pregnancy and fetal growth. Lancet 349: 7-10.

Cicuttini, F. M.; Woodburn, C. M.; Golec, R.; Forbes, A.; Sim, M. (1998) Low lead levels in amniotic fluid and cord blood in a public hospital population. Aust. N. Z. J. Public Health 22: 628-629.

Clark, A. R. L. (1977) Placental transfer of lead and its effects on the newborn. Postgrad. Med. J. 53: 674-678.

Clark, C. S.; Bornschein, R. L.; Succop, P. A.; Que Hee, S. S.; Hammond, P. B.; Peace, B. (1985) Condition and type of housing as an indicator of poential environmental lead exposure and pediatric blood lead levels. Environ. Res. 38: 46-53.

Cleymaet, R.; Bottenberg, P.; Retief, D. H.; Slop, D.; Michotte, Y.; Coomans, D. (1991) In vivo use of a dual acid etch biopsy for the evaluation of lead profiles in human surface enamel. Caries Res. 25: 256-263.

Cocco, P. L.; Carta, P.; Belli, S.; Picchiri, G. F.; Flore, M. V. (1994a) Mortality of Sardinian lead and zinc miners: 1960-88. Occup. Environ. Med. 51: 674-682.

Cocco, P. L.; Carta, P.; Flore, V.; Picchiri, G. F.; Zucca, C. (1994b) Lung cancer mortality among female mine workers exposed to silica. J. Occup. Med. 36: 894-898.

Cocco, P.; Salis, S.; Anni, M.; Cocco, M. E.; Flore, C.; Ibba, A. (1995) Effects of short-term occupational exposure to lead on erythrocyte glucose-6-phosphate dehydrogenase activity and serum cholesterol. J. Appl. Toxicol. 15: 375-378.

Cocco, P.; Carta, P.; Flore, C.; Congia, P.; Manca, M. B.; Saba, G.; Salis, S. (1996) Mortality of lead smelter workers with the glucose-6-phosphate dehydrogenase-deficient phenotype. Cancer Epidemiol. Biomarkers Prev. 5: 223-225.

Cocco, P.; Hua, F.; Boffetta, P.; Carta, P.; Flore, C.; Flore, V.; Onnis, A.; Picchiri, G. F.; Colin, D. (1997) Mortality of Italian lead smelter workers. Scand. J. Work Environ. Health 23: 15-23.

Cocco, P.; Dosemeci, M.; Heineman, E. F. (1998a) Brain cancer and occupational exposure to lead. J. Occup. Environ. Med. 40: 937-942.

Cocco, P.; Dosemeci, M.; Heineman, E. F. (1998b) Occupational risk factors for cancer of the central nervous system: A case-control study of death certificates from 24 U.S. States. Am. J. Ind. Med. 33: 247-255.

Cocco, P.; Ward, M. H.; Dosemeci, M. (1999) Risk of stomach cancer associated with 12 workplace hazards: Analysis of death certificates from 24 states of the United States with the aid of job exposure matrices. Occup. Environ. Med. 56: 781-787.

Cockcroft, D. W.; Gault, M. H. (1976) Prediction of creatinine clearance from serum creatinine. Nephron 6: 31-41.

Cohen, N.; Modai, D.; Golik, A.; Weissgarten, J.; Peller, S.; Katz, A.; Averbukh, Z.; Shaked, U. (1989) Increased concanavalin A-induced suppressor cell activity in humans with occupational lead exposure. Environ. Res. 48: 1-6.

Colleoni, N.; D'Amico, G. (1986) Chronic lead accumulation as a possible cause of renal failure in gouty patients. Nephron 44: 32-35.

Colleoni, N.; Arrigo, G.; Gandini, E.; Corigliano, C.; D'Amico, G. (1993) Blood lead in hemodialysis patients. Am. J. Nephrol. 13: 198-202.

Constantine, N. A.; Kraemer, H. C.; Kendall-Tackett, K. A.; Bennett, F. C.; Tyson, J. E.; Gross, R. T. (1987) Use of physical and neurologic observations in assessment of gestational age in low birth weight infants. J. Pediatr. (St. Louis, MO, U.S.) 110: 921-928.

Cooney, G. H. (1995) Lead research: where do we go from here? Neurotoxicol. Teratol. 17: 215-218.

Cooney, G. H.; Bell, A.; McBride, W.; Carter, C. (1989a) Neurobehavioural consequences of prenatal low level exposures to lead. Neurotoxicol. Teratol. 11: 95-104.

Cooney, G. H.; Bell, A.; McBride, W.; Carter, C. (1989b) Low-level exposures to lead: the Sydney lead study. Dev. Med. Child Neurol. 31: 640-649.

Cooney, G.; Bell, A.; Stavrou, C. (1991) Low level exposures to lead and neurobehavioural development: the Sydney study at seven years. In: Farmer, J. G., ed. International conference: heavy metals in the environment, v. 1; September; Edinburgh, United Kingdom. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 16-19.

Cooper, W. C. (1988) Deaths from chronic renal disease in U. S. battery and lead production workers. In: Victery, W., ed. Symposium on lead-blood pressure relationships; April 1987; Chapel Hill, NC. Environ. Health Perspect. 78: 61-63.

Cooper, W. C.; Gaffey, W. R. (1975) Mortality of lead workers. In: Cole, J. F., ed. Proceedings of the 1974 conference on standards of occupational lead exposure; February 1974; Washington, DC. J. Occup. Med. 17: 100-107.

Cooper, W. C.; Tabershaw, I. R.; Nelson, K. W. (1973) Laboratory studies of workers in lead smelting and refining. In: Barth, D.; Berlin, A.; Engel, R.; Recht, P.; Smeets, J., eds. Environmental health aspects of lead: proceedings [of an] international symposium; October 1972; Amsterdam, The Netherlands. Luxembourg: Commission of the European Communities; pp. 517-530; report no. EUR 5004 d-e-f.

Cooper, W. C.; Wong, O.; Kheifets, L. (1985) Mortality among employees of lead battery plants and lead-producing plants, 1947-1980. Scand. J. Work Environ. Health 11: 331-345.

Cooper, W. C.; Wong, O.; Trent, L. (1989) Case-control study of gastric cancer deaths in a lead battery plant. Report to the International Lead Zinc Research Organization.

Coratelli, P.; Giannattasio, M.; Lomonte, C.; Marzolla, R.; Rana, F.; L'Abbate, N. (1988) Enzymuria to detect tubular injury in workers exposed to lead: a 12-month follow-up. In: Bianchi, C.; Bocci, V.; Carone, F. A.; Rabkin, R., eds. Kidney and proteins in health and disease: fifth international symposium in health and disease; July 1987; Montecatini Terme, Italy. Basel, Switzerland: S. Karger; pp. 207-211.

Cordioli, G.; Cuoghi, L.; Solari, P. L.; Berrino, F.; Crosignani, P.; Riboli, E. (1987) Mortalita per tumore in una coorte di lavoratori della industria del vetro [Tumor mortality in a cohort of glass industry workers]. Epidemiol. Prev. (Italy) 9(30): 16-18.

Cory-Slechta, D. A. (1995) Bridging human and experimental animal studies of lead neurotoxicity: moving beyond IQ. Neurotoxicol. Teratol. 17: 219-221.

Cory-Slechta, D. A. (1996) Legacy of lead exposure: consequences for the central nervous system. Otolaryngol. Head Neck Surg. 114: 224-226.

Coscia, G. C.; Discalzi, G.; Ponzetti, C. (1987) Immunological aspects of occupational lead exposure. Med. Lav. 78: 360-364.

Coscia, J. M.; Ris, M. D.; Succop, P. A.; Dietrich, K. N. (2003) Cognitive development of lead exposed children from ages 6 to 15 years: an application of growth curve analysis. Child Neuropsychol. 9: 10-21.

Coste, J.; Mandereau, L.; Pessione, F.; Bregu, M.; Faye, C.; Hemon, D.; Spira, A. (1991) Lead-exposed workmen and fertility: a cohort study on 354 subjects. Eur. J. Epidemiol. 7: 154-158.

Counter, S. A.; Vahter, M.; Laurell, G.; Buchanan, L. H.; Ortega, F.; Skerfving, S. (1997) High lead exposure and auditory sensory-neural function in Andean children. Environ. Health Perspect. 105: 522-526.

Counter, S. A.; Buchanan, L. H.; Rosas, H. D.; Ortega, F. (1998) Neurocognitive effects of chronic lead intoxication in Andean children. J. Neurol. Sci. 160: 47-53.

Cramer, K.; Goyer, R. A.; Jagenburg, R.; Wilson, M. H. (1974) Renal ultrastructure, renal function, and parameters of lead toxicity in workers with different periods of lead exposure. Br. J. Ind. Med. 31: 113-127.

Craswell, P. W.; Price, J.; Boyle, P. D.; Behringer, D.; Stoeppler, M.; Ritz, E. (1987) Patterns of lead excretion in patients with gout and chronic renal failure -- a comparative German and Australian study. Sci. Total Environ. 66: 17-28.

Cristofolini, A.; Del, D. M.; Manfrini, G.; Vitalone, V.; Ramponi, C.; De Santa, A.; Miori, R. (1995) Blood lead levels in the population of Trento. Ig. Mod. 104: 93-105.

Cristy, M. (1981) Active bone marrow distribution as a function of age in humans. Phys. Med. Biol. 26: 389-400.

Cullen, M. R.; Kayne, R. D.; Robins, J. M. (1984) Endocrine and reproductive dysfunction in men associated with occupational inorganic lead intoxication. Arch. Environ. Health 39: 431-440.

Cunningham, R. D., Jr. (1993) Declining blood lead levels and cognitive change in children [letter]. JAMA J. Am. Med. Assoc. 270: 828.

Dalpra, L.; Tibiletti, M. G.; Nocera, G.; Giulotto, P.; Auriti, L.; Carnelli, V.; Simoni, G. (1983) SCE analysis in children exposed to lead emission from a smelting plant. Mutat. Res. 120: 249-256.

David, O. J.; Clark, J.; Voeller, K. (1972) Lead and hyperactivity. Lancet (7783): 900-903.

David, O. J.; Hoffman, S. P.; Sverd, J.; Clark, J.; Voeller, K. (1976) Lead and hyperactivity. Behavorial response to chelation: a pilot study. Am. J. Psychiatry 133: 1155-1158.

David, O. J.; Clark, J.; Hoffman, S. (1979) Childhood lead poisoning: a re-evaluation. Arch. Environ. Health 34: 106-111.

Davidson, R.; MacKinnon, J. G. (1981) Several tests for model specification in the presence of alternative hypotheses. Econometrica 49: 781-793.

Davies, J. M. (1984a) Lung cancer mortality among workers making lead chromate and zinc chromate pigments at three English factories. Br. J. Ind. Med. 41: 158-169.

Davies, J. M. (1984b) Long term mortality study of chromate pigment workers who suffered lead poisoning. Br. J. Ind. Med. 41: 170-178.

Davis, J. M.; Svendsgaard, D. J. (1987) Lead and child development. Nature (London) 329: 297-300.

Davis, J. M.; Svendsgaard, D. J. (1990) Nerve conduction velocity and lead: a critical review and meta-analysis. In: Johnson, B. L.; Anger, W. K.; Durao, A.; Xintaras, C., eds. Advances in neurobehavioral toxicology: applications in environmental and occupational health: [selected papers presented at the third international symposium on neurobehavioral and occupational health]; December 1988; Washington, DC. Chelsea, MI: Lewis Publishers, Inc.; pp. 353-376.

Davis, J. M. (1990) Risk assessment of the developmental neurotoxicity of lead. Neurotoxicology 11: 285-292.

Davis, D. W.; Chang, F.; Burns, B.; Robinson, J.; Dossett, D. (2004) Lead exposure and attention regulation in children living in poverty. Dev. Med. Child Neurol. 46: 825-831.

De Burbure, C.; Buchet, J. P.; Bernard, A.; Leroyer, A.; Nisse, C.; Haguenoer, J.-M.; Bergamaschi, E.; Mutti, A. (2003) Biomarkers of renal effects in children and adults with low environmental exposure to heavy metals. J. Toxicol. Environ. Health Part A 66: 783-798.

DeCastro, F. J.; Medley, J. (1997) Lead in bone and hypertension [letter]. Matern. Child Health J. 1: 199-200.

De Kort, W. L. A. M.; Verschoor, M. A.; Wibowo, A. A. E.; van Hemmen, J. J. (1987) Occupational exposure to lead and blood pressure: a study in 105 workers. Am. J. Ind. Med. 11: 145-156.

Delves, H. T.; Campbell, M. J. (1988) Measurements of total lead concentrations and of lead isotope ratios in whole blood by use of inductively coupled plasma source mass spectrometry. J. Anal. At. Spectrom. 3: 343-348.

Den Hond, E.; Nawrot, T.; Staessen, J. A. (2002) The relationship between blood pressure and blood lead in NHANES III. J. Hum. Hypertens. 16: 563-568.

Denno, D. (1990) Biology and violence. From birth to adulthood. New York, NY: Cambridge University Press.

Despres, C.; Beuter, A.; Richer, F.; Poitras, K.; Veilleux, A.; Ayotte, P.; Dewailly, E.; Saint-Amour, D.; Muckle, G. (2005) Neuromotor functions in Inuit preschool children exposed to Pb, PCBs, and Hg. Neurotoxicol. Teratol. 27: 245-257.

DiPietro, E. S.; Philips, D. L.; Paschla, D. C.; Neese, J. W. (1989) Determination of trace elements in human hair. Biol. Trace Elem. Res. 22: 83-100.

Diamond, G. L. (1988) Biological monitoring of urine for exposure to toxic metals. In: Clarkson, T. W.; Nordberg, G.; Sager, P., eds. Scientific basis and practical applications of biological monitoring of toxic metals. New York, NY: Plenum Press; pp. 515-529.

Diamond, G. L. (1992) Review of default value for lead plasma-to-urine transfer coefficient (TPLUR) in the U.S. EPA uptake/biokinetic model. Syracuse, NY: Syracuse Research Corporation. Prepared for Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency.

Dietrich, K. N. (1993) [Untitled letter concerning reporting practices of the international prospective studies of lead and child development]. Arch. Environ. Health 48: 125.

Dietrich, K. N. (1995) A higher level of analysis: Bellinger's, interpreting the literature on lead and child development. Neurotoxicol. Teratol. 17: 223-225.

Dietrich, K. N.; Krafft, K. M.; Bier, M.; Succop, P. A.; Berger, O.; Bornschein, R. L. (1986) Early effects of fetal lead exposure: neurobehavioral findings at 6 months. Int. J. Biosoc. Res. 8: 151-168.

Dietrich, K. N.; Krafft, K. M.; Shukla, R.; Bornschein, R. L.; Succop, P. A. (1987a) The neurobehavioral effects of early lead exposure. In: Schroeder, S. R., ed. Toxic substances and mental retardation: neurobehavioral toxicology and teratology. Washington, DC: American Association on Mental Deficiency; pp. 71-95. (Begab, M. J., ed. Monographs of the American Association on Mental Deficiency: no. 8).

Dietrich, K. N.; Krafft, K. M.; Bornschein, R. L.; Hammond, P. B.; Berger, O.; Succop, P. A.; Bier, M. (1987b) Low-level fetal lead exposure effect on neurobehavioral development in early infancy. Pediatrics 80: 721-730.

Dietrich, K. N.; Succop, P. A.; Bornschein, R. L.; Krafft, K. M.; Berger, O.; Hammond, P. B.; Buncher, C. R. (1990) Lead exposure and neurobehavioral development in later infancy. In: Conference on advances in lead research: implications for environmental health; January 1989; Research Triangle Park, NC. Environ. Health Perspect. 89: 13-19.

Dietrich, K. N.; Succop, P. A.; Berger, O. G.; Hammond, P. B.; Bornschein, R. L. (1991) Lead exposure and the cognitive development of urban preschool children: the Cincinnati lead study cohort at age 4 years. Neurotoxicol. Teratol. 13: 203-211.

Dietrich, K. N.; Succop, P. A.; Berger, O. G.; Keith, R. W. (1992) Lead exposure and the central auditory processing abilities and cognitive development of urban children: the Cincinnati lead study cohort at age 5 years. Neurotoxicol. Teratol. 14: 51-56.

Dietrich, K. N.; Berger, O. G.; Succop, P. A.; Hammond, P. B.; Bornschein, R. L. (1993a) The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry. Neurotoxicol. Teratol. 15: 37-44.

Dietrich, K. N.; Berger, O. G.; Succop, P. A. (1993b) Lead exposure and the motor developmental status of urban six-year-old children in the Cincinnati prospective study. Pediatrics 91: 301-307.

Dietrich, K. N.; Ris, M. D.; Succop, P. A.; Berger, O. G.; Bornschein, R. L. (2001) Early exposure to lead and juvenile delinquency. Neurotoxicol. Teratol. 23: 511-518.

Dietrich, K. N.; Ware, J. H.; Salganik, M.; Radcliffe, J.; Rogan, W. J.; Rhoads, G. G.; Fay, M. E.; Davoli, C. T.; Denckla, M. B.; Bornschein, R. L.; Schwarz, D.; Dockery, D. W.; Adubato, S.; Jones, R. L.; for the Treatment of Lead-Exposed Children Clinical Trial Group. (2004) Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics 114: 19-26.

Dietrich, K. N.; Eskenazi, B.; Schantz, S.; Yolton, K.; Rauh, V. A.; Johnson, C. B.; Alkon, A.; Canfield, R. L.; Pessah, I. N.; Berman, R. F. (2005) Principles and practices of neurodevelopmental assessment in children: lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. Environ. Health Perspect. 113: 1437-1446.

Dingwall-Fordyce, I.; Lane, R. E. (1963) A follow-up study of lead workers. Br. J. Ind. Med. 20: 313-315.

Diouf, A.; Garcon, G.; Thiaw, C.; Diop, Y.; Fall, M.; Ndiaye B.; Siby, T.; Hannothiaux, M. H.; Zerimech, F.; Ba, D.; Haguenoer, J. M.; Shirali, P. (2003) Environmental lead exposure and its relationship to traffic density among Senegalese children: a pilot study. Hum. Exp. Toxicol. 22: 559-564.

Discalzi, G. L.; Capellaro, F.; Bottalo, L.; Fabbro, D.; Mocellini, A. (1992) Auditory brainstem evoked potentials (BAEPS) in lead-exposed workers. Neurotoxicology 13: 207-209.

Discalzi, G.; Fabbro, D.; Meliga, F.; Mocellini, A.; Capellaro, F. (1993) Effects of occupational exposure to mercury and lead on brainstem auditory evoked potentials. Int. J. Psychophysiol. 14: 21-25.

Dolenc, P.; Staessen, J. A.; Lauwerys, R. R.; Amery, A., on behalf of the Cadmibel Study Group. (1993) Short report: low-level lead exposure does not increase the blood pressure in the general population. J. Hypertens. 11: 589-593.

Dowd, T. L.; Rosen, J. F.; Gundberg, C. M.; Gupta, R. K. (1997) The displacement of calcium from osteocalcin at submicromolar concentrations of free lead. Biochim. Biophys. Acta. 1226: 131-137.

Draisma, G.; Boer, R.; Otto, S. J.; Van der Cruijsen, I. W.; Damhuis, R. A. M.; Schroder, F. H.; de Koning, H. J. (2003) Lead times and overdetection due to prostate-specific antigen screening: estimates from the European randomized study of screening for prostate cancer. J. Natl. Cancer Inst. 95: 868-878.

Drasch, G. A.; Bohm, J.; Baur, C. (1987) Lead in human bones. Investigations on an occupationally non-exposed population in southern Bavaria (F. R. G.). I. Adults. Sci. Total Environ. 64: 303-315.

Drasch, G.; Wanghofer, E.; Roider, G. (1997) Are blood, urine, hair, and muscle valid biomonitors for the internal burden of men with the heavy metals mercury, lead and cadmium? Trace Elem. Electrolytes 14(3): 116-123.

Driscoll, R. J. (1998) Epidemiologic study of adverse reproductive outcomes among women in the U.S. Forest Service. In: Driscoll, R. J.; Reh, B. D.; Esswein, E. J.; Mattorano, D. A. Health hazard evaluation report no. 93-1035-2686, section 2. Washington, DC: U.S. Department of Agriculture, Forest Service. Available from: NTIS, Springfield, VA; PB99-152241.

Droz, P. O. (1989) Biological monitoring I: Sources of variability in human response to chemical exposure. Appl. Ind. Hyg. 4: F20-F24.

Dudek, B.; Merecz, D. (1997) Impairment of psychological functions in children environmentally exposed to lead. Int. J. Occup. Med. Environ. Health 10: 37-46.

Dundar, M. S.; Pala, M. F. (2003) Monitoring of lead, zinc, cadmium, nickel, chromium and copper in street dust samples in Adapazari, Turkey, after earthquake. Trace Elem. Electrol. 20: 104-107.

Durbin, P. W. (1992) Distribution of transuranic elements in bone. Neurotoxicology 13: 821-824.

Dursun, N.; Tutus, A. (1999) Chronic occupational lead exposure and thyroid function. J. Trace Elem. Exp. Med. 12: 45-49.

Duydu, Y.; Suzen, H. S.; Aydin, A.; Cander, O.; Uysal, H.; Isimer, A.; Vural, N. (2001) Correlation between lead exposure indicators and sister chromatid exchange (SCE) frequencies in lymphocytes from inorganic lead exposed workers. Arch. Environ. Contam. Toxicol. 41: 241-246.

Duydu, Y.; Dur, A.; Suzen, H. S. (2005) Evaluation of increased proportion of cells with unusually high sister chromatid exchange counts as a cytogenetic biomarker for lead exposure. Biol. Trace Elem. Res. 104: 121 129.

Dye, B. A.; Hirsch, R.; Brody, D. J. (2002) The relationship between blood lead levels and periodontal bone loss in the United States, 1988-1994. Environ. Health Perspect. 110: 997-1002.

EL-Safty, I. A.; Afifi, A. M.; Shouman, A. E.; EL-Sady, A. K. R. (2004) Effects of smoking and lead exposure on proximal tubular integrity among Egyptian industrial workers. Arch. Med. Res. 35: 59-65.

Elwood, P. C.; Davey-Smith, G.; Oldham, P. D.; Toothill, C. (1988a) Two Welsh surveys of blood lead and blood pressure. In: Victery, W., ed. Symposium on lead-blood pressure relationships; April 1987; Chapel Hill, NC. Environ. Health Perspect. 78: 119-121.

Elwood, P. C.; Yarnell, J. W. G.; Oldham, P. D.; Catford, J. C.; Nutbeam, D.; Davey-Smith, G.; Toothill, C. (1988b) Blood pressure and blood lead in surveys in Wales. Am. J. Epidemiol. 127: 942-945.

ESA Biosciences, Inc. (1998) Lead care(R) childhood blood lead testing. Chelmsford, MA: ESA Biosciences, Inc.

Egeland, G. M.; Burkhart, G. A.; Schnorr, T. M.; Hornung, R. W.; Fajen, J. M.; Lee, S. T. (1992) Effects of exposure to carbon disulphide on low density lipoprotein cholesterol concentration and diastolic blood pressure. Br. J. Ind. Med. 49: 287-293.

Ehrlich, R.; Robins, T.; Jordaan, E.; Miller, S.; Mbuli, S.; Selby, P.; Wynchank, S.; Cantrell, A.; De Broe, M.; D'Haese, P.; Todd, A.; Landrigan, P. (1998) Lead absorption and renal dysfunction in a South African battery factory. Occup. Environ. Med. 55: 453-460.

Eller, P. M., ed. (1984) NIOSH manual of analytical methods. 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health; publication no. DHHS (NIOSH) 84-100.

Elmarsafawy, S. F.; Tsaih, S.-W.; Korrick, S.; Dickey, J. H.; Sparrow, D.; Aro, A.; Hu, H. (2002) Occupational determinants of bone and blood lead levels in middle aged and elderly men from the general community: the Normative Aging Study. Am. J. Ind. Med. 42: 38-49.

Emmerson, B. T. (1965) The renal excretion of urate in chronic lead nephropathy. Australas. Ann. Med. 14: 295-303.

Emmerson, B. T.; Ravenscroft, P. J. (1975) Abnormal renal urate homeostasis in systemic disorders. Nephron 14: 62-80.

Emory, E.; Pattillo, R.; Archibold, E.; Bayorh, M.; Sung, F. (1999) Neurobehavioral effects of low-level lead exposure in human neonates. Am. J. Obstet. Gynecol. 181: S2-S11.

Endo, G.; Horiguchi, S.; Kiyota, I. (1990) Urinary N-acetyl-"beta"-D-glucosaminidase activity in lead-exposed workers. J. Appl. Toxicol. 10: 235-238.

Endo, G.; Konishi, Y.; Kiyota, A.; Horiguchi, S. (1993) Urinary "alpha"1 microglobulin in lead workers. Bull. Environ. Contam. Toxicol. 50: 744-749.

Englyst, V.; Lundstrom, N. G.; Gerhardsson, L.; Rylander, L.; Nordberg, G. (2001) Lung cancer risks among lead smelter workers also exposed to arsenic. Sci. Total Environ. 273: 77-82.

Erfurth, E. M.; Gerhardsson, L.; Nilsson, A.; Rylander, L.; Schutz, A.; Skerfving, S.; Borjesson, J. (2001) Effects of lead on the endocrine system in lead smelter workers. Arch. Environ. Health 56: 449-455.

Ericson, J. E.; Smith, D. R.; Flegal, A. R. (1991) Skeletal concentrations of lead, cadmium, zinc, and silver in ancient North American Pecos indians. Environ. Health Perspect. 93: 217-223.

Erkkila, J.; Armstrong, R.; Riihimaki, V.; Chettle, D. R.; Paakkari, A.; Scott, M.; Somervaille, L.; Stark, J.; Kock, B.; Aitio, A. (1992) In vivo measurements of lead in bone at four anatomical sites: long term occcupational and consequent edogenous exposure. Br. J. Ind. Med. 49: 631-644.

Ernhart, C. B. (1993) Declining blood lead levels and cognitive change in children [letter]. JAMA J. Am. Med. Assoc. 270: 827-828.

Ernhart, C. B. (1994) [Untitled letter concerning errors in "Effect of low-level body burdens of lead on the mental development of children: limitations of meta-analysis in a review of longitudinal data"]. Arch. Environ. Health 49: 77-78.

Ernhart, C. B. (1995) Inconsistencies in the lead-effects literature exist and cannot be explained by "effect modification." Neurotoxicol. Teratol. 17: 227-233.

Ernhart, C. B. (1995) Environmental lead and children's intelligence: Cleveland study hypothesis was not confirmed [letter]. Br. Med. J. 310: 397.

Ernhart, C. B.; Greene, T. (1990) Low-level lead exposure in the prenatal and early preschool periods: language development. Arch. Environ. Health 45: 342-354.

Ernhart, C. B.; Landa, B.; Wolf, A. W. (1985) Subclinical lead level and developmental deficit; reanalyses of data. J. Learning Disabilities 18: 475-479.

Ernhart, C. B.; Wolf, A. W.; Kennard, M. J.; Erhard, P.; Filipovich, H. F.; Sokol, R. J. (1986) Intrauterine exposure to low levels of lead: the status of the neonate. Arch. Environ. Health 41: 287-291.

Ernhart, C. B.; Morrow-Tlucak, M.; Marler, M. R.; Wolf, A. W. (1987) Low level lead exposure in the prenatal and early preschool periods: early preschool development. Neurotoxicol. Teratol. 9: 259-270.

Ernhart, C. B.; Morrow-Tlucak, M.; Wolf, A. W. (1988) Low level lead exposure and intelligence in the preschool years. Sci. Total Environ. 71: 453-459.

Ernhart, C. B.; Morrow-Tlucak, M.; Wolf, A. W.; Super, D.; Drotar, D. (1989) Low level lead exposure in the prenatal and early preschool periods: intelligence prior to school entry. Neurotoxicol. Teratol. 11: 161-170.

Espy, K. A. (1997) The Shape School: assessing executive function in preschool children. Dev. Neuropsychol. 13: 495-499.

Esteban, E.; Rubin, C. H.; Jones, R. L.; Noonan, G. (1999) Hair and blood substrates for screening children for lead poisoning. Arch. Environ. Health 54: 436-440.

Ettinger, A. S.; Tellez-Rojo, M. M.; Amarasiriwardena, C.; Schwartz, J.; Hu, H.; Hernandez-Avila, M. (2003) Influence of maternal bone lead burden and calcium intake on lead in breast milk. Am. J. Epidemiol. 157(suppl. 11): S105.

Ettinger, A. s.; Tellez-Rojo, M. M.; Amarasiriwardena, C.; Gonzalez-Cossio, T.; Peterson, K. E.; Aro, A.; Hu, H.; Hernandez-Avila, M. (2004) Levels of lead in breast milk and their relation to maternal blood and bone lead levels at one month postpartum. Environ. Health Perspect. 112: 926-931.

Ewers, U.; Stiller-Winkler, R.; Idel, H. (1982) Serum immunoglobulin, complement C3, and salivary IgA levels in lead workers. Environ. Res. 29: 351-357.

Factor-Litvak, P.; Graziano, J. H.; Kline, J. K.; Popovac, D.; Mehmeti, A.; Ahmedi, G.; Shrout, P.; Murphy, M. J.; Gashi, E.; Haxhiu, R.; Rajovic, L.; Nenezic, D. U.; Stein, Z. A. (1991) A prospective study of birthweight and length of gestation in a population surrounding a lead smelter in Kosovo, Yugoslavia. Int. J. Epidemiol. 20: 722-728.

Factor-Litvak, P.; Stein, Z.; Graziano, J. (1993) Increased risk of proteinuria among a cohort of lead-exposed pregnant women. Environ. Health Perspect. 101: 418-421.

Factor-Litvak, P.; Graziano, J.; Kline, J. K. (1996) Letter to editor [re: Al-Saleh, I.; Khalil, M. A.; Taylor, A. (1995) Lead, erythrocyte protoporphyrin, and hematological parameters in normal maternal and umbilical cord blood from subjects of the Riyadh region, Saudi Arabia. Arch. Environ. Health 50: 66-73]. Arch. Environ. Health 51: 468-469.

Factor-Litvak, P.; Kline, J. K.; Popovac, D.; Hadzialjevic, S.; Lekic, V.; Preteni-Rexhepi, E.; Capuni-Paracka, S.; Slavkovich, V.; Graziano, J. (1996) Blood lead and blood pressure in young children. Epidemiology 7: 633-637.

Factor-Litvak, P.; Slavkovich, V.; Liu, X.; Popovac, D.; Preteni, E.; Capuni-Paracka, S.; Hadzialjevic, S.; Lekic, V.; LoIacono, N.; Kline, J.; Graziano, J. (1998) Hyperproduction of erythropoietin in nonanemic lead-exposed children. Environ. Health Perspect. 106: 361-364.

Factor-Litvak, P.; Wasserman, G.; Kline, J. K.; Graziano, J. (1999) The Yugoslavia prospective study of environmental lead exposure. Environ. Health Perspect. 107: 9-15.

Falcon, M.; Vinas, P.; Osuna, E.; Luna, A. (2002) Environmental exposures to lead and cadmium measured in human placenta. Arch. Environ. Health 57: 598-602.

Falcon, M.; Vinas, P.; Luna, A. (2003) Placental lead and outcome of pregnancy. Toxicology 185: 59-66.

Fanning, D. (1988) A mortality study of lead workers, 1926-1985. Arch. Environ. Health 43: 247-251.

Farant, J.-P.; Wigfield, D. C. (1987) Interaction of divalent metal ions with normal and lead-inhibited human erythrocytic porphobilinogen synthase in vitro. Toxicol. Appl. Pharmacol. 89: 9-18.

Farias, P.; Borja-Aburto, V. H.; Rios, C.; Hertz-Picciotto, I.; Rojas-Lopez, M.; Chavez-Ayala, R. (1996) Blood lead levels in pregnant women of high and low socioeconomic status in Mexico City. Environ. Health Perspect. 104: 1070-1074.

Farias, P.; Hu, H.; Rubenstein, E.; Meneses-Gonzalez, F.; Fishbein, E.; Palazuelos, E.; Aro, A.; Hernandez-Avila, M. (1998) Determinants of bone and blood lead levels among teenagers living in urban areas with high lead exposure. Environ. Health Perspect. 106: 733-737.

Farrow, S. (1994) Falling sperm quality: fact of fiction? Br. Med. J. 309: 1-2.

Fels, L. M.; Herbort, C.; Pergande, M.; Jung, K.; Hotter, G.; Rosello, J.; Gelpi, E.; Mutti, A.; De Broe, M.; Stolte, H. (1994) Nephron target sites in chronic exposure to lead. Nephrol. Dial. Transplant. 9: 1740-1746.

Fels, L. M.; Wunsch, M.; Baranowski, J.; Norska-Borowka, I.; Price, R. G.; Taylor, S. A.; Patel, S.; De Broe, M.; Elsevier, M. M.; Lauwerys, R.; Roels, H.; Bernard, A.; Mutti, A.; Gelpi, E.; Rosello, J.; Stolte, H. (1998) Adverse effects of chronic low level lead exposure on kidney function--a risk group study in children. Nephrol. Dial. Transplant 13: 2248-2256.

Fergusson, D. M.; Horwood, L. J. (1993) The effects of lead levels on the growth of word recognition in middle childhood. Int. J. Epidemiol. 22: 891-897.

Fergusson, D. M.; Fergusson, J. E.; Horwood, L. J.; Kinzett, N. G. (1988a) A longitudinal study of dentine lead levels, intelligence, school performance and behaviour. Part II. Dentine lead and cognitive ability. J. Child Psychol. Psychiatry Allied Discip. 29: 793-809.

Fergusson, D. M.; Fergusson, J. E.; Horwood, L. J.; Kinzett, N. G. (1988b) A longitudinal study of dentine lead levels, intelligence, school performance and behaviour. Part III. Dentine lead levels and attention/activity. J. Child Psychol. Psychiatry Allied Discip. 29: 811-824.

Fergusson, D. M.; Fergusson, J. E.; Horwood, L. J.; Kinzett, N. G. (1988) A longitudinal study of dentine lead levels, intelligence, school performance and behaviour. Part I. Dentine lead levels and exposure to environmental risk factors. J. Child Psychol. Psychiatry Allied Discip. 29: 781-792.

Fergusson, J. E.; Kinzett, N. G.; Fergusson, D. M.; Horwood, L. J. (1989) A longitudinal study of dentin lead levels and intelligence school performance and behavior the measurement of dentin lead. Sci. Total Environ. 80: 229-242.

Fergusson, D. M.; Horwood, L. J.; Lynskey, M. T. (1993) Early dentine lead levels and subsequent cognitive and behavioural development. J. Child Psychol. Psych. Allied Disciplines 34: 215-227.

Fergusson, D. M.; Horwood, L. J.; Lynskey, M. T. (1997) Early dentine lead levels and educational outcomes at 18 years. J. Child Psychol. Psychiatry 38: 471-478.

Fewtrell, L. J.; Pruss-Ustun, A.; Landrigan, P.; Ayuso-Mateos, J. L. (2004) Estimating the global burden of disease of mild mental retardation and cardiovascular diseases from environmental lead exposure. Environ. Res. 94: 120-133.

Fisch, H.; Andrews, H.; Hendricks, J.; Goluboff, E. T.; Olson, J. H.; Olsson, C. A. (1997) The relationship of sperm counts to birth rates: a population based study. J. Urol. 157: 840-843.

Fischbein, A.; Alvares, A. P.; Anderson, K. E.; Sassa, S.; Kappas, A. (1977) Lead intoxication among demolition workers: the effect of lead on the hepatic cytochrome P-450 systems in humans. J. Toxicol. Environ. Health 3: 431-437.

Fischbein, A.; Tsang, P.; Luo, J.-C. J.; Roboz, J. P.; Jiang, J. D.; Bekesi, J. G. (1993) Phenotypic aberrations of the CD3+ and CD4+ cells and functional impairments of lymphocytes at low-level occupational exposure to lead. Clin. Immunol. Immunopathol. 66: 163-168.

Flegal, A. R.; Smith, D. R. (1992) Lead levels in preindustrial humans [letter]. N. Engl. J. Med. 326: 1293-1294.

Flegal, A. R.; Smith, D. R. (1995) Measurements of environmental lead contamination and human exposure. Rev. Environ. Contam. Toxicol. 143: 1-45.

Fleming, D. E. B.; Boulay, D.; Richard, N. S.; Robin, J.-P.; Gordon, C. L.; Webber, C. E.; Chettle, D. R. (1997) Accumulated body burden and endogenous release of lead in employees of a lead smelter. Environ. Health Perspect. 105: 224-233.

Fleming, D. E. B.; Chettle, D. R.; Wetmur, J. G.; Desnick, R. J.; Robin, J.-P.; Boulay, D.; Richard, N. S.; Gordon, C. L.; Webber, C. E. (1998) Effect of the delta-aminolevulinate dehydratase polymorphism on the accumulation of lead in bone and blood in lead smelter workers. Environ. Res. 77: 49-61.

Flood, P. R.; Schmidt, P. F.; Wesenberg, G. R.; Gadeholt, H. (1988) The distribution of lead in human hemopoietic tissue and spongy bone after lead poisoning and Ca-EDTA chelation therapy: observations made by atomic absorption spectroscopy, laser microbeam mass analysis and electron microbeam X-ray analysis. Arch. Toxicol. 62: 295-300.

Forbes, G. B.; Bruining, G. B. (1976) Urinary creatinine excretion and lean body mass. Am. J. Clin. Nutr. 29: 1359-1366.

Forni, A.; Cambiaghi, G.; Secchi, G. C. (1976) Initial occupational exposure to lead: chromosome and biochemical findings. Arch. Environ. Health 31: 73-78.

Forni, A.; Sciame, A.; Bertazzi, P. A.; Alessio, L. (1980) Chromosome and biochemical studies in women occupationally exposed to lead. Arch. Environ. Health 35: 139-146.

Fosse, G.; Wesenberg, G. B. R.; Tvinnereim, H. M., Eide, R.; Kristoffersen, O.; Nag, O. H.; Wierzbicka, M.; Banoczy, J.; De Oliveira, A. A.; Srisopak, C.; Zamudio, A. (1995) Lead in deciduous teeth from larger cities of some countries. Int. J. Environ. Stud. 47: 203-210.

Foster, W. G. (1992) Reproductive toxicity of chronic lead exposure in the female cynomolgus monkey. Reprod. Toxicol. 6: 123-131.

Fracasso, M. E.; Perbellini, L.; Solda, S.; Talamini, G.; Franceschetti, P. (2002) Lead induced DNA strand breaks in lymphocytes of exposed workers: role of reactive oxygen species and protein kinase C. Mutat. Res. 515: 159-169.

Frank, R. M.; Sargentini-Maier, M. L.; Leroy, M. J. F.; Turlot, J. C. (1988) Age-related lead increase in human permanent teeth demonstrated by energy dispersive X-ray fluorescence. J. Trace Elem. Electrolytes Health Dis. 2: 175-179.

Franklin, C. A.; Inskip, M. J.; Baccanale, C. L.; Edwards, C. M.; Manton, W. I.; Edwards, E.; O'Flaherty, E. J. (1997) Use of sequentially administered stable lead isotopes to investigate changes in blood lead during pregnancy in a nonhuman primate (Macaca fascicularis). Fundam. Appl. Toxicol. 39: 109-119.

Franks, P. A.; Laughlin, N. K.; Dierschke, D. J.; Bowman, R. E.; Meller, P. A. (1989) Effects of lead on luteal function in rhesus monkeys. Biol. Reprod. 41: 1055-1062.

Froom, P.; Kristal-Boneh, E.; Benbassat, J.; Ashkanazi, R.; Ribak, J. (1998) Predictive value of determinations of zinc protoporphyrin for increased blood lead concentrations. Clin. Chem. 44(6): 1283-1288.

Froom, P.; Kristal-Boneh, E.; Benbassat, J., Ashkanazi, R.; Ribak, J. (1999) Lead exposure in battery-factory workers is not associated with anemia. J. Occup. Environ. Med. 41: 120-123.

Fu, H.; Boffetta, P. (1995) Cancer and occupational exposure to inorganic lead compounds: a meta-analysis of published data. Occup. Environ. Med. 52: 73-81.

Fulton, M.; Raab, G.; Thomson, G.; Laxen, D.; Hunter, R.; Hepburn, W. (1987) Influence of blood lead on the ability and attainment of children in Edinburgh. Lancet (8544): 1221-1226.

Furman, A.; Laleli, M. (2001) Maternal and umbilical cord blood lead levels: an Istanbul study. Arch. Environ. Health 56: 26-28.

Galeas, T.; Tselepatiotis, E.; Katsanos, D.; Lappas, C. (1996) Chronic renal failure, caused by lead poisoning, among traditional-spirit drinkers in Greece. Nephrol. Dial. Transplant. 11: A127.

Garcon, G.; Leleu, B.; Zerimech, F.; Marez, T.; Haguenoer, J.-M.; Furon, D.; Shirali, P. (2004) Biologic markers of oxidative stress and nephrotoxicity as studied in biomonitoring and adverse effects of occupational exposure to lead and cadmium. J. Occup. Environ. Med. 46: 1180-1186.

Gardner, J. M.; Walker, S. P.; Chang, S. M.; Vutchkov, M.; Lalor, G. C. (1998) Undernutrition and elevated blood lead levels: effects on psychomotor development among Jamaican children. Public Health Nutr. 1: 177-179.

Garman, S.; Anderson, H. A.; Moen, T. (2000) Occupational and adult lead exposure in Wisconsin. Wis. Med. J. 99: 25-29.

Garrido Latorre, F.; Hernandez-Avila, M.; Orozco, J. T.; Medina, C. A. A.; Aro, A.; Palazuelos, E.; Hu, H. (2003) Relationship of blood and bone lead to menopause and bone mineral density among middle-age women in Mexico City. Environ. Health Perspect. 111: 631-636.

Gartside, P. S. (1988) The relationship of blood lead levels and blood pressure in NHANES II: additional calculations. In: Victery, W., ed. Symposium on lead-blood pressure relationships; April 1987; Chapel Hill, NC. Environ. Health Perspect. 78: 31-34.

Gemmel, A.; Tavares, M.; Alperin, S.; Soncini, J.; Daniel, D.; Dunn, J.; Crawford, S.; Braveman, N.; Clarkson, T. W.; McKinlay, S.; Bellinger, D. C. (2002) Blood lead level and dental caries in school-age children. Environ. Health Perspect. 110: A625-A630.

Gennart, J. P.; Bernard, A.; Lauwerys, R. (1992) Assessment of thyroid, testes, kidney and autonomic nervous system function in lead-exposed workers. Int. Arch. Occup. Environ. Health 64: 49-57.

Gerhard, I.; Waibel, S.; Daniel, V.; Runnebaum, B. (1998) Impact of heavy metals on hormonal and immunological factors in women with repeated miscarriages. Hum. Reprod. Update 4: 301-309.

Gerhardsson, L.; Brune, D.; Nordberg, G. F.; Wester, P. O. (1986) Distribution of cadmium, lead and zinc in lung, liver and kidney in long-term exposed smelter workers. Sci. Total Environ. 50: 65-85.

Gerhardsson, L.; Chettle, D. R.; Englyst, V.; Nordberg, G. F.; Nyhlin, H.; Scott, M. C.; Todd, A. C.; Vesterberg, O. (1992) Kidney effects in long term exposed lead smelter workers. Br. J. Ind. Med. 49: 186-192.

Gerhardsson, L.; Attewell, R.; Chettle, D. R.; Englyst, V.; Lundstrom, N.-G.; Nordberg, G. F.; Nyhlin, H.; Scott, M. C.; Todd, A. C. (1993) In vivo measurements of lead in bone in long-term exposed lead smelter workers. Arch. Environ. Health 48: 147-156.

Gerhardsson, L.; Hagmar, L.; Rylander, L.; Skerfving, S. (1995a) Mortality and cancer incidence among secondary lead smelter workers. Occup. Environ. Med. 52: 667-672.

Gerhardsson, L.; Englyst, V.; Lundstrom, N.G.; Nordberg, G.; Sandberg, S.; Steinvall, F. (1995b) Lead in tissues of deceased lead smelter worker. J. Trace Elem. Med. Biol. 9: 136-143.

Gerr, F.; Letz, R.; Stokes, L.; Chettle, D.; McNeill, F.; Kaye, W. (2002) Association between bone lead concentration and blood pressure among young adults. Am. J. Ind. Med. 42: 98-106.

Gershanik, J. J.; Brooks, G. G.; Little, J. A. (1974) Blood lead values in pregnant women and their offspring. Am. J. Obstet. Gynecol. 119: 508-511.

Gidlow, D. A. (2004) Lead toxicity. Occup. Med. (London) 54: 76-81.

Gil, F.; Perez, M. L.; Facio, A.; Villanueva, E.; Tojo, R.; Gil, A. (1994) Dental lead levels in the Galacian population, Spain. Sci. Total Environ. 156: 145-150.

Glenn, B. S.; Stewart, W. F.; Schwartz, B. S.; Bressler, J. (2001) Relation of alleles of the sodium-potassium adenosine triphosphatase alpha2 gene with blood pressure and lead exposure. Am. J. Epidemiol. 153: 537 545.

Glenn, B. S.; Stewart, W. F.; Links, J. M.; Todd, A. C.; Schwartz, B. S. (2003) The longitudinal association of lead with blood pressure. Epidemiology 14: 30-36.

Glickman, L.; Valciukas, J. A.; Lilis, R.; Weisman, I. (1984) Occupational lead exposure: effects on saccadic eye movements. Int. Arch. Occup. Environ. Health 54: 115-125.

Gomaa, A.; Hu, H.; Bellinger, D.; Schwartz, J.; Tsaih, S.-W.; Gonzalez-Cossio, T.; Schnaas, L.; Peterson, K.; Aro, A.; Hernandez-Avila, M. (2002) Maternal bone lead as an independent risk factor for fetal neurotoxicity: a prospective study. Pediatrics 110: 110-118.

Gompertz, D.; Chettle, D. R.; Fletcher, J. G.; Mason, H.; Perkins, J.; Scott, M. C.; Smith, N. J.; Topping, M. D.; Blindt, M. (1983) Renal dysfunction in cadmium smelters: relation to in vivo liver and kidney cadmium concentrations. Lancet (8335): 1185-1187.

Gonick, H. C.; Behari, J. R. (2002) Is lead exposure the principal cause of essential hypertension? Med. Hypotheses 59: 239-246.

Gonick, H. C.; Cohen, A. H.; Ren, Q.; Saldanha, L. F.; Khalil-Manesh, F.; Anzalone, J.; Sun, Y. Y. (1996) Effect of 2,3-dimercaptosuccinic acid on nephrosclerosis in the Dahl rat. I. Role of reactive oxygen species. Kidney Int. 50: 1572-1581.

Gonzalez-Cossio, T.; Peterson, K. E.; Sanin, L.-H.; Fishbein, E.; Palazuelos, E.; Aro, A.; Hernandez-Avila, M.; Hu, H. (1997) Decrease in birth weight in relation to maternal bone-lead burden. Pediatrics 100: 856-862.

Gordon, C. L.; Chettle, D. R.; Webber, C. E. (1993) An improved instrument for the in vivo detection of lead in bone. Br. J. Ind. Med. 50: 637-641.

Governa, M.; Valentino, M.; Visona, I. (1987) In vitro impairment of human granulocyte functions by lead. Arch. Toxicol. 59: 421-425.

Govoni, S.; Battaini, F.; Fernicola, C.; Castelletti, L.; Trabucchi, M. (1987) Plasma prolactin concentrations in lead exposed workers. J. Environ. PathoI. Toxicol. Oncol. 7: 13-15.

Goyer, R. A. (1990) Lead toxicity: from overt to subclinical to subtle health effects. Environ. Health Perspect. 86: 177-181.

Goyer, R. A.; Epstein, S.; Bhattacharyya, M.; Korach, K. S.; Pounds, J. (1994) Environmental risk factors for osteoporosis. Environ. Health Perspect. 102: 390-394.

Grandjean, P. (1979) Occupational lead exposure in Denmark: screening with the haematofluorometer. Br. J. Ind. Med. 36: 52-58.

Grandjean, P.; Arnvig, E.; Beckmann, J. (1978) Psychological dysfunctions in lead-exposed workers: relation to biological parameters of exposure. Scand. J. Work Environ. Health 4: 295-303.

Grandjean, P.; Wulf, H. C.; Niebuhr, E. (1983) Sister chromatid exchange in response to variations in occupational lead exposure. Environ. Res. 32: 199-204.

Grandjean, P.; Hollnagel, H.; Hedegaard, L.; Christensen, J. M.; Larsen, S. (1989) Blood lead-blood pressure relations: alcohol intake and hemoglobin as confounders. Am. J. Epidemiol. 129: 732-739.

Graves, A. B.; Van Duijn, C. M.; Chandra, V.; Fratiglioni, L.; Heyman, A.; Jorm, A. F.; Kokmen, E.; Kondo, K.; Mortimer, J. A.; Rocca, W. A.; Shalat, S. L.; Soininen, H.; Hofman, A. (1991) Occupational exposures to solvents and lead as risk factors for Alzheimer's disease: a collaborative re-analysis of case-control studies. Int. J. Epidemiol. 20(suppl. 2): S58-S61.

Graziano, J. H. (1994) Validity of lead exposure markers in diagnosis and surveillance. Clin. Chem. 40: 1387-1390.

Graziano, J. H.; Popovac, D.; Factor-Litvak, P.; Shrout, P.; Kline, J.; Murphy, M. J.; Zhao, Y.-H.; Mehmeti, A.; Ahmedi, X.; Rajovic, B.; Zvicer, Z.; Nenezic, D. U.; Lolacono, N. J.; Stein, Z. (1990) Determinants of elevated blood lead during pregnancy in a population surrounding a lead smelter in Kosovo, Yugoslavia. In: Conference on advances in lead research: implications for environmental health; January 1989; Research Triangle Park, NC. Environ. Health Perspect. 89: 95-100.

Graziano, J.; Slavkovich, V.; Liu X., Factor-Litvak, P.; Todd, A. (2004) A prospective study of prenatal and childhood lead exposure and erythropoietin production. J. Occup. Environ. Med. 46: 924-929.

Green, S.; Bradley, D. A.; Palethorpe, J. E.; Mearman, D.; Chettle, D. R.; Lewis, A. D.; Mountford, P. J.; Morgan, W. D. (1993) An enhanced sensitivity K-shell x-ray fluorescence technique for tibial lead determination. Phys. Med. Biol. 38: 389-396.

Griffin, T. B.; Coulston, F.; Wills, H.; Russell, J. C.; Knelson, J. H. (1975) Clinical studies on men continuously exposed to airborne particulate lead. In: Griffin, T. B.; Knelson, J. H., eds. Lead. Stuttgart, Federal Republic of Germany: Georg Thieme Publishers; pp. 221-240. (Coulston, F.; Korte, F., eds. Environmental quality and safety: supplement v. 2).

Groth-Marnat, G. (2003). Handbook of Psychological Assessment. 4th ed. Hoboken, NJ, John Wiley & Sons.

Guerra-Tamayo, J. L.; Hernandez-Cadena, L.; Tellez-Rojo, M. M.; Mercado-Garcia, A. del S.; Solano-Gonzalez, M.; Hernandez-Avila, M.; Hu, H. L. (2003) Exposicion al plomo y su relacion con el tiempo requerido para embarazo [Lead exposure and time to pregnancy]. Salud Publica Mex. 45(suppl. 2): S189-S195.

Guidetti, D.; Bondavalli, M.; Sabadini, R.; Marcello, N.; Vinceti, M.; Cavalletti, S.; Marbini, A.; Gemignani, F.; Colombo, A.; Ferriari, A.; Vivoli, G.; Solime, F. (1996) Epidemiological survey of amyotrophic lateral sclerosis in the province of Reggio Emilia, Italy: influence of environmental exposure to lead. Neuroepidemiology 15: 301-312.

Gulson, B. L. (1996) Tooth analyses of sources and intensity of lead exposure in children. Environ. Health Perspect. 104: 306-312.

Gulson, B.; Wilson, D. (1994) History of lead exposure in children revealed from isotopic analyses of teeth. Arch. Environ. Health 49: 279-283.

Gulson, B. L.; Mahaffey, K. R.; Mizon, K. J.; Korsch, M. J.; Cameron, M. A.; Vimpani, G. (1995) Contribution of tissue lead to blood lead in adult female subjects based on stable lead isotope methods. J. Lab. Clin. Med. 125: 703-712.

Gulson, B. L.; Jameson, C. W.; Mahaffey, K. R.; Mizon, K. J.; Korsch, M. J.; Vimpani, G. (1997) Pregnancy increases mobilization of lead from maternal skeleton. J. Lab. Clin. Med. 130: 51-62.

Gulson, B. L.; Mahaffey, K. R.; Jameson, C. W.; Mizon, K. J.; Korsch, M. J.; Cameron, M. A.; Eisman, J. A. (1998a) Mobilization of lead from the skeleton during the postnatal period is larger than during pregnancy. J. Lab. Clin. Med. 131: 324-329.

Gulson, B. L.; Jameson, C. W.; Mahaffey, K. R.; Mizon, K. J.; Patison, N.; Law, A. J.; Korsch, M. J.; Salter, M. A. (1998b) Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. Environ. Health Perspect. 106: 667-674.

Gulson, B. L.; Gray, B.; Mahaffey, K. R.; Jameson, C. W.; Mizon, K. J.; Patison, N.; Korsch, M. J. (1999a) Comparison of the rates of exchange of lead in the blood of newly born infants and their mothers with lead from their current environment. J. Lab. Clin. Med. 133: 171-178.

Gulson, B. L.; Mahaffey, K. R.; Jameson, C. W.; Patison, N.; Law, A. J.; Mizon, K. J.; Korsch, M. J.; Pederson, D. (1999b) Impact of diet on lead in blood and urine in female adults and relevance to mobilization of lead from bone stores. Environ. Health Perspect. 107: 257-263.

Gulson, B. L.; Mizon, K. J.; Palmer, J. M.; Korsch, M. J.; Donnelly, J. B. (2000) Urinary excretion of lead during pregnancy and postpartum. Sci. Total Environ. 262: 49-55.

Gulson, B. L.; Mizon, K. J.; Palmer, J. M.; Korsch, M. J.; Taylor, A. J. (2001) Contribution of lead from calcium supplements to blood lead. Environ. Health Perspect. 109: 283-288.

Gulson, B.; Mizon, K.; Smith, H.; Eisman, J.; Palmer, J.; Korsch, M.; Donnelly, J.; Waite, K. (2002) Skeletal lead release during bone resorption: effect of bisphosphonate treatment in a pilot study. Environ. Health Perspect. 110: 1017-1023.

Gulson, B. L.; Mizon, K. J.; Korsch, M. J.; Palmer, J. M.; Donnelly, J. B. (2003) Mobilization of lead from human bone tissue during pregnancy and lactation--a summary of long-term research. Sci. Total Environ. 303: 79-104.

Gulson, B. L.; Mizon, K. J.; Palmer, J. M.; Korsch, M. J.; Taylor, A. J.; Mahaffey, K. R. (2004) Blood lead changes during pregnancy and postpartum with calcium supplementation. Environ. Health Perspect. 112: 1499-1507.

Gunnarsson, L. G.; Bodin, L.; Soderfeldt, B.; Axelson, O. (1992) A case-control study of motor neurone disease: its relation to heritability, and occupational exposures, particularly to solvents. Br. J. Ind. Med. 49: 791-798.

Guo, T. L.; Mudzinski, S. P.; Lawrence, D. A. (1996a) The heavy metal lead modulates the expression of both TNF-"alpha" and TNF-"alpha" receptors in lipopolysaccharide-activated human peripheral blood mononuclear cells. J. Leukoc. Biol. 59: 932-939.

Guo, T. L.; Mudzinski, S. P.; Lawrence, D. A. (1996b) Regulation of HLA-DR and invariant chain expression by human peripheral blood mononuclear cells with lead, interferon-"gamma", or interleukin-4. Cell. Immunol. 171: 1-9.

Gurer-Orhan, H.; Sabir, H.D.; Ozgunes, H. (2004) Correlation between clinical indicators of lead poisoning and oxidative stress parameters in controls and lead-exposed workers. Toxicology 195: 147-154.

Gustafson, A.; Hedner, P.; Schutz, A.; Skerfving, S. (1989) Occupational lead exposure and pituitary function. Int. Arch. Occup. Environ. Health 61: 277-281.

Gustavsson, P.; Plato, N.; Hallqvist, J.; Hogstedt, C.; Lewne, M.; Reuterwall, C.; Scheele, P. (2001) A population-based case-referent study of myocardial infarction and occupational exposure to motor exhaust, other combustion products, organic solvents, lead, and dynamite. stockholm heart epidemiology program (SHEEP) study group. Epidemiology 12: 222-228.

Gwiazda, R.; Campbell, C.; Smith, D. (2005) A noninvasive isotopic approach to estimate the bone lead contribution to blood in children: implications for assessing the efficacy of lead abatement. Environ. Health Perspect. 113: 104-110.

Gyllenborg, J.; Skakkebaek, N. E.; Nielsen, N. C.; Keiding, N.; Giwercman, A. (1999) Secular and seasonal changes in semen quality among young Danish men: a statistical analysis of semen samples from 1927 donor candidates during 1977-1995. Int. J. Androl. 22: 28-36.

Hafeez, A.; Malik, Q. U. (1996) Blood lead levels in preschool children in Rawalpindi. JPMA J. Pak. Med. Assoc. 46: 272-274.

Hagmar, L.; Stromberg, U.; Bonassi, S.; Hansteen, I.-L.; Knudsen, L. E.; Lindholm, C.; Norppa, H. (2004) Impact of types of lymphocyte chromosomal aberrations on human cancer risk: results from Nordic and Italian cohorts. Cancer Res. 64: 2258-2263.

Hajem, S.; Moreau, T.; Hannaert, P.; Lellouch, J.; Huel, G.; Hellier, G.; Orssaud, G.; Claude, J. R.; Juguet, B.; Festy, B.; Garay, R. P. (1990) Influence of environmental lead on membrane ion transport in a French urban male population. Environ. Res. 53: 105-118.

Hammond, P. B.; Lerner, S. I.; Gartside, P. S.; Hanenson, I. B.; Roda, S. B.; Foulkes, E. C.; Johnson, D. R.; Pesce, A. J. (1980) The relationship of biological indices of lead exposure to the health status of workers in a secondary lead smelter. J. Occup. Med. 22: 475-484.

Haenninen, H.; Hernberg, S.; Mantere, P.; Vesanto, R.; Jalkanen, M. (1978) Psychological performance of subjects with low exposure to lead. J. Occup. Med. 20: 683-689.

Han, S.; Pfizenmaier, D. H.; Garcia, E.; Eguez, M. L.; Ling, M.; Kemp, F. W.; Bogden, J. D. (2000) Effects of lead exposure before pregnancy and dietary calcium during pregnancy on fetal development and lead accumulation. Environ. Health Perspect. 108: 527-531.

Hanninen, H.; Aitio, A.; Kovala, T.; Luukkonen, R.; Matikainen, E.; Mannelin, T.; Erkkila, J.; Riihimaki, V. (1998) Occupational exposure to lead and neuropsychological dysfunction. Occup. Environ. Med. 55: 202-209.

Haraguchi, T.; Ishizu, H.; Takehisa, Y.; Kawai, K.; Yokota, O.; Terada, S.; Tsuchiya, K.; Ikeda, K.; Morita, K.; Horike, T.; Kira, S.; Kuroda, S. (2001) Lead content of brain tissue in diffuse neurofibrillary tangles with calcification (DNTC): the possibility of lead neurotoxicity. Neuroreport 12: 3887-3890.

Haraguchi, T.; Ishizu, H.; Takehisa, Y.; Kawai, K.; Yokota, O.; Terada, S.; Tsuchiya, K.; Ikeda, K.; Morita, K.; Horike, T.; Kira, S.; Kuroda, S. (2002) Lead content of brain tissue in diffuse neurofibrillary tangles with calcification (DNTC): the possibility of lead neurotoxicity [erratum to Neuroreport 12: 3887-3890]. Neuroreport 13(1): inside back cover.

Harville, E. W.; Hertz-Picciotto, I.; Schramm, M.; Watt-Morse, M.; Chantala, K.; Osterloh, J.; Parsons, P. J.; Rogan, W. (2005) Factors influencing the difference between maternal and cord blood lead. Occup. Environ. Med. 62: 263-290.

Hasselblad, V.; Nelson, W. (1975) Additional analysis of the seven city lead study. In: Griffin, T. B.; Knelson, J. H., eds. Lead. Stuttgart, Federal Republic of Germany: Georg Thieme Publishers; pp. 147-151. (Coulston, F.; Korte, F., eds. Environmental quality and safety: supplement v. 2).

Hasselblad, V.; Stead, A. G.; Galke, W. (1980) Analysis of coarsely grouped data from the lognormal distribution. JASA J. Am. Stat. Assoc. 75: 771-778.

Hatzakis, A.; Salaminios, F.; Kokevi, A.; Katsouyanni, K.; Maravelias, K.; Kalandidi, A.; Koutselinis, A.; Stefanis, K.; Trichopoulos, D. (1985) Blood lead and classroom behaviour of children in two communities with different degree of lead exposure: evidence of a dose-related effect? In: Lekkas, T. D., ed. International conference: heavy metals in the environment, v. 1; September; Athens, Greece. Edinburgh, United Kingdom: CEP Consultants, Ltd.; p. 47.

Hatzakis, A.; Kokkevi, A.; Maravelias, C.; Katsouyanni, K.; Salaminios, F.; Kalandidi, A.; Koutselinis, A.; Stefanis, C.; Trichopoulos, D. (1989) Psychometric intelligence deficits in lead-exposed children. In: Smith, M. A.; Grant, L. D.; Sors, A. I., eds. Lead exposure and child development: an international assessment [workshop organized by the Commission of the European Communities and the U.S. Environmental Protection Agency]; September 1986; Edinburgh, United Kingdom. Dordrecht, The Netherlands: Kluwer Academic Publishers BV; pp. 211-223.

Haynes, E. N.; Kalkwarf, H. J.; Hornung, R.; Wenstrup, R.; Dietrich, K.; Lanphear, B. P. (2003) Vitamin D receptor Fok1 polymorphism and blood lead concentration in children. Environ. Health Perspect. 111: 1665-1669.

He, F. S.; Zhang, S. L.; Li, G.; Zhang, S. C.; Huang, J. X.; Wu, Y. Q. (1988) An electroneurographic assessment of subclinical lead neurotoxicity. Int. Arch. Occup. Environ. Health 61: 141-146.

Hellstrom, L.; Elinder, C.-G.; Dahlberg, B.; Lundberg, M.; Jarup, L.; Persson, B.; Axelson, O. (2001) Cadmium exposure and end-stage renal disease. Am. J. Kidney Dis. 38: 1001-1008.

Hemdan, N. Y. A.; Emmrich, F.; Adham, K.; Wichmann, G.; Lehmann, I.; El-Massry, A.; Ghoneim, H.; Lehmann, J.; Sack, U. (2005) Dose-dependent modulation of the in vitro cytokine production of human immune competent cells by lead salts. Toxicol. Sci. 86: 75-83.

Henderson, D. A. (1954) A follow-up of cases of plumbism in children. Australas. Ann. Med. 33: 219-224.

Henderson, D. A. (1955) Chronic nephritis in Queensland. Australas. Ann. Med. 4: 163-177.

Hense, H. W.; Filipiak, B.; Keil, U. (1993) The association of blood lead and blood pressure in population surveys. Epidemiology 4: 173-179.

Hense, H. W.; Filipiak, B.; Keil, U. (1994) Alcohol consumption as a modifier of the relation between blood lead and blood pressure. Epidemiology 5: 120-123.

Heo, Y.; Lee, B.-K.; Ahn, K.-D.; Lawrence, D. A. (2004) Serum IgE elevation correlates with blood lead levels in battery manufacturing workers. Hum. Exp. Toxicol. 23: 209-213.

Hernandez-Avila, M.; Gonzalez-Cossio, T.; Palazuelos, E.; Romieu, I.; Aro, A.; Fishbein, E.; Peterson, K. E.; Hu, H. (1996) Dietary and environmental determinants of blood and bone lead levels in lactating postpartum women living in Mexico City. Environ. Health Perspect. 104: 1076-1082.

Hernandez-Avila, M.; Sanin, L. H.; Romieu, I.; Palazuelos, E.; Tapia-Conyer, R.; Olaiz, G.; Rojas, R.; Navarrete, J. (1997) Higher milk intake during pregnancy is associated with lower maternal and umbilical cord lead levels in postpartum women. Environ. Res. 74: 116-121.

Hernandez-Avila, M.; Smith, D.; Meneses, F.; Sanin, L. H.; Hu, H. (1998) The influence of bone and blood lead on plasma lead levels in environmentally exposed adults. Environ. Health Perspect. 106: 473-477.

Hernandez-Avila, M.; Villalpano, C. G.; Palazuelos, E.; Villapando, M. E. G. (2000) Determinants of blood lead levels across the menopausal transition. Arch. Environ. Health 53: 355-360.

Hernandez-Avila, M.; Peterson, K. E.; Gonzalez-Cossio, T.; Sanin, L. H.; Aro, A.; Schnaas, L.; Hu, H. (2002) Effect of maternal bone lead on length and head circumference of newborns and 1-month-old infants. Arch. Environ. Health 57: 482-488.

Hernandez-Avila, M.; Gonzalez-Cossio, T.; Hernandez-Avila, J. E.; Romieu, I.; Peterson, K. E.; Aro, A.; Palazuelos, E.; Hu, H. (2003) Dietary calcium supplements to lower blood lead levels in lactating women: a randomized placebo-controlled trial. Epidemiology 14: 206-212.

Hernandez-Ochoa, I; Garcia-Vargas, G; Lopez-Carrillo, L; Rubio-Andrade, M; Moran-Martinez, J; Cebrian, M. E.; Quintanilla-Vega, B. (2005) Low lead environmental exposure alters semen quality and sperm chromatin condensation in northern Mexico. Reprod. Toxicol. 20: 221-228.

Hernberg, S.; Nikkanen, J.; Mellin, G.; Lilius, H. (1970) "delta"-aminolevulinic acid dehydrase as a measure of lead exposure. Arch. Environ. Health 21: 140-145.

Hertz-Picciotto, I.; Croft, J. (1993) Review of the relation between blood lead and blood pressure. Epidemiol. Rev. 15: 352-373.

Hertz-Picciotto, I.; Schramm, M.; Watt-Morse, M.; Chantala, K.; Anderson, J.; Osterloh, J. (2000) Patterns and determinants of blood lead during pregnancy. Am. J. Epidemiol. 152: 829-837.

Hill, A. B. (1965) The environment and disease: association or causation? Proc. R. Soc. Med. 58: 295-300.

Hirata, M.; Kosaka, H.; Yoshida, T. (2004) A study on the effect of lead on event-related potentials among lead-exposed workers. Ind. Health 42: 431-434.

Hisanaga, A.; Eguchi, Y.; Hirata, M.; Ishinishi, N. (1988) Lead levels in ancient and contemporary Japanese bones. Biol. Trace Elem. Res. 16: 77-85.

Hogstedt, C.; Hane, M.; Agrell, A; Bodin, L. (1983) Neuropsychological test results and symptoms among workers with well-defined long-term exposure to lead. Br. J. Ind. Med. 40: 99-105.

Holness, D. L.; Nethercott, J. R. (1988) Acute lead intoxication in a group of demolition workers. Appl. Ind. Hyg. 3: 338-341.

Holstein, Y.; Pratt, H.; Goldsher, M.; Rosen, G.; Shenhav, R.; Linn, S.; Mor, A.; Barkai, A. (1986) Auditory brainstem evoked potentials in asymptomatic lead-exposed subjects. J. Laryngol. Otol. 100: 1031-1036.

Hoppin, J. A.; Aro, A.; Hu, H.; Ryan, P. B. (2000) Measurement variability associated with KXRF bone lead measurement in young adults. Environ. Health Perspect. 108: 239-242.

Horiguchi, S.; Endo, G.; Kiyota, I. (1987) Measurement of total triiodothyronine (T3), total thyroxine (T4) and thyroid-stimulating hormone (TSH) levels in lead-exposed workers. Osaka City Med J. 33: 51-56.

Horiguchi, S.; Matsumura, S.; Fukumoto, K.; Karai, I.; Endo, G.; Teramoto, K.; Shinagawa, K.; Kiyota, I.; Wakitani, F.; Takise, S.; Kawaraya, T. (1991) Erythrocyte deformability in workers exposed to lead. Osaka City Med. J. 37: 149-155.

Hotz, P.; Buchet, J. P.; Bernard, A.; Lison, D.; Lauwerys, R. (1999) Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. Lancet 354: 1508-1513.

Houston, D. K.; Johnson, M. A. (1999) Lead as a risk factor for hypertension in women. Nutr. Rev. 57: 277-279.

Hsiao, C. Y.; Wu, H. D.; Lai, J. S.; Kuo, H. W. (2001) A longitudinal study of the effects of long-term exposure to lead among lead battery factory workers in Taiwan (1989-1999). Sci. Total Environ. 279: 151-158.

Hsieh, L. L.; Liou, S. H.; Chen, Y. H.; Tsai, L. C.; Yang, T.; Wu, T. N. (2000) Association between aminolevulinate dehydrogenase genotype and blood lead levels in Taiwan. J. Occup. Environ. Med. 42(2): 151-155.

Hu, H. (1991) A 50-year follow-up of childhood plumbism: hypertension, renal function, and hemoglobin levels among survivors. Am. J. Dis. Child. 145: 681-687.

Hu, H. (1998) Bone lead as a new biologic marker of lead dose: recent findings and implications for public health. Environ. Health Perspect. 106(suppl. 4): 961-967.

Hu, H.; Hernandez-Avila, M. (2002) Lead, bones, women, and pregnancy--the poison within? Am. J. Epidemiol. 156: 1088-1091.

Hu, H.; Milder, F. L.; Burger, D. E. (1990) X-ray fluorescence measurements of lead burden in subjects with low-level community lead exposure. Arch. Environ. Health 45: 335-341.

Hu, H.; Milder, F. L.; Burger, D. E. (1991) The use of K X-ray fluorescence for measuring lead burden in epidemiological studies: high and low lead burdens and measurement uncertainty. Environ. Health Perspect. 94: 107-110.

Hu, H.; Watanabe, H.; Payton, M.; Korrick, S.; Rotnitzky, A. (1994) The relationship between bone lead and hemoglobin. JAMA J. Am. Med. Assoc. 272: 1512-1517.

Hu, H.; Aro, A.; Rotnitzky, A. (1995) Bone lead measured by X-ray fluorescence: epidemiologic methods. Environ. Health Perspect. 103(suppl. 1): 105-110.

Hu, H.; Aro, A.; Payton, M.; Korrick, S.; Sparrow, D.; Weiss, S. T.; Rotnitzky, A. (1996) The relationship of bone and blood lead to hypertension. The Normative Aging Study. JAMA J. Am. Med. Assoc. 275: 1171-1176.

Hu, H.; Rabinowitz, M.; Smith, D. (1998) Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. Environ. Health Perspect. 106: 1-8.

Hu, J.; La Vecchia, C.; Negri, E.; Chatenoud, L.; Bosetti, C.; Jia, X.; Liu, R.; Huang, G.; Bi, D.; Wang, C. (1999) Diet and brain cancer in adults: a case-control study in northeast China. Int. J. Cancer 81: 20-23.

Hu, H.; Wu, M.-T.; Cheng, Y.; Sparrow, D.; Weiss, S.; Kelsey, K. (2001) The "delta"-aminolevulinic acid dehydratase (ALAD) polymorphism and bone and blood lead levels in community-exposed men: the Normative Aging Study. Environ. Health Perspect. 109: 827-832.

Huang, J.; He, F.; Wu, Y.; Zhang, S. (1988) Observations on renal function in workers exposed to lead. Sci. Total Environ. 71: 535-537.

Huel, G.; Boudene, C.; Ibrahim, M. A. (1981) Cadmium and lead content of maternal and newborn hair: relationship to parity, birth weight, and hypertension. Arch. Environ. health 36: 221-227.

Huel, G.; Campagna, D.; Moreau, T.; Tubert-Bitter, P. (1995) Environmental lead and children's intelligence: hair lead studies were excluded [letter]. Br. Med. J. 310: 397-398.

Hunter, J.; Urbanowicz, M. A.; Yule, W.; Lansdown, R. (1985) Automated testing of reaction time and its association with lead in children. Int. Arch. Occup. Environ. Health 57: 27-34.

Hwang, K.-Y.; Lee, B.-K.; Bressler, J. P.; Bolla, K. I.; Stewart, W. F.; Schwartz, B. S. (2002) Protein kinase C activity and the relations between blood lead and neurobehavioral function in lead workers. Environ. Health Perspect. 110: 133-138.

Inskip, M. J.; Franklin, C. A.; Baccanale, C. L.; Manton, W. I.; O'Flaherty, E. J.; Edwards, C. M. H.; Blenkinsop, J. B.; Edwards, E. B. (1996) Measurement of the flux of lead from bone to blood in a nonhuman primate (Macaca fascicularis) by sequential administration of stable lead isotopes. Fundam. Appl. Toxicol. 33: 235-245.

Irgens, A.; Kruger, K.; Skorve, A. H.; Irgens, L. M. (1998) Reproductive outcome in offspring of parents occupationally exposed to lead in Norway. Am. J. Ind. Med. 34: 431-437.

International Agency for Research on Cancer. (1980) Some metals and metallic compounds. World Health Organization, International Agency for Research on Cancer, Lyon, France; IARC Monogr. Eval. Carcinog. Risks Hum. Vol. 23.

International Agency for Research on Cancer. (2005) Inorganic and organic lead compounds. World Health Organization, International Agency for Research on Cancer, Lyon, France; IARC Monogr. Eval. Carcinog. Risks Hum. Vol. 87: in preparation.

International Commission on Radiological Protection. (1973) Alkaline earth metabolism in adult man. ICRP Publication 20. Health Phys. 24: 125-221.

International Commission on Radiological Protection. (1981) Report of the task group on reference man. Oxford, United Kingdom: Elsevier Science Publishers; ICRP Publication 23.

International Commission on Radiological Protection. (1996) Basic anatomical & physiological data for use in radiological protection: the skeleton. Oxford, United Kingdom: Elsevier Science Publishers; ICRP publication 70; Annals of the ICRP, v. 25, no. 2.

Ishida, M.; Ishizaki, M.; Yamada, Y. (1996) Decreases in postural change of finger blood flow in ceramic painters chronically exposed to low level lead. Am. J. Ind. Med. 29: 547-553.

Ito, Y.; Niiya, Y.; Kurita, H.; Shima, S.; Sarai, S. (1985) Serum lipid peroxide level and blood superoxide dismutase activity in workers with occupational exposure to lead. Int. Arch. Occup. Environ. Health 56: 119-127.

Jackson, L. W.; Correa-Villasenor, A.; Lee, P. S. J.; Dominici, F.; Stewart, P. A.; Breysse, P. N. (2004) Parental lead exposure and total anomalous pulmonary venous return. Birth Defects Res. Part A 70: 185-193.

Jarup, L.; Hellstrom, L.; Alfven, T.; Carlsson, M. D.; Grubb, A.; Persson, B.; Pettersson, C.; Spang, G.; Schutz, A.; Elinder, C.-G. (2000) Low level exposure to cadmium and early kidney damage: the OSCAR study. Occup. Environ. Med. 57: 668-672.

Jemal, A.; Graubard, B. I.; Devesa, S. S.; Flegal, K. M. (2002) The association of blood lead level and cancer mortality among whites in the United States. Environ. Health Perspect. 110: 325-329.

Jiun, Y. S.; Hsien, L. T. (1994) Lipid peroxidation in workers exposed to lead. Arch. Environ. Health 49: 256-259.

Johnson, R. J.; Kang, D.-H.; Feig, D.; Kivlighn, S.; Kanellis, J.; Watanabe, S.; Tuttle, K. R.; Rodriguez-Iturbe, B.; Herrera-Acosta, J.; Mazzali, M. (2003) Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 41: 1183-1190.

Jones, R. R. (1995) Environmental lead and children's intelligence: obvious hypothesis is ignored [letter]. Br. Med. J. 310: 397.

Jones, S. J.; Williams, A. J.; Kudlac, H.; Hainsworth, I. R.; Morgan, W. D. (1990) The measurement of bone lead content in patients with end stage failure. In: Yasumura, S.; Harrison, J. E., eds. In vivo body composition studies: recent advances. New York, NY: Plenum Press; pp. 259-262. (Basic life sciences: v. 55)

Jordan, C.; Lee, P.; Shapiro, E. (2000) Measuring developmental outcomes of lead exposure in an urban neighborhood: the challenges of community-based research. J. Exposure Anal. Environ. Epidemiol. 10:-732-742.

Juarez-Perez, C. A.; Aguilar-Madrid, G.; Smith, D. R.; Lacasana-Navarro, M.; Tellez-Rojo, M. M.; Piacitteli, G.; Hu, H.; Hernandez-Avila, M. (2004) Predictors of plasma lead among lithographic print shop workers in Mexico City. Am. J. Ind. Med. 46: 245-252.

Juberg, D. R.; Kleiman, C. F.; Kwon, S. C. (1997) Position paper of the American Council on Science and Health: lead and human health. Ecotoxicol. Environ. Saf. 38: 162-180.

Jung, K.-Y.; Lee, S.-J.; Kim, J.-Y.; Hong, Y.-S.; Kim, S.-R.; Kim, D.-I.; Song, J.-B. (1998) Renal dysfunction indicators in lead exposed workers. J. Occup. Health 40: 103-109.

Jurek, A. M.; Greenland, S.; Maldonado, G.; Church, T. R. (2005) Proper interpretation of non-differential misclassification effects: expectations vs observations. Int. J. Epidemiol. 34: 680-687.

Kahn, C. A.; Kelly, P. C.; Walker, W. O., Jr. (1995) Lead screening in children with attention deficit hyperactivity disorder and developmental delay. Clin. Pediatr. 34: 498-501.

Kamel, F.; Umbach, D.; Munsat, T.; Shefner, J.; Hu, H.; Sandler, D. (2002) Lead exposure and amyotrophic later sclerosis. Epidemiology 13: 311-319.

Kamel, F.; Umbach, D. M.; Lehman, T. A.; Park, L. P.; Munsat, T. L.; Shefner, J. M.; Sandler, D. P.; Hu, H.; Taylor, J. A. (2003) Amyotrophic lateral sclerosis, lead, and genetic susceptibility: polymorphisms in the "delta"-aminolevulinic acid dehydratase and vitamin D receptor genes. Environ. Health Perspect. 111: 1335-1339.

Kandiloris, D. C.; Goletsos, G. A.; Nikolopoulos, T. P.; Ferekidis, E. A.; Tsomis, A. S.; Adamopoulos, G. K. (1997) Effect of subclinical lead intoxication on laryngeal cancer. Br. J. Clin. Practice 51: 69-70.

Kannel, W. B. (1996) Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA J. Am. Med. Assoc. 275: 1571-1576.

Kannel, W. B. (2000a) Elevated systolic blood presure as a cardiovascular risk factor. Am. J. Cardiol. 85: 251-255.

Kannel, W. B. (2000b) Risk stratification in hypertension: new insights from the Framingham Study. Am. J. Hypertens. 13: 3S-10S.

Kannel, W. B.; Wilson, P. W. F.; Nam, B.-H.; D'Agostino, R. B.; Li, J. (2004) A likely explanation for the J-curve of blood pressure cardiovascular risk. Am. J. Cardiol. 94: 380-384.

Karakaya, A. E.; Ozcagli, E.; Ertas, N.; Sardas, S. (2005) Assessment of abnormal DNA repair responses and genotoxic effects in lead exposed workers. Am. J. Ind. Med. 47: 358-363.

Karimi, P. G.; Moodley, J.; Jinabhai, C. C.; Nriagu, J. (1999) Maternal and fetal blood lead levels. S. Afr. Med. J. 89: 676-679.

Karmaus, W.; Brooks, K. R.; Nebe, T.; Witten, J.; Obi-Osius, N.; Kruse, H. (2005) Immune function biomarkers in children exposed to lead and organochlorine compounds: a cross-sectional study. Environ. Health Glob. Access Sci. 4: 1-10.

Kasperczyk, S.; Dziwisz, M.; Kasperczyk, A.; Birkner, E. (2002) Wplyw olowiu na wystepowanie nadcisnienia tetniczego [Influence of lead exposure on arterial hypertension]. Wiad. Lek. 55(suppl. 1): 230-234.

Kaufman, A. S.; Kaufman, N. L. (1983) Kaufman assessment battery for children. Circle Pines, MN: American Guidance Service.

Kauppinen, T.; Riala, R.; Seitsamo, J.; Hernberg, S. (1992) Primary liver cancer and occupational exposure. Scand. J. Work Environ. Health. 18: 18-25.

Kavlock, R. J.; Daston, G. P.; DeRosa, C.; Fenner-Crisp. P.; Gray, L. E.; Kaattari, S.; Lucier, G.; Luster, M.; Mac, M. J.; Maczka, C.; Miller, R.; Moore, J.; Rolland, R.; Scott, G.; Sheehan, D. M.; Sinks, T.; Tilson, H. A. (1996) Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop. Environ. Health Perspect. Suppl. 104(4): 715-740.

Kehoe, R. A. (1987) Studies of lead administration and elimination in adult volunteers under natural and experimentally induced conditions over extended periods of time. Food Chem. Toxicol. 25: 425-493.

Keiding, N.; Skakkebaek, N. E. (1996) Sperm decline--real or artifact? Fertil. Steril. 65: 450-453.

Keiding, N.; Giwercman, A.; Carlsen, E.; Skakkebaek, N. E. (1994) Comment on "Farrow, S. (1994) Falling sperm quality: fact or fiction? Br. Med. J. 309: 1-2." Br. Med. J. 309: 131.

Keinonen, M. (1992) The isotopic composition of lead in man and the environment in Finland 1966-1987: isotope ratios of lead as indicators of pollutant source. Sci. Total Environ. 113: 251-268.

Kelada, S. N.; Shelton, E.; Kaufmann, R. B.; Khoury, M. J. (2001) "Delta"-aminolevulinic acid dehydratase genotype and lead toxicity: a HuGE review. Am. J. Epidemiol. 154: 1-13.

Kemp, F. W.; Penn-Erskine, C.; Coba, V.; Wenger, P.; Palmer-Keenan, D.; Lundt, M. R.; Davidow, A.; Louria, D. B.; Bogden, J. D. (2002) Recent increases in dietary calcium intake in young urban children at high risk of lead poisoning. FASEB J. 16: A253.

Kemper, A. R.; Cohn, L. M.; Fant, K. E.; Dombkowski, K. J.; Hudson, S. R. (2005) Follow-up testing among children with elevated screening blood lead levels. JAMA J. Am. Med. Assoc. 293: 2232-2237.

Kessler, M.; Durand, P. Y.; Huu, T. C.; Royer-Morot, M. J.; Chanliau, J.; Netter, P.; Duc, M. (1999) Mobilization of lead from bone in end-stage renal failure patients with secondary hyperparathyroidism. Nephrol. Dial. Transplant. 14: 2731-2733.

Khalil-Manesh, F.; Gonick, H. C. Cohen, A. H.; Alinovi, R.; Bergamaschi, E.; Mutti, A.; Rosen, V. J. (1992a) Experimental model of lead nephropathy. I. Continuous high-dose lead administration. Kidney Int. 41: 1192-1203.

Khalil-Manesh, F.; Gonick, H. C.; Cohen, A.; Bergamaschi, E.; Mutti, A. (1992b) Experimental model of lead nephropathy. II. Effect of removal from lead exposure and chelation treatment with dimercaptosuccinic acid (DMSA). Environ. Res 58: 35-54.

Khalil-Manesh, F.; Gonick, H. C.; Cohen, A. H. (1993) Experimental model of lead nephropathy. III. Continuous low-level lead administration. Arch. Environ. Health 48: 271-278.

Kim, R.; Aro, A.; Rotnitzky, A.; Amarasiriwardena, C.; Hu, H. (1995) K x-ray fluorescence measurements of bone lead concentration: the analysis of low-level data. Phys. Med. Biol. 40: 1475-1485.

Kim, R.; Hu, H.; Rotnitzky, A.; Bellinger, D.; Needleman, H. (1995) A longitudinal study of chronic lead exposure and physical growth in Boston children. Environ. Health Perspect. 103: 952-957.

Kim, R.; Rotnitsky, A.; Sparrow, D.; Weiss, S. T.; Wager, C.; Hu, H. (1996) A longitudinal study of low-level lead exposure and impairment of renal function. The Normative Aging Study. JAMA J. Am. Med. Assoc. 275: 1177-1181.

Kim, Y.; Lee, H.; Lee, C. R.; Park, D. U.; Yang, J. S.; Park, I. J.; Lee, K. Y.; Lee, M.; King, T. K.; Sohn, N. S.; Cho, Y. S.; Lee, N.; Chung, H. K. (2002) Evaluation of lead exposure in workers at secondary lead smelters in South Korea: with focus on activity of erythrocyte pyrimidine 5'-nucleotidase (P5N). Sci. Total Environ. 286: 181-189.

Kimber, I.; Stonard, M. D.; Gidlow, D. A.; Niewola, Z. (1986) Influence of chronic low-level exposure to lead on plasma immunoglobulin concentration and cellular immune function in man. Int. Arch. Occup. Environ. Health 57: 117-125.

Kline, J.; Stein, Z.; Hutzler, M. (1987) Cigarettes, alcohol and marijuana: varying associations with birthweight. Int. J. Epidemiol. 16: 44-51.

Klitzman, S.; Sharma, A.; Nicaj, L.; Vitkevich, R.; Leighton, J. (2002) Lead poisoning among pregnant women in New York City: risk factors and screening practices. Bull. N. Y. Acad. Med. 79: 225-237.

Koller, K.; Brown, T.; Spurgeon, A.; Levy, L. (2004) Recent developments in low-level lead exposure and intellectual impairment in children. Environ. Health Perspect. 112: 987-994.

Konishi, Y.; Endo, G.; Kiyota, A.; Horiguchi, S. (1994) Fractional clearances of low molecular weight proteins in lead workers. Ind. Health 32: 119-127.

Koo, W. W. K.; Succop, P. A.; Bornschein, R. L.; Krugwispe, S. K.; Steinchen, J. J.; Tsang, R. C.; Berger, O.G. (1991) Serum vitamin D metabolites and bone mineralization in young children with chronic low to moderate lead exposure. Pediatrics 87: 680-687.

Kordas, K.; Lopez, P.; Rosado, J. L.; Vargas, G. G.; Rico, J. A.; Ronquillo, D.; Cebrian, M. E.; Stoltzfus, R. J. (2004) Blood lead, anemia, and short stature are independently associated with cognitive performance in Mexican school children. J. Nutr. 134: 363-371.

Kordas, K.; Stoltzfus, R. J.; Lopez, P.; Rico, J. A.; Rosado, J. L. (2005) Iron and zinc supplementation does not improve parent orteacher ratings of behavior in first grade Mexican children exposed to lead. J. Pediatr. 147: 632-639.

Korrick, S.; Hunter, D.; Rotnitzky, A.; Hu, H.; Nurses' Health Study Research Group. (1996) Lead and hypertension in a sample of the Nurses' Health Study. Am. J. Epidemiol. 143(11 suppl.): S44.

Korrick, S. A.; Hunter, D. J.; Rotnitzky, A.; Hu, H.; Speizer, F. E. (1999) Lead and hypertension in a sample of middle-aged women. Am. J. Public Health 89: 330-335.

Korrick, S. A.; Schwartz, J.; Tsaih, S.-W.; Hunter, D. J.; Aro, A.;Rosner, B.; Speizer, F. E.; Hu, H. (2002) Correlates of bone and blood lead levels among middle-aged and elderly women. Am. J. Epidemiol. 156: 335-343.

Kosnett, M. J.; Becker, C. E.; Osterloh, J. D.; Kelly, T. J.; Pasta, D. J. (1994) Factors influencing bone lead concentration in a suburban community assessed by noninvasive K x-ray. JAMA J. Am. Med. Assoc. 271: 197-203.

Koster, J.; Erhardt, A.; Stoeppler, M.; Mohl, C.; Ritz, E. (1989) Mobilizable lead in patients with chronic renal failure. Eur. J. Clin. Invest. 19: 228-233.

Kovala, T.; Matikainen, E.; Mannelin, T.; Erkkila, J.; Riihimaki, V.; Hanninen, H.; Aitio, A. (1997) Effects of low level exposure to lead on neurophysiological functions among lead battery workers. Occup. Environ. Med. 54: 487-493.

Kramer, M. S. (1987) Intrauterine growth and gestational duration determinants. Pediatrics 80: 502-511.

Kramer, M. S.; McLean, F. H.; Boyd, M. E.; Usher, R. H. (1988) The validity of gestational age estimation by menstrual dating in term, preterm, and postterm gestations. JAMA J. Am. Med. Assoc. 260: 3306-3308.

Kristal-Boneh, E.; Froom, P.; Yerushalmi, N.; Harari, G.; Ribak, J. (1998) Calcitropic hormones and occupational lead exposure. Am. J. Epidemiol. 147: 458-463.

Kristal-Boneh, E.; Coller, D.; Froom, P.; Harari, G.; Ribak, J. (1999) The association between occupational lead exposure and serum cholesterol and lipoprotein levels. Am. J. Public Health 89: 1083-1087.

Kristensen, P.; Irgens, L. M.; Daltveit, A. K.; Andersen, A. (1993) Perinatal outcome among children of men exposed to lead and organic solvents in the printing industry. Am. J. Epidemiol. 137: 134-144.

Kromhout, D.; Wibowo, A. A. E.; Herber, R. F. M.; Dalderup, L. M.; Heerdink, H.; de Lezenne Coulander, C.; Zielhuis, R. L. (1985) Trace metals and coronary heart disease risk indicators in 152 elderly men (the Zutphen study). Am. J. Epidemiol. 122: 378-385.

Kumar, B. D.; Krishnaswamy, K. (1995) Detection of occupational lead nephropathy using early renal markers. J. Toxicol. Clin. Toxicol. 33: 331-335.

Kumar, A.; Dey, P. K.; Singla, P. N.; Ambasht, R. S.; Upadhyay, S. K. (1998) Blood lead levels in children with neurological disorders. J. Trop. Pediatr. 44: 320-322.

Kuo, H.-W.; Hsiao, T.-Y.; Lai, J.-S. (2001) Immunological effects of long-term lead exposure among Taiwanese workers. Arch. Toxicol. 75: 569-573.

Kurtin, D.; Therrell, B. L., Jr.; Patterson, P. (1997) Demographic risk factors associated with elevated lead levels in Texas children covered by Medicaid. Environ. Health Perspect. 105: 66-68.

Lacey, R. F.; Moore, M. R.; Richards, W. N. (1985) Lead in water, infant diet and blood: the Glasgow Duplicate Diet Study. Sci. Total Environ. 41: 235-257.

Lagerkvist, B. J.; Ekesrydh, S.; Englyst, V.; Nordberg, G. F.; Soderberg, H.-A.; Wiklund, D.-E. (1996) Increased blood lead and decreased calcium levels during pregnancy: a prospective study of Swedish women living near a smelter. Am. J. Public Health 86: 1247-1252.

Lancranjan, I.; Popescu, H. I.; Gavanescu, O.; Klepsch, I.; Serbanescu, M. (1975) Reproductive ability of workmen occupationally exposed to lead. Arch. Environ. Health 30: 396-401.

Landrigan, P. J. (2000) Pediatric lead poisoning: is there a threshold? Public Health Rep. 115: 530-531.

Lanphear, B. P. (2005) Childhood lead poisoning prevention: too little, too late. JAMA J. Am. Med. Assoc. 293: 2274-2276.

Lanphear, B. P.; Winter, N. L.; Apetz, L.; Eberly, S.; Weitzman, M. (1996) A randomized trial of the effect of dust control on children's blood lead levels. Pediatrics 98: 35-40.

Lanphear, B. P.; Burgoon, D. A.; Rust, S. W.; Eberly, S.; Galke, W. (1998) Environmental exposures to lead and urban children's blood lead levels. Environ. Res. 76: 120-130.

Lanphear, B. P.; Howard, C.; Eberly, S.; Auinger, P.; Kolassa, J.; Weitzman, M.; Schaffer, S. J.; Alexander, K. (1999) Primary prevention of childhood lead exposure: a randomized trial of dust control. Pediatrics 103: 772-777.

Lanphear, B. P.; Dietrich, K.; Auinger, P.; Cox, C. (2000) Cognitive deficits associated with blood lead concentrations < 10 "mu"g/dL in U.S. children and adolescents. Public Health Rep. 115: 521-529.

Lanphear, B. P.; Dietrich, K. N.; Berger, O. (2003) Prevention of lead toxicity in US children. Ambul. Pediatr. 3: 27-36.

Lanphear, B. P.; Hornung, R.; Khoury, J.; Yolton, K.; Baghurst, P.; Bellinger, D. C.; Canfield, R. L.; Dietrich, K. N.; Bornschein, R.; Greene, T.; Rothenberg, S. J.; Needleman, H. L.; Schnaas, L.; Wasserman, G.; Graziano, J.; Roberts, R. (2005) Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ. Health Perspect. 113: 894-899.

Last, J. M. (2001) A dictionary of epidemiology. New York, NY: Oxford University Press.

Laudanski, T.; Sipowicz, M.; Modzelewski, P.; Bolinski, J.; Szamatowicz, J.; Razniewska, G.; Akerlund, M. (1991) Influence of high lead and cadmium soil content on human reproductive outcome. Int. J. Gynecol. Obstet. 36: 309-315.

Laughlin, N. K. (1995) A new approach for the study of the neurotoxicity of lead. Neurotoxicol. Teratol. 17: 235-236.

Laughlin, N. K.; Bowman, R. E.; Franks, P. A.; Dierschke, D. J. (1987) Altered menstural cycles in rhesus monkeys induced by lead. Fundam. Appl. Toxicol. 9: 722-729.

Lauwers, M. C.; Hauspie, R. C.; Susanne, C.; Verheyden, J. (1986) Comparison of biometric data of children with high and low levels of lead in the blood. Am. J. Phys. Anthropol. 69: 107-116.

Laxen, D. P. H.; Raab, G. M.; Fulton, M. (1987) Children's blood lead and exposure to lead in household dust and water -- a basis for an environmental standard for lead in dust. Sci. Total Environ. 66: 235-244.

Lazutka, J. R.; Lekevicius, R.; Dedonyte, V.; Maciuleviciute-Gervers, L.; Mierauskiene, J.; Rudaitiene, S.; Slapsyte, G. (1999) Chromosomal aberrations and sister-chromatid exchanges in Lithuanian populations: effects of occupational and environmental exposures. Mutat. Res. 445: 225-239.

Leal-Garza, C.; Moates, D. O. R.; Cerda-Flores, R. M.; et al. (1986) Frequency of sister-chromatid exchanges (SCE) in lead exposed workers. Arch. Invest. Med. 17: 267-276.

Lee, B.-K.; Ahn, K.-D.; Lee, S.-S.; Lee, G.-S.; Kim, Y.-B.; Schwartz, B. S. (2000) A comparison of different lead biomarkers in their associations with lead-related symptoms. Int. Arch. Occup. Environ. Health 73: 298-304.

Lee, B.-K.; Lee, G.-S.; Stewart, W. F.; Ahn, K.-D.; Simon, D.; Kelsey, K. T.; Todd, A. C.; Schwartz, B. S. (2001) Associations of blood pressure and hypertension with lead dose measures and polymorphisms in the vitamin D receptor and "delta"-aminolevulinic acid dehydratase genes. Environ. Health Perspect. 109: 383-389.

Leggett, R. W. (1993) An age-specific kinetic model of lead metabolism in humans. Environ. Health Perspect. 101: 598-616.

Lerchl, A. (1995) Evidence for decreasing quality of sperm. Presentation of data on sperm concentration was flawed. Br. Med. J. 311: 569-570.

Lerda, D. (1992) Study of sperm characteristics in persons occupationally exposed to lead. Am. J. Ind. Med. 22: 567-571.

Levey, A. S.; Bosc, J. P.; Lewis, J. B.; Greene, T.; Rogers, N.; Roth, D. (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann. Intern. Med. 130: 461-470.

Levey, A. S.; Coresh, J.; Balk, E.; Kausz, A. T.; Levin, A.; Steffes, M. W.; Hogg, R. J.; Perrone, R. D.; Lau, J.; Eknoyan, G. (2003) National kidney foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann. Intern. Med. 139: 137-147.

Leviton, A.; Bellinger, D.; Allred, E. N.; Rabinowitz, M.; Needleman, H.; Schoenbaum, S. (1993) Pre- and postnatal low-level lead exposure and children's dysfunction in school. Environ. Res. 60: 30-43.

Lezak, M. (1995) Neuropsychological assessment. New York, NY: Oxford University Press.

Lidsky, T. I.; Schneider, J. S. (2003) Lead neurotoxicity in children: basic mechanisms and clinical correlates. Brain 126: 5-19.

Liebelt, E. L.; Schonfeld, D. J.; Gallagher, P. (1999) Elevated blood lead levels in children are associated with lower erythropoietin concentrations. J. Pediatr. 134: 107-109.

Lilienthal, H.; Winneke, G.; Ewert, T. (1990) Effects of lead on neurophysiological and performance measures: animal and human data. In: Conference on advances in lead research: implications for environmental health; January 1989; Research Triangle Park, NC. Environ. Health Perspect. 89: 21-25.

Lilis, R.; Gavrilescu, N.; Nestorescu, B.; Dumitriu, C.; Roventa, A. (1968) Nephropathy in chronic lead poisoning. Br. J. Ind. Med. 25: 196-202.

Lilis, R.; Eisinger, J.; Blumberg, W.; Fischbein, A.; Selikoff, I. J. (1978) Hemoglobin, serum iron, and zinc protoporphyrin in lead-exposed workers. Environ. Health Perspect. 25: 97-102.

Lim, J.; Kang, E.; Choi, B.; Seo, J.; Hong, Y.; Chang, I.; Park, J. (2000) The distribution of blood lead concentration by age and sex in growing students. Chungang Uidaechi 25: 87-91.

Lim, Y. C.; Chia, K. S.; Ong, H. Y.; Ng, V.; Chew, Y. L. (2001) Renal dysfunction in workers exposed to inorganic lead. Ann. Acad. Med. Singapore 30: 112-117.

Lin, J. L.; Huang, P. T. (1994) Body lead stores and urate excretion in men with chronic renal disease. J. Rheumatol. 21: 705-709.

Lin, J.-L.; Lim, P.-S. (1992) Elevated lead burden in Chinese patients without occupational lead exposure. Miner. Electrolyte Metab. 18: 1-5.

Lin, J.-L.; Lim, P.-S. (1994) Does lead play a role in the development of renal insufficiency in some patients with essential hypertension? J. Hum. Hypertens. 8: 495-500.

Lin, J.-L.; Yeh, K.-H.; Tseng, H.-C.; Chen, W- Y.; Lai, H.-H.; Lin, Y.-C.; Green Cross Health Service Association Study Group. (1993) Urinary N-acetyl-glucosaminidase excretion and environmental lead exposure. Am. J. Nephrol. 13: 442-447.

Lin, S.; Hwang, S. A.; Marshall, E. G.; Stone, R.; Chen, J. (1996) Fertility rates among lead workers and professional bus drivers: a comparative study. Ann. Epidemiol. 6: 201-208.

Lin, S.; Hwang, S.-A.; Marshall, E. G.; Marion, D. (1998) Does paternal occupational lead exposure increase the risks of low birth weight or prematurity? Am. J. Epidemiol. 148: 173-181.

Lin, J.-L.; Ho, H.-H.; Yu, C.-C. (1999) Chelation therapy for patients with elevated body lead burden and progressive renal insufficiency. A randomized, controlled trial. Ann. Intern. Med. 130: 7-13.

Lin, J.-L.; Tan, D.-T.; Hsu, K.-H.; Yu, C.-C. (2001) Environmental lead exposure and progressive renal insufficiency. Arch. Intern. Med. 161: 264-271.

Lin, J.-L.; Yu, C.-C.; Lin-Tan, D.-T.; Ho, H.-H. (2001) Lead chelation therapy and urate excretion in patients with chronic renal diseases and gout. Kidney Int. 60: 266-271.

Lin, J.-L.; Tan, D.-T.; Ho, H.-H.; Yu, C.-C. (2002) Environmental lead exposure and urate excretion in the general population. Am. J. Med. 113: 563-568.

Lin, J.-L.; Lin-Tan, D.-T.; Hsu, K.-H.; Yu, C.-C. (2003) Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. N. Engl. J. Med. 348: 277-286.

Lin, C.; Kim, R.; Tsaih, S.-W.; Sparrow, D.; Hu, H. (2004) Determinants of bone and blood lead levels among minorities living in the Boston area. Environ. Health Perspect. 112: 1147-1151.

Lindbohm, M.-L.; Hemminki, K.; Bonhomme, M. G.; Anttila, A.; Rantala, K.; Heikkila, P.; Rosenberg, M. J. (1991) Effects of paternal occupational exposure on spontaneous abortions. Am. J. Public Health 81: 1029-1033.

Lindeman, R. D.; Tobin, J.; Shock, N. W. (1985) Longitudinal studies on the rate of decline in renal function with age. J. Am. Geriatr. Soc. 33: 278-285.

Lindgren, K.; Masten, V.; Ford, D.; Bleecker, M. (1996) Relation of cumulative exposure to inorganic lead and neuropsychological test performance. Occup. Environ. Med. 53: 472-477.

Lindgren, K. N.; Masten, V. L.; Tiburzi, M. J.; Ford, D. P.; Bleecker, M. L. (1999) The factor structure of the profile of mood states (POMS) and its relationship to occupational lead exposure. J. Occup. Environ. Med. 41: 3-10.

Liu, X.; Dietrich, K. N.; Radcliffe, J.; Ragan, N. B.; Rhoads, G. G.; Rogan, W. J. (2002) Do children with falling blood lead levels have improved cognition? Pediatrics 110: 787-791.

Lochen, M. L.; Rasmussen, K.; Macfarlane, P. W.; Arnesen, E. (1996) Can single lead computerized electrocardiography predict myocardial infarction in young and middle-aged men? The Tromso Study. Eur. Heart J. 17(abstr. suppl.): 432.

Lockett, C. J.; Arbuckle, D. (1987) Lead, ferritin, zinc, and hypertension. Bull. Environ. Contam. Toxicol. 38: 975-980.

Loeber, R. (1991) Initiation, escalation and desistance in juvenile offending and their correlates. J. Criminal Law Criminol. 82: 36-82.

Loghman-Adham, M. (1998) Aminoaciduria and glycosuria following severe childhood lead poisoning. Pediatr. Nephrol. 12: 218-221.

Lopez, C. M.; Pineiro, A. E.; Nunez, N.; Avagnina, A. M.; Villaamil, E. C.; Roses, O. E. (2000) Thyroid hormone changes in males exposed to lead in the Buenos Aires area (Argentina). Pharmacol. Res. Commun. 42(6): 599-602.

Louis, E. D.; Applegate, L.; Graziano, J. H.; Parides, M.; Slavkovich, V.; Bhat, H. K. (2005) Interaction between blood lead concentration and delta-amino-levulinic acid dehydratase gene polymorphisms increases the odds of essential tremor. Mov. Disord. 20: 1170-1177.

Lucchini, R.; Albini, E.; Cortesi, I.; Placidi, D.; Bergamaschi, E.; Traversa, F.; Alessio, L. (2000) Assessment of neurobehavioral performance as a function of current and cumulative occupational lead exposure. Neurotoxicology 21: 805-811.

Lundstrom, N. G.; Nordberg, G.; Englyst, V.; Gerhardsson, L.; Hagmar, L.; Jin, T.; Rylander, L.; Wall, S. (1997) Cumulative lead exposure in relation to mortality and lung cancer morbidity in a cohort of primary smelter workers. Scand. J. Work Environ. Health 23: 24-30.

Lustberg, M. (2003) I know lead exposure is dangerous for children, but what about adults? Health News 9(March): 12.

Lustberg, M.; Silbergeld, E. (2002) Blood lead levels and mortality. Arch. Intern. Med. 162: 2443-2449.

Lustberg, M. E.; Schwartz, B. S.; Lee, B. K.; Todd, A. C.; Silbergeld, E. K. (2004) The g(894)-t(894)polymorphism in the gene for endothelial nitric oxide synthase and blood pressure in lead-exposed workers from Korea. J. Occup. Environ. Med. 46: 584-590.

Lutz, P. M.; Wilson, T. J.; Ireland, A. L.; Gorman, J. S.; Gale, N. L.; Johnson, J. C.; Hewett, J. E. (1999) Elevated immunoglobulin E (IgE) levels in children with exposure to environmental lead. Toxicology 134: 63-78.

Lyngbye, T. (1997) Methodological problems in assessing health-related, neuropsychological effects of lead absorption in a very low-level exposed area. Cent. Eur. J. Public Health 5: 70-74.

Lyngbye, T.; Hansen, O. N.; Grandjean, P. (1991) Lead concentration in deciduous teeth from Danish school children. Dan. Med. Bull. 38: 89-93.

Mahaffey, K. R. (1992) Exposure to lead in childhood. N. Engl. J. Med. 327: 1308-1309.

Mahaffey, K. R.; Annest, J. L.; Roberts, J.; Murphy, R. S. (1982) National estimates of blood lead levels: United States, 1976-1980. Association with selected demographic and socioeconomic factors. N. Engl. J. Med. 307: 573-579.

Maheswaran, R.; Gill, J. S.; Beevers, D. G. (1993) Blood pressure and industrial lead exposure. Am. J. Epidemiol. 137: 645-653.

Maizlish, N. A.; Parra, G.; Feo, O. (1995) Neurobehavioural evaluation of Venezuelan workers exposed to inorganic lead. Occup. Environ. Med. 52: 408-414.

Makino, S.; Shimizu, Y.; Takata, T. (1997) A study on the relationship between blood lead levels and anemia indicators in workers exposed to low levels of lead. Ind. Health 35: 537-541.

Maki-Paakkanen, J.; Sorsa, M.; Vainio, H. (1981) Chromosome aberrations and sister chromatid exchanges in lead-exposed workers. Hereditas 94: 269-275.

Malcolm, D.; Barnett, H. A. (1982) A mortality study of lead workers 1925-76. Br. J. Ind. Med. 39: 404-410.

Malczyk, E.; Darewicz, B.; Pawlak, D.; Darewicz, J.; Buczko, W. (1999) Investigations of urinary lead concentration in patients with urinary bladder carcinoma. Int. Urol. Nephrol. 31: 661-663.

Mallin et al. (1989) [240,table 7.3]

Mamdani, M.; Sykora, K.; Li, P.; Normand, S.-L. T.; Streiner, D. L.; Austin, P. C.; Rochon, P. A.; Anderson, G. M. (2005) Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. Br. Med. J. BMJ 330: 960-962.

Manea-Krichten, M.; Patterson, C.; Miller, G.; Settle, D.; Erel, Y. (1991) Comparative increases of lead and barium with age in human tooth enamel, rib and ulna. Sci. Total Environ. 107: 179-203.

Mantere, P.; Hanninen, H.; Hernberg, S. (1982) Subclinical neurotoxic lead effects: two-year follow-up studies with psychological test methods. Neurobehav. Toxicol. Teratol. 4: 725-727.

Manton, W. I. (1985) Total contribution of airborne lead to blood lead. Br. J. Ind. Med. 42: 168-172.

Manton, W. I.; Cook, J. D. (1984) High accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid. Br. J. Ind. Med. 41: 313-319.

Manton, W. I.; Malloy, C. R. (1983) Distribution of lead in body fluids after ingestion of soft solder. Br. J. Ind. Med. 40: 51-57.

Manton, W. I.; Angle, C. R.; Stanek, K. L.; Reese, Y. R.; Kuehnemann, T. J. (2000) Acquisition and retention of lead by young children. Environ. Res. 82: 60-80.

Manton, W. I.; Rothenberg, S. J.; Manalo, M. (2001) The lead content of blood serum. Environ. Res. 86: 263-273.

Manton, W. I.; Angle, C. R.; Stanek, K. L.; Kuntzelman, D.; Reese, Y. R.; Kuehnemann, T. J. (2003) Release of lead from bone in pregnancy and lactation. Environ. Res. 92: 139-151.

Markowitz, M. E.; Rosen, J. F. (1981) Zinc (Zn) and copper (Cu) metabolism in CaNa2 EDTA-treated children with plumbism. Pediatr. Res. 15: 635.

Markowitz, M. E.; Shen, X.-M. (2001) Assessment of bone lead during pregnancy: a pilot study. Environ. Res. 85: 83-89.

Markowitz, M. E.; Weinberger, H. L. (1990) Immobilization-related lead toxicity in previously lead-poisoned children. Pediatrics 86: 455-457.

Markowitz, M. E.; Gundberg, C. M.; Rosen, J. F. (1988) Sequential osteocalcin campling as a biochemical marker of the success of treatment of moderately lead poisoned children [abstract]. Pediatr. Res. 23: 393A.

Markowitz, M. E.; Shen, X. M.; Balbi, K.; Rosen, J. F. (1996) Growing up in an era of increased lead (Pb) exposure: is there a risk to the next generation? Pediatr. Res. 39(4 Part 2): 109A.

Marti, J. B.; Cabo, M.; Marhuenda, D.; Cardona, A. (1999) Accumulation of lead and chromium in the teeth of the population in the southeast of the province Alicante, Spain. Trace Elem. Electrol. 16: 137-141.

Martin, C. J.; Werntz, C. L., III; Ducatman, A. M. (2004) The interpretation of zinc protoporphyrin changes in lead intoxication: a case report and review of the literature. Occup. Med. (London) 54: 587-591.

Mason, H. J.; Somervaille, L. J.; Wright, A. L.; Chettle, D. R.; Scott, M. C. (1990) Effect of occupational lead exposure on serum 1,25-dihydroxyvitamin D levels. Hum. Exp. Toxicol. 9: 29-34.

Mason, P. J.; Manson, J. E.; Sesso, H. D.; Albert, C. M.; Chown, M. J.; Cook, N. R.; Greenland, P.; Ridker, P. M.; Glynn, R. J. (2004) Blood pressure and risk of secondary cardiovascular events in women: the Women's Cardiovascular Study (WACS). Circulation 109: 1623-1629.

Matte, T.; Binder, S. (1993) Costs and benefits of lead screening [reply]. JAMA J. Am. Med. Assoc. 270: 2054-2055.

Matte, T. D.; Figueroa, J. P.; Burr, G.; Flesch, J. P.; Keenlyside, R. A.; Baker, E. L. (1989) Lead exposure among lead-acid battery workers in Jamaica. Am. J. Ind. Med. 16: 167-177.

McBride, W. G.; Carter, C. J.; Bratel, J. R.; Cooney, G.; Bell, A. (1989) The Sydney study of health effects of lead in urban children. In: Smith, M. A.; Grant, L. D.; Sors, A. I., eds. Lead exposure and child development: an international assessment [workshop organized by the Commission of the European Communities and the U.S. Environmental Protection Agency]; September 1986; Edinburgh, United Kingdom. Dordrecht, The Netherlands: Kluwer Academic Publishers BV; pp. 255-259.

McCabe, M. J.; Lawrence, D. A. (1991) Lead, a major environmental pollutant, is immunomodulatory by its differential effects on CD4+ T cell subsets. Toxicol. Appl. Pharmacol. 111: 13-23.

McDonald, J. (1981) The lead contamination problem with emphasis on the lead content of wine. Am. J. Enol. Vitic. 32: 219-222.

McDonald, J. A.; Potter, N. U. (1996) Lead's legacy? Early and late mortality of 454 lead-poisoned children. Arch. Environ. Health. 51: 116-121.

McGregor, A. J.; Mason, H. J. (1990) Chronic occupational lead exposure and testicular endocrine function. Hum. Exp. Toxicol. 9: 371-376.

McMichael, A. J. (1993) [Untitled letter concerning a critique paper of five main cohort studies of environmental lead and child mental development]. Arch. Environ. Health 48: 125-126.

McMichael, A. J. (1993) (Response to Thacker et al. article on lead and child mental development [letter]). Arch. Environ. Health 48: 125-126.

McMichael, A. J. (1995) Environmental lead and intellectual development: strengths and limitations of epidemiological research. Neurotoxicol. Teratol. 17: 237-240.

McMichael, A. J. (1997) Lead exposure and child intelligence: interpreting or misinterpreting, the direction of causality? J. Paediatr. Child Health 33: 7-8.

McMichael, A. J.; Johnson, H. M. (1982) Long-term mortality profile of heavily-exposed lead smelter workers. J. Occup. Med. 24: 375-378.

McMichael, A. J.; Vimpani, G. V.; Robertson, E. F.; Baghurst, P. A.; Clark, P. D. (1986) The Port Pirie cohort study: maternal blood lead and pregnancy outcome. J. Epidemiol. Commun. Health 40: 18-25.

McMichael, A. J.; Baghurst, P. A.; Wigg, N. R.; Vimpani, G. V.; Robertson, E. F.; Roberts, R. J. (1988) Port Pirie cohort study: environmental exposure to lead and children's abilities at the age of four years. N. Engl. J. Med. 319: 468-475.

McMichael, A. J.; Baghurst, P. A.; Vimpani, G. V.; Robertson, E. F.; Wigg, N. R.; Tong, S.-L. (1992) Sociodemographic factors modifying the effect of environmental lead on neuropsychological development in early childhood. Neurotoxicol. Teratol. 14: 321-327.

McMichael, A. J.; Baghurst, P. A.; Vimpani, G. V.; Wigg, N. R.; Robertson, E. F.; Tong, S. (1994) Tooth lead levels and IQ in school-age children: the Port Pirie cohort study. Am. J. Epidemiol. 140: 489-499.

McNeill, F. E.; Stokes, L.; Brito, J. A.; Chettle, D. R.; Kaye, W. E. (2000) 109Cd K x-ray fluorescence measurements of tibial lead content in young adults exposed to lead in early childhood. Occup. Environ. Med. 57: 465-471.

Menditto, A.; Morisi, G.; Spagnolo, A.; Menotti, A.; NFR Study Group. (1994) Association of blood lead to blood pressure in men aged 55 to 75 years: effect of selected social and biochemical confounders. NFR study group. Environ. Health Perspect. 102(suppl. 9): 107-111.

Meng, X.-M.; Zhu, D.-M.; Ruan, D.-Y.; She, J.-Q.; Luo, L. (2005) Effects of chronic lead exposure on H MRS of hippocampus and frontal lobes in children. Neurology 64: 1644-1647.

Meredith, P. A.; Campbell, B. C.; Moore, M. R.; Goldberg, A. (1977) The effects of industrial lead poisoning on cytochrome P450 mediated phenazone (antipyrine) hydroxylation. Eur. J. Clin. Pharmacol. 12: 235-239.

Merlo, J.; Asplund, K.; Lynch, J.; Rastam, L.; Dobson, A.; World Health Organization MONICA Project. (2004) Population effects on individual systolic blood pressure: a multilevel analysis of the World Health Organization MONICA Project. Am. J. Epidemiol. 159: 1168-1179.

Michaels, D.; Zoloth, S. R.; Stern, F. B. (1991) Does low-level lead exposure increase risk of death? A mortality study of newspaper printers. Int. J. Epidemiol. 20: 978-983.

Milanov, I.; Kolev, P. (2001) Clinical and electromyographic examinations of patients with tremor after chronic occupational lead exposure. Occup. Med. (London) 51: 157-162.

Millstone, E.; Russell, J. (1995) Environmental lead and children's intelligence: Britain must replace its lead pipes to meet WHO standards for drinking water [letter]. Br. Med. J. 310: 1408-1409.

Milne, R.; Gamble, G.; Whitlock, G.; Jackson, R. (2003) Framingham Heart Study risk equation predicts first cardiovascular event rates in New Zealanders at the population level. N. Z. Med. J. 116(1185): U662.

Min, Y.-I.; Correa-Villasenor, A.; Stewart, P. A. (1996) Parental occupational lead exposure and low birth weight. Am. J. Ind. Med. 30: 569-578.

Minozzo, R.; Deimling, L. I.; Gigante, L. P.; Santos-Mello, R. (2004) Micronuclei in peripheral blood lymphocytes of workers exposed to lead. Mutat. Res. 565: 53-60.

Miranda-Carus, E.; Mateos, F. A.; Sanz, A. G.; Herrero, E.; Ramos, T.; Puig, J. G. (1997) Purine metabolism in patients with gout: the role of lead. Nephron 75: 327-335.

Mirsky, A. F. (1987) Behavioral and psychophysiological makers of disordered attention. Environ. Health Perspect. 74: 191-199.

Mishra, K. P.; Singh, V. K.; Rani, R.; Yadav, V. S.; Chandran, V.; Srivastava, S. P.; Seth, P. K. (2003) Effect of lead exposure on the immune response of some occupationally exposed individuals. Toxicology 188: 251-259.

Moel, D. I.; Sachs, H. K. (1992) Renal function 17 to 23 years after chelation therapy for childhood plumbism. Kidney Int. 42: 1226-1231.

Mohammed-Brahim, B.; Buchet, J. P.; Lauwerys, R. (1985) Erythrocyte pyrimidine 5'-nucleotidase activity in workers exposed to lead, mercury or cadmium. Int. Arch. Occup. Environ. Health 55: 247-252.

Moline, J.; Carrillo, L. L.; Sanchez, L. T.; Godbold, J.; Todd, A. (2000) Lactation and lead body burden turnover: a pilot study in Mexico. J. Occup. Environ. Med. 42: 1070-1075.

Møller, L.; Kristensen, T. S. (1992) Blood lead as a cardiovascular risk factor. Am. J. Epidemiol. 136: 1091-1100.

Montgomery, L. E.; Carter-Pokras, O. (1993) Health status by social class and/or minority status: implications for environmental equity research. Toxicol. Ind. Health 9: 729-773.

Moore, M. R.; Goldberg, A.; Bushnell, I. W. R.; Day, R.; Fyfe, W. M. (1982) A prospective study of the neurological effects of lead in children. Neurobehav. Toxicol. Teratol. 4: 739-743.

Moore, M. R.; McIntosh, M. J.; Bushnell, I. W. R. (1986) The neurotoxicology of lead. Neurotoxicology 7: 541-556.

Morgan, J. M. (1975) Chelation therapy in lead nephropathy. South. Med. J. 68: 1001-1006.

Morgan, W. D.; Ryde, S. J.; Jones, S. J.; Wyatt, R. M.; Hainsworth, I. R.; Cobbold, S. S.; Evans, C. J.; Braithwaite, R. A. (1990) In vivo measurements of cadmium and lead in occupationally-exposed workers and an urban population. Biol. Trace Elem. Res. 26-27: 407-414.

Morita, Y.; Sakai, T.; Araki, S.; Araki, T.; Masuyama, Y. (1997) Nicotinamide adenine dinucleotide synthetase activity in erythrocytes as a tool for the biological monitoring of lead exposure. Int. Arch. Occup. Environ. Health 70: 195-198.

Morris, C.; McCarron, D. A.; Bennett, W. M. (1990) Low-level lead exposure, blood pressure, and calcium metabolism. Am. J. Kidney Dis. 15: 568-574.

Morrow-Tlucak, M.; Ernhart, C. B. (1987) The relationship of low level lead exposure and language development in the pre-school years. In: Lindberg, S. E.; Hutchinson, T. C., eds. International conference: heavy metals in the environment, v. 1; September; New Orleans, LA. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 57-59.

Mortada, W. I.; Sobh, M. A.; El-Defrawy, M. M.; Farahat, S. E. (2001) Study of lead exposure from automobile exhaust as a risk for nephrotoxicity among traffic policemen. Am. J. Nephrol. 21: 274-279.

Mortada, W. I.; Sobh, M. A.; El-Defrawy, M. M. (2004) The exposure to cadmium, lead and mercury from smoking and its impact on renal integrity. Med. Sci. Monit. 10: CR112-CR116.

Moss, M. E.; Lanphear, B. P.; Auinger, P. (1999) Association of dental caries and blood lead levels. JAMA J. Am. Med. Assoc. 281: 2294-2298.

Moura, M.; Valente, J. G. (2002) Blood lead levels during pregnancy in women living in Rio de Janeiro, Brazil. Sci. Total Environ. 299: 123-129.

Muldoon, S. B.; Cauley, J. A.; Kuller, L. H. ; Morrow, L.; Needleman, H. L. ; Scott, J.; Hooper, F. J. (1996) Effects of blood lead levels on cognitive function of older women. Neuroepidemiology 15: 62-72.

Muldoon, S. B.; Cauley, J. A.; Garzarella, L.; Salamone, L.; Bradshaw, P. (2000) Blood lead levels and blood pressure in perimenopausal women. Am. J. Epidemiol. 151(11 suppl.): S79.

Muntner, P.; He, J.; Hamm, L.; Loria, C.; Whelton, P. K. (2002) Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J. Am. Soc. Nephrol. 13: 745-753.

Muntner, P.; He, J.; Vupputuri, S.; Coresh, J.; Batuman, V. (2003) Blood lead and chronic kidney disease in the general United States population: results from NHANES III. Kidney Int. 63: 1044-1050.

Murphy, M. J.; Graziano, J. H.; Popovac, D.; Kline, J. K.; Mehmeti, A.; Factor-Litvak, P.; Ahmedi, G.; Shrout, P.; Rajovic, B.; Nenezic, D. U.; Stein, Z. A. (1990) Past pregnancy outcomes among women living in the vicinity of a lead smelter in Kosovo, Yugoslavia. Am. J. Public Health 80: 33-35.

Mushak, P. (1991) Gastro-intestinal absorption of lead in children and adults: overview of biological and biophysico-chemical aspects. Chem. Speciation Bioavailability 3(3/4): 87-104.

Mushak, P. (1993) New directions in the toxicokinetics of human lead exposure. Presented at: Ninth international neurotoxicology conference; October 1991; Little Rock, AR. Neurotoxicology 14(2-3): 29-42.

Nash, D.; Silbergeld, E.; Magder, L.; Stolley, P. (1998) Menopause, hormone replacement therapy (HRT), and blood lead levels among adult women from NHANES III, 1988-1994. Am. J. Epidemiol. 147(suppl. 11): S93.

Nash, D.; Magder, L.; Lustberg, M.; Sherwin, R. W.; Rubin, R. J.; Kaufmann, R. B.; Silbergeld, E. K. (2003) Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. JAMA J. Am. Med. Assoc. 289: 1523-1532.

Nash, D.; Magder, L. S.; Sherwin, R.; Rubin, R. J.; Silbergeld, E. K. (2004) Bone density-related predictors of blood lead level among peri- and postmenopausal women in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. Am. J. Epidemiol. 160: 901-911.

National Institute for Occupational Safety and Health. (1977a) Manual of analytical methods. 2nd ed. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHEW (NIOSH) publication no. 77/157-A. Method No. P&CAM 102. V. 1.

National Institute for Occupational Safety and Health. (1977b) Manual of analytical methods. 2nd ed. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHEW (NIOSH) publication no. 77/157-A. Method No. P&CW 195. V. 1.

National Institute for Occupational Safety and Health. (1977c) Manual of analytical methods. 2nd ed. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 200-1 to 200- ?. Method No. P&CAM 200. Vol. 1.

National Institute for Occupational Safety and Health. (1977d) Manual of analytical methods. 2nd ed. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control. National Institute for Occupational Safety and Health. 214-1 to 214-8. Method No. P&CAM 214. Vol. 1.

National Institute for Occupational Safety and Health. (1977e) Manual of analytical methods. 2nd ed. Cincinnati, OH: U.S. Department of Health, Education and Welfare. Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Method No. P&CAM 262. Vol. 1.

National Institute for Occupational Safety and Health. (1977f) Manual of analytical methods. 2nd ed. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. Method No. P&CAM 208. Vol. 1.

National Institute for Occupational Safety and Health. (1984) Manual of analytical methods. 3rd ed. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health. Method No. 7300, 8003, and 8310. Vol. 1.

National Institute for Occupational Safety and Health. (1994) Manual of analytical methods. 4rd ed. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health; DHHS (NIOSH) publication 94-113; method no. 7105.

National Institutes of Health. (1994) Consensus development panel on optimal calcium uptake. JAMA J. Am. Med. Assoc. 272: 1942-1948.

National Toxicology Program. (2004) Lead (CAS no. 7439-92-1) and lead compounds. In: Report on carcinogens, eleventh edition. Research Triangle Park, NC: U.S. Department of Health and Human Services. Available: http://ntp.niehs.nih.gov/ntp/roc/eleventh/profiles/s101lead.pdf [28 November, 2005].

Navarro, J. A.; Granadillo, V. A.; Salgado, O.; Rodriguez-Iturbe, B.; Garcia, R.; Delling, G.; Romero, R. A. (1992) Bone metal content in patients with chronic renal failure. Clin. Chim. Acta 211: 133-142.

Navas-Acien, A.; Selvin, E.; Sharrett, A. R.; Calderon-Aranda, E.; Silbergeld, E.; Guallar, E. (2004) Lead, cadmium, smoking, and increased risk of peripheral arterial disease. Circulation 109: 3196-3201.

Nawrot, T. S.; Thijs, L.; Den Hond, E. M.; Roels, H. A.; Staessen, J. A. (2002) An epidemiological re-appraisal of the association between blood pressure and blood lead: a meta-analysis. J. Hum. Hypertens. 16: 123-131.

Neaton, J. D.; Kuller, L.; Stamler, J.; Wentworth, D. N. (1995) Impact of systolic and diastolic blood pressure on cardiovascular mortality. In: Laragh, J. H.; Brenner, B. M., eds. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York, NY: Raven Press Ltd.; pp. 127-144.

Needleman, H. L. (1983) Lead at low dose and the behavior of children. Neurotoxicology 4: 121-133.

Needleman, H. L. (1983) Low level lead exposure and neuropsychological performance. In: Rutter, M.; Russell Jones, R., eds. Lead versus health. New York, NY: John Wiley & Sons, Ltd.; pp. 229-248.

Needleman, H. L. (1995) Environmental lead and children's intelligence: studies included in the meta-analysis are not representative [letter]. Br. Med. J. 310: 1408.

Needleman, H. L. (1995) Making models of real world events: the use and abuse of inference. Neurotoxicol. Teratol. 17: 241-242.

Needleman, H. L. (2004) Low level lead exposure and the development of children. Southeast Asian J. Trop. Med. Public Health 35: 252-254.

Needleman, H. L.; Bellinger, D. (1988) Recent developments. Environ. Res. 46: 190-191.

Needleman, H. L.; Gatsonis, C. A. (1990) Low-level lead exposure and the IQ of children: a meta-analysis of modern studies. JAMA J. Am. Med. Assoc. 263: 673-678.

Needleman, H. L.; Gunnoe, C.; Leviton, A.; Reed, R.; Peresie, H.; Maher, C.; Barrett, P. (1979) Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N. Engl. J. Med. 300: 689-695.

Needleman, H. L.; Leviton, A.; Bellinger, D. (1982) Lead-associated intellectual deficit. N. Engl. J. Med. 306: 367.

Needleman, H. L.; Rabinowitz, M.; Leviton, A.; Linn, S.; Schoenbaum, S. (1984) The relationship between prenatal exposure to lead and congenital anomalies. JAMA J. Am. Med. Assoc. 251: 2956-2959.

Needleman, H. L.; Schell, A.; Bellinger, D.; Leviton, A.; Allred, E. N. (1990) The long-term effects of exposure to low doses of lead in childhood; an 11-year follow-up report. N. Engl. J. Med. 322: 83-88.

Needleman, H. L.; Riess, J. A.; Tobin, M. J.; Biesecker, G. E.; Greenhouse, J. B. (1996) Bone lead levels and delinquent behavior. JAMA J. Am. Med. Assoc. 275: 363-369.

Needleman, H. L.; McFarland, C.; Ness, R. B.; Fienberg, S. E.; Tobin, M. J. (2002) Bone lead levels in adjudcated delinquents. A case control study. Neurotoxicol. Teratol. 24: 711-717.

Neisser, U.; Boodoo, G.; Bouchard, T. J.; Boykin, A. W.; Brody, N.; Ceci, S. J.; Halpern, D. F.; Loehlin, J. C.; Perloff, R.; Sternberg, R. J.; Urbina, S. (1996) Intelligence: knowns and unknowns. Am. Psychol. 51: 77-101.

Nenov, V. D.; Taal, M. W.; Sakharova, O. V.; Brenner, B. M. (2000) Multi-hit nature of chronic renal disease. Curr. Opin. Nephrol. Hypertens. 9: 85-97.

Neri, L. C.; Hewitt, D.; Orser, B. (1988) Blood lead and blood pressure: analysis of cross-sectional and longitudinal data from Canada. In: Victery, W., ed. Symposium on lead-blood pressure relationships; April 1987; Chapel Hill, NC. Environ. Health Perspect. 78: 123-126.

Nevin, R. (2000) How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environ. Res. 83: 1-22.

Nezhdanova, M. V. (1996) Frequency and structure of renal pathology in Saransk in dependence of degree of lead pollution. Pediatriya (Moscow) (2): 72-73.

Ng, T. P.; Goh, H. H.; Ng, Y. L.; Ong, H. Y.; Ong, C. N.; Chia, K. S.; Chia, S. E.; Jeyaratnam, J. (1991) Male endocrine functions in workers with moderate exposure to lead. Br. J. Ind. Med. 48: 485-491.

Nilsson, U.; Attewell, R.; Christoffersson, J.-O.; Schutz, A.; Ahlgren, L.; Skerfving, S.; Mattsson, S. (1991) Kinetics of lead in bone and blood after end of occupational exposure. Pharmacol. Toxicol. (Copenhagen) 68: 477-484.

Niu, Q.; He, S. C.; Li, H. Y.; Wang, J. Y.; Dai, F. Y.; Chen, Y. L. (2000) A comprehensive neurobehavioral and neurophysiological study for low level lead-exposed workers. G. Ital. Med. Lav. Ergon. 22: 299-304.

Noda, H.; Sugiyama, S.; Yamaguchi, M.; Tatsumi, S.; Sano, Y.; Konishi, S.; Furutani, A.; Yoshimura, M. (1993) Studies on secular changes in the concentration of lead accumulated in organs and rib of Japanese. Jpn. J. Leg. Med. 47: 147-152.

Nolte, J. (1993). The human brain: an introduction to its functional anatomy. Mosby Year Book Publishers: St. Louis, MO.

Nomiyama, K.; Nomiyama, H.; Liu, S. J.; Tao, Y. X.; Nomiyama, T.; Omae, K. (2002) Lead induced increase of blood pressure in female lead workers. Occup. Environ. Med. 59: 734-738.

Noonan, C. W.; Sarasua, S. M.; Campagna, D.; Kathman, S. J.; Lybarger, J. A.; Mueller, P. W. (2002) Effects of exposure to low levels of environmental cadmium on renal biomarkers. Environ. Health Perspect. 110: 151-155.

Nordberg, M.; Winblad, B.; Fratiglioni, L.; Basun, H. (2000) Lead concentrations in elderly urban people related to blood pressure and mental performance: results from a population-based study. Am. J. Ind. Med. 38: 290-294.

Nordenson, I.; Beckman, G.; Beckman, L.; Nordstrom, S. (1978) Occupational and environmental risks in and around a smelter in northern Sweden. IV. Chromosomal aberrations in workers exposed to lead. Hereditas 88: 263-267.

Nordstrom, S.; Beckman, L.; Nordenson, I. (1978a) Occupational and environmental risks in and around a smelter in northern Sweden: I. variations in birth weight. Hereditas (Lund, Swed.) 88: 43-46.

Nordstrom, S.; Beckman, L.; Nordenson, I. (1978b) Occupational and environmental risks in and around a smelter in northern Sweden: III. frequencies of spontaneous abortion. Hereditas (Lund, Swed.) 88: 51-54.

Nordstrom, S.; Beckman, L.; Nordenson, I. (1979) Occupational and environmental risks in and around a smelter in northern Sweden. V. Spontaneous abortion among female employees and decreased birth weight in their offspring. Hereditas 90: 291-296.

Nowack, R.; Wiecek, A.; Ritz, E. (1992) Lead and hypertension. In: Berlyne, G. M., ed. The kidney today. Selected topics in renal science. Basel, Switzerland: Karger; pp. 25-34. (Contributions to nephrology: v. 100).

Nuyts, G. D.; D'Haese, P. C.; Elseviers, M. M.; De Broe, M. E. (1989) Renal dysfunction and lead exposure [letter]. Am. J. Nephrol. 9: 85-86.

Nuyts, G. D.; Van Vlem, E.; Thys, J.; De Leersnijder, D.; D'Haese, P. C.; Elseviers, M. M.; De Broe, M. E. (1995) New occupational risk factors for chronic renal failure. Lancet 346: 7-11.

Nystrom-Rosander, C.; Lindh, U.; Friman, G.; Lindqvist, O.; Thelin, S.; Ilback, N. G. (2004) Trace element changes in sclerotic heart valves from patients are expressed in their blood. Biometals 17: 121-128.

O'Dowd, P. (2002) Controversies regarding low blood lead level harm. Med. Health 85: 345-348.

O'Flaherty, E. J. (1991) Physiologically based models for bone-seeking elements. III. Human skeletal and bone growths. Toxicol. Appl. Pharmacol. 111: 332-341.

O'Flaherty, E. J. (1993) Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans. Toxicol. Appl. Pharmacol. 118: 16-29.

O'Flaherty, E. J. (1995) Physiologically based models for bone-seeking elements: V. Lead absorption and disposition in childhood. Toxicol. Appl. Pharmacol. 131: 297-308.

O'Flaherty, E. J.; Hammond, P. B.; Lerner, S. I. (1982) Dependence of apparent blood lead half-life on the length of previous lead exposure in humans. Fundam. Appl. Toxicol. 2: 49-54.

O'Flaherty, E. J.; Inskip, M. J.; Franklin, C. A.; Durbin, P. W.; Manton, W. I.; Baccanale, C. L. (1998) Evaluation and modification of a physiologically based model of lead kinetics using data from a sequential isotope study in cynomolgus monkeys. Toxicol. Appl. Pharmacol. 149: 1-16.

Oishi, H.; Nomiyama, H.; Nomiyama, K.; Tomokuni, K. (1996) Comparison between males and females with respect to the porphyrin metabolic disorders found in workers occupationally exposed to lead. Int. Arch. Occup. Environ. Health 68: 298-304.

Oliveira, S.; Aro, A.; Sparrow, D.; Hu, H. (2002) Season modifies the relationship between bone and blood lead levels: the Normative Aging Study. Arch. Environ. Health 57: 466-472.

Oliver, T. (1911) Lead poisoning and the race. Br. Med. J. 1(2628): 1096-1098.

Olsen, G. W.; Bodner, K. M.; Ramlow, J. M.; Ross, C. E.; Lipshultz, L. I. (1995) Have sperm counts been reduced 50 percent in 50 years? A statistical model revisited. Fertil. Steril. 63: 887-893.

Olsson, I.-M.; Bensryd, I.; Lundh, T.; Ottosson, H.; Skerfving, S.; Oskarsson, A. (2002) Cadmium in blood and urine--impact of sex, age, dietary intake, iron status, and former smoking--association of renal effects. Environ. Health Perspect. 110: 1185-1190.

Omae, K.; Sakurai, H.; Higashi, T.; Muto, T.; Ichikawa, M.; Sasaki, N. (1990) No adverse effects of lead on renal function in lead-exposed workers. Ind. Health 28: 77-83.

Onalaja, A. O.; Claudio, L. (2000) Genetic susceptibility to lead poisoning. Environ. Health Perspect. Suppl. 108(1): 23-28.

Oneglia, C.; Apostoli, P.; Rusconi, C. (1998) Vasospastic angina in a patient with chronic lead intoxication: a possible cause-effect relationship? Cardiovasc. Drugs Ther. 12: 71-73.

Ong, C. N.; Endo, G.; Chia, K. S.; Phoon, W. O.; Ong, H. Y. (1987) Evaluation of renal function in workers with low blood lead levels. In: Foa, V.; Emmett, E. A.; Maroni, M.; Colombi, A., eds. Occupational and environmental chemical hazards: cellular and biochemical indices for monitoring toxicity. New York, NY: Halstead Press; pp. 327-333.

Opler, M. G. A.; Brown, A. S.; Graziano, J.; Desai, M.; Zheng, W.; Schaefer, C.; Factor-Litvak, P.; Susser, E. S. (2004) Prenatal lead exposure, "delta"-aminolevulinic acid, and schizophrenia. Environ. Health Perspect. 112: 548-552.

Orban B. (1953) Oral Histology and Embryology. Mosby Year Book Publishers: St. Louis, MO.

O'Riordan, M. L.; Evans, H. J. (1974) Absence of significant chromosome damage in males occupationally exposed to lead. Nature (London) 247: 50-53.

Orssaud, G.; Claude, J. R.; Moreau, T.; Lellouch, J.; Juguet, B.; Festy, B. (1985) Blood lead concentration and blood pressure. Br. Med. J. 290: 244.

Osman, K.; Pawlas, K.; Schutz, A.; Gazdzik, M.; Sokal, J. A.; Vahter, M. (1999) Lead exposure and hearing effects in children in Katowice, Poland. Environ. Res. 80: 1-8.

Osterberg, K.; Borjesson, J.; Gerhardsson, L.; Schutz, A.; Skerfving, S. (1997) A neurobehavioural study of long-term occupational inorganic lead exposure. Sci. Total Environ. 201: 39-51.

Osterloh, J. D.; Kelly, T. J. (1999) Study of the effect of lactational bone loss on blood lead concentrations in humans. Environ. Health Perspect. 107: 187-194.

Osterloh, J. D.; Selby, J. V.; Bernard, B. P.; Becker, C. E.; Menke, D. J.; Tepper, E.; Ordonez, J. D.; Behrens, B. (1989) Body burdens of lead in hypertensive nephropathy. Arch. Environ. Health 44: 304-310.

Osterode, W.; Barnas, D.; Geissler, K. (1999) Dose dependent reduction of erythroid progenitor cells and inappropriate erythropoietin response in exposure to lead: new aspects of anaemia induced by lead. Occup. Environ. Med. 56: 106-109.

Otto, D. A.; Fox, D. A. (1993) Auditory and visual dysfunction following lead exposure. Presented at: Ninth international neurotoxicology conference; October 1991; Little Rock, AR. Neurotoxicology 14(2-3): 191-207.

Otto, D.; Robinson, G.; Baumann, S.; Schroeder, S.; Mushak, P.; Kleinbaum, D.; Boone, L. (1985) Five-year follow-up study of children with low-to-moderate lead absorption: electrophysiological evaluation. Environ. Res. 38: 168-186.

Paksy, K.; Gati, I.; Naray, M.; Rajczy, K. (2001) Lead accumulation in human ovarian follicular fluid, and in vitro effect of lead on progesterone production by cultured human ovarian granulosa cells. J. Toxicol. Environ. Health A 62: 359-366.

Palus, J.; Rydzynski, K.; Dziubaltowska, E.; Wyszynska, K.; Natarajan, A. T.; Nilsson, R. (2003) Genotoxic effects of occupational exposure to lead and cadmium. Mutat. Res. 540: 19-28.

Parkinson, D. K.; Hodgson, M. J.; Bromet, E. J.; Dew, M. A.; Connell, M. M. (1987) Occupational lead exposure and blood pressure. Br. J. Ind. Med. 44: 744-748.

Paschal, D. C.; Burt, V.; Caudill, S. P.; Gunter, E. W.; Pirkle, J. L.; Sampson, E. J.; Miller, D. T.; Jackson, R. J. (2000) Exposure of the U.S. population aged 6 years and older to cadmium: 1988-1994. Arch. Environ. Contam. Toxicol. 38: 377-383.

Paterson, L. J.; Raab, G. M.; Hunter, R.; Laxen, D. P. H.; Fulton, M.; Fell, G. S.; Halls, D. J.; Sutcliffe, P. (1988) Factors influencing lead concentrations in shed deciduous teeth. Sci. Total Environ. 74: 219-233.

Payton, M.; Hu, H.; Sparrow, D.; Weiss, S. T. (1994) Low-level lead exposure and renal function in the normative aging study. Am. J. Epidemiol. 140: 821-829.

Payton, M.; Riggs, K. M.; Spiro, A., III; Weiss, S. T.; Hu, H. (1998) Relations of bone and blood lead to cognitive function: the VA Normative Aging Study. Neurotoxicol. Teratol. 20: 19-27.

Peplow, D.; Edmonds, R. (2004) Health risks associated with contamination of groundwater by abandoned mines near Twisp in Okanogan County, Washington, USA. Environ. Geochem. Health 26: 69-79.

Perez-Bravo, F.; Ruz, M; Moran-Jimenez, M. J.; Olivares, M.; Rebolledo, A.; Codoceo, J.; Sepulveda, J.; Jenkin, A.; Santos, J. L.; Fontanellas, A. (2004) Association between aminolevulinate dehydrase genotypes and blood lead levels in children from a lead-contaminated area in Antofagasta, Chile. Arch. Environ. Contam. Toxicol. 47(2): 276-280.

Pergande, M.; Jung, K.; Precht, S.; Fels, L. M.; Herbort, C.; Stolte, H. (1994) Changed excretion of urinary proteins and enzymes by chronic exposure to lead. Nephrol. Dial. Transplant. 9: 613-618.

Pesch, B.; Haerting, J.; Ranft, U.; Klimpel, A.; Oelschlagel, B.; Schill, W.; MURC Study Group. (2000) Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. Int. J. Epidemiol. 29: 1014-1024.

Peterson, K. E.; Salganik, M.; Campbell, C.; Rhoads, G. G.; Rubin, J.; Berger, O.; Ware, J. H.; Rogan, W. (2004) Effect of succimer on growth of preschool children with moderate blood lead levels. Environ. Health Perspect. 112: 233-237.

Pilion, J. J.; Schmitt, N.; Rowe, J.; Gelpke, P. M. (1997) Effect of lead on fetal growth in a Canadian smelter city, 1961-1990. Arch. Environ. Health 52: 472-475.

Pineda-Zavaleta, A. P.; Gracia-Vargas, G.; Borja-Aburto, V. H.; Acosta-Saavedea, L. C.; Vera Aguilar, E.; Gomez-Munoz, A.; Cebrian, M. E. Calderon-Aranda, E. S. (2004) Nitric oxide and superoxide anion production in monocytes from children exposed to arsenic and lead in region Lagunera, Mexico. Toxicol. Appl. Pharmacol. 198: 283-290.

Pinkerton, L. E.; Biagini, R. E.; Ward, E. M.; Hull, R. D.; Deddens, J. A.; Boeniger, M. F.; Schnorr, T. M.; MacKenzie, B. A.; Luster, M. I. (1998) Immunologic findings among lead-exposed workers. Am. J. Ind. Med. 33: 400-408.

Pinto de Almeida, A. R.; Carvalho, F. M.; Spinola, A. G.; Rocha, H. (1987) Renal dysfunction in Brazilian lead workers. Am. J. Nephrol. 7: 455-458.

Piomelli, S.; Seaman, C.; Zullow, D.; Curran, A.; Davidow, B. (1982) Threshold for lead damage to heme synthesis in urban children. Proc. Natl. Acad. Sci. U. S. A. 79: 3335-3339.

Pirkle, J. L.; Brody, D. J.; Gunter, E. W.; Kramer, R. A.; Paschal, D. C.; Flegal, K. M.; Matte, T. D. (1994) The decline in blood lead levels in the United States: the National Health and Nutrition Examination Surveys (NHANES). JAMA J. Am. Med. Assoc. 272: 284-291.

Pirkle, J. L.; Kaufmann, R. B.; Brody, D. J.; Hickman, T.; Gunter, E. W.; Paschal, D. C. (1998) Exposure of the U.S. population to lead, 1991-1994. Environ. Health Perspect. 106: 745-750.

Poblano, A.; Rothenberg, S. J.; Schnaas, L.; Elias, Y.; Cruz, M. L. (2001) Spatial distribution of EEG theta activity as a function of lifetime lead exposure in 9-year-old children. Neurotoxicology 22: 439-446.

Pocock, S. J.; Shaper, A. G.; Walker, M.; Wale, C. J.; Clayton, B.; Delves, T.; Lacey, R. F.; Packham, R. F.; Powell, P. (1983) The effects of tap water lead, water hardness, alcohol, and cigarettes on blood lead concentrations. J. Epidemiol. Community Health 37: 1-7.

Pocock, S. J.; Shaper, A. G.; Ashby, D.; Delves, T.; Whitehead, T. P. (1984) Blood lead concentration, blood pressure, and renal function. Br. Med. J. 289: 872-874.

Pocock, S. J.; Ashby, D.; Smith, M. A. (1987) Lead exposure and children's intellectual performance. Int. J. Epidemiol. 16: 57-67.

Pocock, S. J.; Smith, M.; Baghurst, P. (1994) Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. Br. Med. J. 309: 1189-1197.

Pocock, S. J.; Smith, M.; Baghurst, P. (1995) Environmental lead and children's intelligence [author's reply]. Br. Med. J. 310: 1409.

Poleckinger, B.; Ulm, M. R.; Golaszewski, T.; Meisinger, V.; Suzin, J.; Grudzinska, M.; Zdziennicki, A.; Dadak, D. (1996) Lead, mercury, and cadmium exposure of neonates in Poland compared to Austria and other European countries. Trace Elem. Electrol. 13: 22-25.

Pollock, C. A.; Ibels, L. S. (1988) Lead intoxication in Sydney Harbour bridge workers. Aust. N. Z. J. Med. 18: 46-52.

Popovac, D.; Graziano, J.; Seaman, C.; Kaul, B.; Colakovic, B.; Popovac, R.; Osmani, I.; Haxhiu, M.; Begraca, M.; Bozovic, Z.; Mikic, M. (1982) Elevated blood lead in a population near a lead smelter in Kosovo, Yugoslavia. Arch. Environ. Health 37: 19-23.

Popovic, M.; McNeill, F. E.; Chettle, D. R.; Webber, C. E.; Lee, C. V.; Kaye, W. E. (2005) Impact of occupational exposure on lead levels in women. Environ. Health Perspect. 113: 478-484.

Port, S.; Garfinkel, A.; Boyle, N. (2000) There is a non-linear relationship between mortality and blood pressure. Eur. Heart J. 21: 1635-1638.

Poulos, L.; Qammaz, S.; Athanaselis, S.; Maravelias, C.; Koutselinis, A. (1986) Statistically significant hematopoietic effects of low blood lead levels. Arch. Environ. Health 41: 384-386.

Pounds, J. G.; Long, G. J.; Rosen, J. F. (1991) Cellular and molecular toxicity of lead in bone. Environ. Health Perspect. 91: 17-32.

Powell, J. J.; Greenfield, S. M.; Thompson, R. P. H.; Cargnello, J. A.; Kendall, M. D.; Landsberg, J. P.; Watt, F.; Delves, H. T.; House, I. (1995) Assessment of toxic metal exposure following the Camelford water pollution incident: evidence of acute mobilization of lead into drinking water. Analyst (Cambridge, U. K.) 120: 793-798.

Price, J.; Grudzinski, A. W.; Craswell, P. W.; Thomas, B. J. (1992) Bone lead measurements in patients with chronic renal disease studied over time. Arch. Environ. Health 47: 330-335.

Price, R. G.; Patel, S.; Chivers, I.; Milligan, P.; Taylor, S. A. (1999) Early markers of nephrotoxicity: detection of children at risk from environmental pollution. Ren. Fail. 21: 303-308.

Pringle, E.; Phillips, C.; Thijs, L.; Davidson, C.; Staessen, J. A.; de Leeuw, P. W.; Jaaskivi, M.; Nachev, C.; Parati, G.; O'Brien, E. T.; Tuomilehto, J.; Webster, J.; Bulpitt, C. J.; Fagard, R. H.; Syst-Eur Investigators. (2003) Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. J. Hypertens. 21: 2251-2257.

Proctor, S. P.; Rotnitzky, A.; Sparrow, D.; Weiss, S. T.; Hu, H. (1996) The relationship of blood lead and dietary calcium to blood pressure in the normative aging study. Int. J. Epidemiol. 25: 528-536.

Prospective Studies Collaboration. (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 360: 1903-1913.

Prpic-Majic, D.; Bobic, J.; Simic, D.; House, D. E.; Otto, D. A.; Jurasovic, J.; Pizent, A. (2000) Parental education as a confounder in the assessment of low level lead effect on psychological functions in children. Cent. Eur. J. Public Health 8(suppl.): 69.

Prpic-Majic, D.; Bobicc, J.; Simicc, D.; House, D. E.; Otto, D. A.; Jurasovicc, J.; Pizent, A. (2000) Lead absorption and psychological function in Zabreb (Croatia) school children. Neurotoxicol. Teratol. 22: 347-356.

Pueschel, S. M.; Kopito, L.; Schwachman, H. (1972) Children with an increased lead burden. A screening and follow-up study. JAMA J. Am. Med. Assoc. 222: 462-466.

Puzas, J. E. (2000) Osteotoxicology: the role of lead in bone disease. Curr. Opin. Orthop. 11: 360-365.

Puzas, J. E.; Sickel, M. J.; Felter, M. E. (1992) Osteoblasts and chondrocytes are important target cells for the toxic effects of lead. Neurotoxicology 13: 783-788.

Pyatt, D. W.; Zheng, J.-H.; Stillman, W. S.; Irons, R. D. (1996) Inorganic lead activates NF-kB in primary human CD4+ T lymphocytes. Biochem. Biophys. Res. Commun. 227: 380-385.

Quandt, R. E. (1958) The estimation of the parameters of a linear regression system obeying two separate regimes. J. Am. Stat. Assoc. 53: 873-880.

Que Hee, S.S.; Boyle, J.R. (1988) Simultaneous multielemental analysis of some environmental and biological samples by inductively coupled plasma atomic emission spectrometry. Anal. Chem. 60: 1033-1042.

Que Hee, S. S.; MacDonald, T. J.; Bornschein, R. L. (1985) Blood lead by furnace-Zeeman atomic absorption spectrophotometry. Microchem. J. 32: 55-63.

Queiroz, M. L. S.; Almeida, M.; Gallao, M. I.; Hoehr, N. F. (1993) Defective neutrophil function in workers occupationally exposed to lead. Pharmacol. Toxicol. 72: 73-77.

Queiroz, M. L.; Costa, F. F.; Bincoletto, C.; Perlingeiro, R. C. R.; Dantas, D. C. M.; Cardoso, M. P.; Almeida, M. (1994a) Engulfment and killing capabilities of neutrophils and phagocytic splenic function in persons occupationally exposed to lead. Int. J. Immunopharmacol. 16: 239-244.

Queiroz, M. L. S.; Perlingeiro, R. C. R.; Bincoletto, C.; Almeida, M.; Cardoso, M. P.; Dantas, D. C. M. (1994b) Immunoglobulin levels and cellular immune function in lead exposed workers. Immunopharmacol. Immunotoxicol. 16: 115-128.

Raab, G. M.; Thomson, G. O. B.; Boyd, L.; Fulton, M.; Laxen, D. P. H. (1990) Blood lead levels, reaction time, inspection time and ability in Edinburgh children. Br. J. Dev. Psychol. 8: 101-118.

Rabinowitz, M. B. (1991) Toxicokinetics of bone lead. Environ. Health Perspect. 91: 33-37.

Rabinowitz, M. (1993) Declining blood lead levels and cognitive change in children [letter]. JAMA J. Am. Med. Assoc. 270: 827-829.

Rabinowitz, M. B. (1995) Environmental lead and children's intelligence: Taiwan results are not included [letter]. Br. Med. J. 310: 397.

Rabinowitz, M. B.; Wetherill, G. W.; Kopple, J. D. (1973) Lead metabolism in the normal human: stable isotope studies. Science (Washington, DC) 182: 725-727.

Rabinowitz, M. B.; Wetherill, G. W.; Kopple, J. D. (1976) Kinetic analysis of lead metabolism in healthy humans. J. Clin. Invest. 58: 260-270.

Rabinowitz, M. B.; Wetherill, G. W.; Kopple, J. D. (1977) Magnitude of lead intake from respiration by normal man. J. Lab. Clin. Med. 90: 238-248.

Rabinowitz, M.; Needleman, H.; Burley, M.; Finch, H.; Rees, J. (1984) Lead in umbilical blood, indoor air, tap water, and gasoline in Boston. Arch. Environ. Health 39: 299-301.

Rabinowitz, M.; Bellinger, D.; Leviton, A.; et al. (1987) Pregnancy hypertension, blood pressure during labor, and blood lead levels. Hypertension 10: 447-451.

Rabinowitz, M. B.; Leviton, A.; Bellinger, D. C. (1989) Blood lead--tooth lead relationship among Boston Children. Bull. Environ. Contam. Toxicol. 43: 485-492.

Rabinowitz, M. B.; Allred, E. N.; Bellinger, D. C.; Leviton, A.; Needleman, H. L. (1990) Lead and childhood propensity to infectious and allergic disorders: is there an association? Bull. Environ. Contam. Toxicol. 44: 657-660.

Rabinowitz, M. B.; Bellinger, D.; Leviton, A.; Wang, J.-D. (1991) Lead levels among various deciduous tooth types. Bull. Environ. Contam. Toxicol. 47: 602-608.

Rabinowitz, M. B.; Wang, J.-D.; Soong, W. T. (1992) Children's classroom behavior and lead in Taiwan. Bull. Environ. Contam. Toxicol. 48: 282-288.

Rabinowitz, M. B.; Leviton, A.; Bellinger, D. (1993) Relationships between serial blood lead levels and exfoliated tooth dentin lead levels: models of tooth lead kinetics. Calcif. Tissue Int. 53: 338-341.

Rahman, A.; Hakeem, A. (2003) Blood lead levels during pregnancy and pregnancy outcome in Karachi women. J. Pakistan Med. Assoc. 53: 529-533.

Rahman, A.; Maqbool, E.; Zuberi, H. S. (2002) Lead-associated deficits in stature, mental ability and behaviour in children in Karachi. Ann. Trop. Paediatr. 22: 301-311.

Rajah, T.; Ahuja, Y. R. (1995) In vivo genotoxic effects of smoking and occupational lead exposure in printing press workers. Toxicol. Lett. 76: 71-75.

Rajah, T. T.; Ahuja, Y. R. (1996) In vivo genotoxicity of alcohol consumption and lead exposure in printing press workers. Alcohol 13: 65-68.

Rajegowda, B. K.; Glass, L.; Evans, H. E. (1972) Lead concentrations in the newborn infant. J. Pediatr. 80: 116-117.

Ratzon, N.; Froom, P.; Leikin, E.; Kristal-Boneh, E.; Ribak, J. (2000) Effect of exposure to lead on postural control in workers. Occup. Environ. Med. 57: 201-203.

Refowitz, R. M. (1984) Thyroid function and lead: no clear relationship. J. Occup. Med. 26: 579-583.

Reigart, J. R.; Graber, C. D. (1976) Evaluation of the humoral immune response of children with low level lead exposure. Bull. Environ. Contam. Toxicol. 16: 112-117.

Reimer, W.; Tittelbach, U. (1989) Verhalten von Herzfrequenz, Blutdruck und systolischen Zeitintervallen in Ruhe und wahrend Einhandarbeit bei Bleiexponierten und Kontrollpersonen [Heart rate, blood pressure and systolic time interval in rest and during single-hand exertion in persons exposed to lead and in control subjects]. Z. Gesamte Hyg. Ihre Grenzgeb. 35: 491-492.

Rencher, A. C.; Carter, M. W.; McKee, D. W. (1977) A retrospective epidemiological study of mortality at a large western copper smelter. J. Occup. Med. 19: 754-758.

Research Triangle Institute. (1999) Health effects. In: Toxicological profile for lead. Atlanta, GA: U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

Rhainds, M.; Levallois, P. (1997) Effects of maternal cigarette smoking and alcohol consumption on blood lead levels of newborns. Am. J. Epidemiol. 145: 250-257.

Rhainds, M.; Levallois, P.; Dewailly, E.; Ayotte, P. (1999) Lead, mercury, and organochlorine compound levels in cord blood in Quebec, Canada. Arch. Environ. Health 54: 40-47.

Rhodes, D.; Spiro, A.; Aro, A.; Hu, H. (2003) Relationship of bone and blood lead levels to psychiatric symptoms: The Normative aging Study. J. Occup. Environ. Med. 45: 1144-1151.

Rico, J.; Kordas, K.; et al. (2005) The efficacy of iron and/or zinc supplementation on cognitive performance of lead-exposed mexican school children: a randomized, placebo-controlled trial. Pediatrics: in press.

Ris, M. D. (2003) Causal inference in lead research: introduction to the special section on the neurobehavioral effects of environmental lead. Child Neuropsychol. 9: 1-9.

Ris, M. D.; Dietrich, K. N.; Succop, P. A.; Berger, O. G.; Bornschein, R. L. (2004) Early exposure to lead and neuropsychological outcome in adolescence. J. Int. Neuropsychol. Soc. 10: 261-270.

Risch, H. A.; Burch, J. D.; Miller, A. B.; Hill, G. B.; Steele, R.; Howe, G. R. (1988) Occupational factors and the incidence of cancer of the bladder in Canada. Br. J. Ind. Med. 45: 361-367.

Robertson, W. O. (1996) Elevated environmental lead levels in a day care setting. Arch. Pediatr. Adolesc. Med. 150: 556.

Robins, J. M.; Cullen, M. R.; Connors, B. B.; Kayne, R. D. (1983) Depressed thyroid indexes associated with occupational exposure to inorganic lead. Arch. Intern. Med. 143: 220-224.

Rodamilans, M.; Osaba, M. J. M.; To-Figueras, J.; Rivera Fillat, F.; Marques, J. M.; Perez, P.; Corbella, J. (1988) Lead toxicity on endocrine testicular function in an occupationally exposed population. Hum. Toxicol. 7: 125-128.

Roderer, G.; Doenges, K. H. (1983) Influence of trimethyl lead and inorganic lead on the in vitro assembly of microtubules from mammalian brain. Neurotoxicology 4: 171-180.

Roelofs-Iverson, R. A.; Mulder, D. W.; Elveback, L. R.; Kurland, L. T.; Molgaard, C. A. (1984) Amyotrophic lateral sclerosis and heavy metals: a pilot case study. Neurology 34: 393-395.

Roels, H.; Lauwerys, R. (1987) Evaluation of dose-effect and dose-response relationships for lead exposure in different Belgian population groups (fetus, child, adult men and women). Trace Elem. Med. 4: 80-87.

Roels, H. A.; Balis-Jacques, M. N.; Buchet, J.-P.; Lauwerys, R. R. (1979) The influence of sex and of chelation therapy on erythrocyte protoporphyrin and urinary "delta"-aminolevulinic acid in lead-exposed workers. J. Occup. Med. 21: 527-539.

Roels, H. A.; Lauwerys, R. R.; Buchet, J. P.; Bernard, A. M.; Vos, A.; Oversteyns, M. (1989) Health significance of cadmium induced renal dysfunction: a five year follow up. Br. J. Ind. Med. 46: 755-764.

Roels, H.; Lauwerys, R.; Konings, J.; Buchet, J.-P.; Bernard, A.; Green, S.; Bradley, D.; Morgan, W.; Chettle, D. (1994) Renal function and hyperfiltration capacity in lead smelter workers with high bone lead. Occup. Environ. Med. 51: 505-512.

Roels, H.; Konings, J.; Green, S.; Bradley, D.; Chettle, D.; Lauwerys, R. (1995) Time-integrated blood lead concentration is a valid surrogate for estimating the cumulative lead dose assessed by tibial lead measurement. Environ. Res. 69: 75-82.

Roels, H. A.; Van Assche, F. J.; Oversteyns, M.; De Groof, M.; Lauwerys, R. R.; Lison, D. (1997) Reversibility of microproteinuria in cadmium workers with incipient tubular dysfunction after reduction of exposure. Am. J. Ind. Med. 31: 645-652.

Rogan, W. J.; Ware, J. H. (2003) Exposure to lead in children -- how low is low enough? N. Engl. J. Med. 348: 1515-1516.

Rogan, W. J.; Treatment of Lead-Exposed Clinical Trial Group. (1998) The treatment of lead-exposed children (TLC) trial: design and recruitment for a study of the effect of oral chelation on growth and develpment in toddlers. Paediatr. Perinat. Epidemiol. 12: 313-333.

Rogan, W. J.; Dietrich, K. N.; Ware, J. H.; et al. (2001) The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. New Engl. J. Med. 344: 1421-1426.

Rom, W. N. (1976) Effects of lead on the female and reproduction: a review. Mt. Sinai J. Med. 43: 542-552.

Romeo, R.; Aprea, C.; Boccalon, P.; Orsi. D; Porcelli, B.; Sartorelli, P. (1996) Serum erthropoietin and blood lead concentrations. Int. Arch. Occup. Environ. Health 69: 73-75.

Romieu, I.; Carreon, T.; Lopez, L.; Palazuelos, E.; Rios, C.; Manuel, Y.; Hernandez-Avila, M. (1995) Environmental urban lead exposure and blood lead levels in children of Mexico City. Environ. Health Perspect. 103: 1036-1040.

Rose, G.; Day, S. (1990) The population mean predicts the number of deviant individuals. Br. Med. J. 301: 1031-1034.

Rosen, J. F.; Mushak, P. (2001) Primary prevention of childhood lead poisoning -- the only solution [comment]. N. Engl. J. Med. 344: 1470-1471.

Rosen, J. F.; Pounds, J. G. (1998) "Severe chronic lead insult that maintains body burdens of lead related to those in the skeleton": observations by Dr. Clair Patterson conclusively demonstrated. Environ. Res. 78: 140-151.

Rosen, J. F.; Chesney, R. W.; Hamstra, A.; DeLuca, H. F.; Mahaffey, K. R. (1980) Reduction in 1,25-dihydroxyvitamin D in children with increased lead absorption. N. Engl. J. Med. 302: 1128-1131.

Rosen, J. F.; Markowitz, M. E.; Bijur, P. E.; Jenks, S. T.; Wielopolski, L.; Kalef-Ezra, J. A.; Slatkin, D. N. (1989) L-line x-ray fluorescence of cortical bone lead compared with the CaNa2EDTA test in lead-toxic children: public health implications. Proc. Natl. Acad. Sci. U. S. A. 86: 685-689,

Rosenthal, R. (1984) Meta-analytic procedures for social research. Beverly Hills, CA: Sage Publications.

Roses, O. E.; Alvarez, S.; Conti, M. I.; Nobile, R. A.; Villaamil, E. C. (1989) Correlation between lead and prolactin in males exposed and unexposed to lead in Buenos Aires (Argentina) area. Bull. Environ. Contam. Toxicol. 42: 438-442.

Rossner, P.; Boffetta, P.; Ceppi, M.; Bonassi, S.; Smerhovsky, Z.; Landa, K.; Juzova, D.; Sram, R. J. (2005) Chromosomal aberrations in lymphocytes of healthy subjects and risk of cancer. Environ. Health Perspect. 113: 517-520.

Rothenberg, S. J.; Rothenberg, J. C. (2005) Testing the dose-response specification in epidemiology: public health and policy consequences for lead. Environ. Health Perspect.: in press.

Rothenberg, S. J.; Schnaas, L.; Cansino-Ortiz, S.; Perroni-Hernandez, E.; de la Torre, P.; Neri-Mendez, C.; Ortega, P.; Hidalgo-Loperena, H.; Svendsgaard, D. (1989) Neurobehavioral deficits after low level lead exposure in neonates: the Mexico City pilot study. Neurotoxicol. Teratol. 11: 85-93.

Rothenberg, S. J.; Karchmer, S.; Schnaas, L.; Perroni, E.; Zea, F.; Alba, J. F. (1994) Changes in serial blood lead levels during pregnancy. Environ. Health Perspect. 102: 876-880.

Rothenberg, S. J.; Cansino, S.; Sepkoski, C.; Torres, L. M.; Medina, S.; Schnaas, L.; Poblano, A.; Karchmer, S. (1995) Prenatal and perinatal lead exposures alter acoustic cry parameters of neonate. Neurotoxicol. Teratol. 17: 151-160.

Rothenberg, S. J.; Karchmer, S.; Schnaas, L.; Perroni, E.; Zea, F.; Salinas, V.; Alba, J. F. (1996) Maternal influences on cord blood lead levels. J. Exposure Anal. Environ. Epidemiol. 6: 211-227.

Rothenberg, S. J.; Manalo, M.; Jiang, J.; Cuellar, R.; Reyes, S.; Sanchez, M.; Diaz, M.; Khan, F.; Aguilar, A.; Reynoso, B.; Juaregui, M.; Acosta, S.; Johnson, C. (1999) Blood lead level and blood pressure during pregnancy in south central Los Angeles. Arch. Environ. Health 54: 382-389.

Rothenberg, S. J.; Khan, F.; Manalo, M.; Jian, J.; Cuellar, R.; Reyes, S.; Acosta, S.; Jauregui, M.; Diaz, M.; Sanchez, M.; Todd, A. C.; Johnson, C. (2000) Maternal bone lead contribution to blood lead during and after pregnancy. Environ. Res. 82: 81-90.

Rothenberg, S. J.; Kondrashov, V.; Manalo, M.; Manton, W. I.; Khan, F.; Todd, A. C.; Johnson, C. (2001) Seasonal variation in bone lead contribution to blood lead during pregnancy. Environ. Res. 85: 191-194.

Rothenberg, S. J.; Kondrashov, V.; Manalo, M.; Jiang, J.; Cuellar, R.; Garcia, M.; Reynoso, B.; Reyes, S.; Diaz, M.; Todd, A. C. (2002) Increases in hypertension and blood pressure during pregnancy with increased bone lead levels. Am. J. Epidemiol. 156: 1079-1087.

Rothenberg, S. J.; Schnaas, L.; Salgado-Valladares, M.; Casanueva, E.; Geller, A. M.; Hudnell, H. K.; Fox, D. A. (2002) Increased ERG a- and b-wave amplitudes in 7- to 10-year-old children resulting from prenatal lead exposure. Invest. Ophthalmol. Vis. Sci. 43: 2036-2044.

Rowe, J. W.; Andres, R.; Tobin, J. D.; Norris, A. H.; Shock, N. W. (1976) Age adjusted standards for creatinine clearance. Ann. Intern. Med. 84: 567-569.

Rowland, A.; Wilcox, A. (1987) Maternal blood lead [letter]. J. Epidemiol. Community Health 41: 184.

Rucoba, R. J.; Cajolet, L.; Loy, G.; Binns, H. J. (1998) Prevalence of elevated blood lead levels in inner-city pregnant women. Pediatr. Res. 43: 118A.

Ruff, H. A. (1999) Population-based data and the development of individual children: the case of low to moderate lead levels and intelligence. J. Dev. Behav. Pediatr. 20: 42-49.

Ruff, H. A.; Bijur P. E.; Markowitz, M.; Ma, Y.-C.; Rosen, J. F. (1993) Declining blood lead levels and cognitive changes in moderately lead-poisoned children. JAMA J. Am. Med. Assoc. 269: 1641-1646.

Ruff, H. A.; Markowitz, M. E.; Bijur, P. E.; Rosen, J. F.; Ma, Y.-C. (1993) Declining blood lead levels and cognitive change in children [author reply]. JAMA J. Am. Med. Assoc. 270: 828-829.

Ruff, H. A.; Markowitz, M. E.; Bijur, P. E.; Rosen, J. F. (1996) Relationships among blood lead levels, iron deficiency, and cognitive development in two-year-old children. Environ. Health Perspect. 104: 180-185.

Ryu, J. E.; Ziegler, E. E.; Nelson, S. E.; Fomon, S. J. (1983) Dietary intake of lead and blood lead concentration in early infancy. Am. J. Dis. Child. 137: 886-891.

Saenger, P.; Markowitz, M. E; Rosen, J. F. (1984) Depressed excretion of 6Beta-hydroxycortisol in lead-toxic children. J. Clin. Endocrinol. Metab. 58: 363-367.

Salkever, D. S. (1995) Updated estimates of earnings benefits from reduced exposure of children to environmental lead. Environ. Res. 70: 1-6.

Sallmen, M.; Lindbohm, M.-L.; Anttila, A.; Taskinen, H.; Hemminki, K. (1992) Paternal occupational lead exposure and congenital malformations. J. Epidemiol. Community Health 45: 519-522.

Sallmen, M.; Anttila, A.; Lindbohm, M.-L.; Kyyronen, P.; Taskinen, H.; Hemminki, K. (1995) Time to pregnancy among women occupationally exposed to lead. J. Occup. Environ. Med. 37: 931-934.

Sallmen, M.; Lindbohm, M. L.; Anttila, A.; Taskinen, H.; Hemminki, K. (2000) Time to pregnancy among the wives of men occupationally exposed to lead. Epidemiology 11: 141-147.

Salmon, P. L.; Bondarenko, O. A.; Henshaw, D. L. (1999) DOSE210, a semi-empirical model for prediction of organ distribution and radiation doses from long-term exposure to ^{210}Pb and ^{210}Po. Radiation Protection Dosimetry 82: 175-192.

Sanchez, S. E.; Larrabure, G.; Zhang, C.; Williams, M. A. (2001) Red blood cell selenium, zinc and lead levels in relation to preeclampsia risk among Peruvian women. Am. J. Epidemiol. 153(11 suppl.): S157.

Sanchez-Fructuoso, A. I.; Torralbo, A.; Arroyo, M.; Luque, M.; Ruilope, L. M.; Santos, J. L.; Cruceyra, A.; Barrientos, A. (1996) Occult lead intoxication as a cause of hypertension and renal failure. Nephrol. Dial. Transplant. 11: 1775-1780.

Sanin, L. H.; Gonzalez-Cossio, T.; Romieu, I.; Peterson, K. E.; Ruiz, S.; Palazuelos, E.; Hernandez-Avila, M.; Hu, H. (2001) Effect of maternal lead burden on infant weight and weight gain at one month of age among breastfed infants. Pediatrics 107: 1016-1023.

Sankila, R.; Karjalainen, S.; Pukkala, E.; Oksanen, H.; Hakulinen, T.; Teppo, L.; Hakama, M. (1990) Cancer risk among glass factory workers: an excess of lung cancer? Br. J. Ind. Med. 47: 815-818.

Sarasua, S. M.; Vogt, R. F.; Henderson, L. O.; Jones, P. A.; Lybarger, J. A. (2000) Serum immunoglobulins and lymphocyte subset distributions in children and adults living in communities assessed for lead and cadmium exposure. J. Toxicol. Environ. Health A. 60(1): 1-15.

Sarasua, S. M.; Mueller, P.; Kathman, S.; Campagna, D.; Uddin, M. S.; White, M. C. (2003) Confirming the utility of four kidney biomarker tests in a longitudinal follow-up study. Renal Failure 25: 797-817.

Sargent, J. D.; Dalton, M. A.; O'Connor, G. T.; Olmstead, E. M.; Klein, R. Z. (1999) Randomized trial of calcium glycerophosphate-supplemented infant formula to prevent lead absorption. Am. J. Clin. Nutr. 69: 1224-1230.

Sarto, F; Stella, M; Acqua, A. (1978) Cytogenetic study of a group of workers with increased lead absorption indices. Med. Lav. 69: 172-180.

Sata, F.; Araki, S.; Sakai, T.; Nakata, A.; Yamashita, K.; Morita, Y.; Tanigawa, T.; Miki, A. (1997) Immunological effects of CaEDTA injection: observations in two lead workers. Am. J. Ind. Med. 32: 674-680.

Sata, F.; Araki, S.; Tanigawa, T.; Morita, Y.; Sakurai, S.; Nakata, A.; Katsuno, N. (1998) Changes in T cell subpopulations in lead workers. Environ. Res. 76: 61-64.

Satarug, S.; Nishijo, M.; Ujjin, P.; Vanavanitkun, Y.; Baker, J. R.; Moore, M. R. (2004) Evidence for concurrent effects of exposure to environmental cadmium and lead on hepatic CYP2A6 phenotype and renal function biomarkers in nonsmokers. Environ. Health Perspect. 112: 1512-1518.

Satarug, S.; Ujjin, P.; Vanavanitkun, Y.; Nishijo, M.; Baker, J. R.; Moore, M. R. (2004) Effects of cigarette smoking and exposure to cadmium and lead on phenotypic variability of hepatic CYP2A6 and renal function biomarkers in men. Toxicology 204: 161-173.

Savitz, D. A.; Whelan, E. A.; Rowland, A. S.; Kleckner, R. C. (1990) Maternal employment and reproductive risk factors. Am. J. Epidemiol. 132: 933-945.

Schafer, J. H.; Glass, T. A.; Bressler, J.; Todd, A. C.; Schwartz, B. S. (2005) Blood lead in a predictor of homocysteine levels in a population-based study of older adults. Environ. Health Perspect. 113: 31-35.

Scharer, K.; Veits, G.; Brockhaus, A.; Ewers, U. (1991) High lead content of deciduous teeth in chronic renal failure. Pediatr. Nephrol. 5: 704-707.

Schaumberg, D. A.; Mendes, F.; Balaram, M.; Dana, M. R.; Sparrow, D.; Hu, H. (2004) Accumulated lead exposure and risk of age-related cataract in men. JAMA J. Am. Med. Assoc. 292: 2750-2754.

Schell, L. M.; Stark, A. D.; Gomez, M. I.; Grattan, W. A. (1997) Blood lead level, by year and season, among poor pregnant women. Arch. Environ. Health 52: 286-291.

Schell, L. M.; Czerwinski, S.; Stark, A. D.; Parsons, P. J.; Gomez, M.; Samelson, R. (2000) Variation in blood lead and hematocrit levels during pregnancy in a socioeconomically disadvantaged population. Arch. Environ. Health 55: 134-140.

Schildcrout, J. S.; Heagerty, P. J. (2005) Regressions analysis of longitudinal binary data with time-dependent environmental covariates: bias and efficiency. Biostatistics: doi: 10.1093/biostatistics/kxi033.

Schindler, A. M.; Haecker, T.; Gould, J.; Turner, E.; Torchia, M.; Kaye, R.; Cockerill, M.; Spachman, S. (1993) Declining blood lead levels and cognitive change in children [letter]. JAMA J. Am. Med. Assoc. 270: 828.

Schmid, E.; Bauchinger, M.; Pietruck, S.; Hall, G. (1972) Die cytogenetische Wirkung von Blei in menschlichen peripheren Lymphocyten in vitro und in vivo [The cytogeneticeffect of lead in human peripehral lymphocytes in vitro and in vivo]. Mutat. Res. 16: 401-406.

Schnaas, L.; Rothenberg, S. J.; Perroni, E.; Martinez, S.; Hernandez, C.; Hernandez, R. M. (2000) Temporal pattern in the effect of postnatal blood lead level on intellectual development of young children. Neurotoxicol. Teratol. 22: 805-810.

Schoen, E. J. (1993) Childhood lead poisoning: definitions and priorities. Pediatrics 91: 504-505.

Schroeder, S. R.; Hawk, B. (1987) Psycho-social factors, lead exposure, and IQ. In: Schroeder, S. R., ed. Toxic substances and mental retardation: neurobehavioral toxicology and teratology. Washington, DC: American Association on Mental Deficiency; pp. 97-137. (Begab, M. J., ed. Monographs of the American Association on Mental Deficiency: no. 8).

Schroeder, H. A.; Tipton, I. H. (1968) The human body burden of lead. Arch. Environ. Health 17: 965-978.

Schuhmacher, M.; Hernandez, M.; Domingo, J. L.; Fernandez-Ballart, J. D.; Llobet, J. M.; Corbella, J. (1996) A longitudinal study of lead mobilization during pregnancy: concentrations in maternal and umbilical cord blood. Trace Elem. Electrol. 13: 177-181.

Schuhmacher, M.; Patemain, J. L.; Domingo, J. L.; Corbella, J. (1997) An assessment of some biomonitors indicative of occupational exposure to lead. Trace Elem. Electrolytes 14(3): 145-149.

Schumacher, C.; Brodkin, C. A.; Alexander, B.; Cullen, M.; Rainey, P. M.; van Netten, C.; Faustman, E.; Checkoway, H. (1998) Thyroid function in lead smelter workers: absence of subacute or cumulative effects with moderate lead burdens. Int. Arch. Occup. Environ. Health 71: 453-458.

Schutz, A.; Skerfving, S.; Christoffersson, J. O.; Ahlgren, L.; Mattson, S. (1987) Lead in vertebral bone biopsies from active and retired lead workers. Arch. Environ. Health 42: 340-346.

Schutz, A.; Skerfving, S.; Christoffersson, J. O.; Tell, I. (1987) Chelatable lead versus lead in human trabecular and compact bone. Sci. Total Environ. 61: 201-209.

Schutz, A.; Skerfving, S.; Ranstam, J.; Christoffersson, J.-O. (1987) Kinetics of lead in blood after the end of occupational exposure. Scand. J. Work Environ. Health 13: 221 231.

Schwanitz, G.; Lehnert, G.; Gebhart, E. (1970) Chromosomenschaden bei beruflicher Bleibelastung [Chromosome damage after occupational exposure to lead]. Dtsch. Med. Wochenschr. 95: 1636-1641.

Schwanitz, G.; Gebhart, E.; Rott, H.-D.; Schaller, K.-H.; Essing, H.-G.; Lauer, O.; Prestele, H. (1975) Chromosomenuntersuchungen bei Personen mit beruflicher Bleiexposition [Chromosome investigations in subjects with occupational lead exposure]. Dtsch. Med. Wochenschr. 100: 1007-1011.

Schwartz, J. (1985) Evidence for a blood lead-blood pressure relationship [memorandum to the Clean Air Science Advisory Committee]. Washington, DC: U.S. Environmental Protection Agency, Office of Policy Analysis. Available for inspection at: U.S. Environmental Protection Agency, Central Docket Section, Washington, DC; docket no. ECAO-CD-81-2 IIA.F.60.

Schwartz, J. (1991) Lead, blood pressure, and cardiovascular disease in men and women. Environ. Health Perspect. 91: 71-75.

Schwartz, J. (1994) Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ. Res. 65: 42-55.

Schwartz, J. (1995) Lead, blood pressure, and cardiovascular disease in men. Arch. Environ. Health 50: 31-37.

Schwartz, J.; Otto, D. (1987) Blood lead, hearing thresholds, and neurobehavioral development in children and youth. Arch. Environ. Health 42: 153-160.

Schwartz, J.; Otto, D. (1991) Lead and minor hearing impairment. Arch. Environ. Health 46: 300-305.

Schwartz, B. S.; Stewart, W. F. (2000) Different associations of blood lead, meso 2,3-dimercaptosuccinic acid (DMSA)-chelatable lead, and tibial lead levels with blood pressure in 543 former organolead manufacturing workers. Arch. Environ. Health 55: 85-92.

Schwartz, J.; Angle, C.; Pitcher, H. (1986) Relationship between childhood blood lead and stature. Pediatrics 77: 281-288.

Schwartz, J.; Landrigan, P. J.; Baker, E. L., Jr.; Orenstein, W. A.; von Lindern, I. H. (1990) Lead-induced anemia: dose-response relationships and evidence for a threshold. Am. J. Public. Health 80: 165-168.

Schwartz, B. S.; Bolla, K. I.; Stewart, W.; Ford, D. P.; Agnew, J.; Frumkin, H. (1993) Decrements in neurobehavioral performance associated with mixed exposure to organic and inorganic lead. Am. J. Epidemiol. 137: 1006-1021.

Schwartz, B. S.; Lee, B.-K.; Stewart, W.; Ahn, K.-D.; Kelsey, K.; Bresssler, J. (1997) Associations of subtypes of hemoglobin with delta-aminolevulinic acid dehydratase genotype and dimercaptosuccinic acid-chelatable lead levels. Arch. Environ. Health 52: 97-103.

Schwartz, B. S.; Lee, B.-K.; Stewart, W.; Sithisarankul, P.; Strickland, P. T.; Ahn, K.-D.; Kelsey, K. (1997) l3 Aminolevulinic acid dehydratase genotype modifies four hour urinary lead excretion after oral administration of dimercaptosuccinic acid. Occup. Environ. Med. 54: 241-246.

Schwartz, B. S.; Lee, B.-K.; Lee, G.-S.; Stewart, W. F.; Simon, D.; Kelsey, K.; Todd, A. C. (2000a) Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with polymorphisms in the vitamin D receptor and "delta"-aminolevulinic acid dehydratase genes. Environ. Health Perspect. 108: 949-954.

Schwartz, B. S.; Stewart, W. F.; Todd, A. C.; Simon, D.; Links, J. M. (2000b) Different associations of blood lead, meso 2,3-dimercaptosuccinic acid (DMSA)-chelatable lead, and tibial lead levels with blood pressure in 543 former organolead manufacturing workers. Arch. Environ. Health. 55: 85-92.

Schwartz, B. S.; Stewart, W. F.; Kelsey, K. T.; Simon, D.; Park, S.; Links, J. M.; Todd, A. C. (2000c) Associations of tibial lead levels with BsmI polymorphisms in the vitamin D receptor in former organolead manufacturing workers. Environ. Health Perspect. 108: 199-203.

Schwartz, B. S.; Stewart, W. F.; Bolla, K. I.; Simon, P. D.; Bandeen-Roche, K.; Gordon, P. B.; Links, J. M.; Todd, A. C. (2000d) Past adult lead exposure is associated with longitudinal decline in cognitive function. Neurology 55: 1144-1150.

Schwartz, B. S.; Lee, B. K.; Lee, G. S.; Stewart, W. F.; Lee, S. S.; Hwang, K. Y.; Ahn, K.-D.; Kim, Y.-B.; Bolla, K. I.; Simon, D.; Parsons, P. J.; Todd, A. C. (2001a) Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with neurobehavioral test scores in South Korean lead workers. Am. J. Epidemiol. 153: 453-464.

Schwartz, B. S.; Stewart, W. F.; Bolla, K. I.; Simon, P. D.; Bandeen-Roche, K.; Gordon, P. B.; Links, J. M.; Todd, A. C. (2001b) Past adult lead exposure is associated with longitudinal decline in cognitive function. [erratum to Neurology 55: 1144-1150]. Neurology 56: 283.

Schwartz, B. S.; Lee, B.-K.; Bandeen-Roche, K.; Stewart, W.; Bolla, K. I.; Links, J.; Weaver, V.; Todd, A. (2005) Occupational lead exposure and longitudinal decline in neurobehavioral test scores. Epidemiology 16: 106-113.

Schwela, D. (2000) Air pollution and health in urban areas. Rev. Environ. Health 15: 13-42.

Sciarillo, W. G.; Alexander, G.; Farrell, K. P. (1992) Lead exposure and child behavior. Am. J. Public Health 82: 1356-1360.

Selander, S.; Cramer, K. (1970) Interrelationships between lead in blood, lead in urine, and ALA in urine during lead work. Br. J. Ind. Med. 27: 28-39.

Selbst, S. M.; Sokas, R. K.; Henretig, F. M.; Weller, S. C.; Tershakovec, A. M. (1993) The effect of blood lead on blood pressure in children. J. Environ. Pathol. Toxicol. Oncol. 12: 213-218.

Selevan, S. G.; Landrigan, P. J.; Stern, F. B.; Jones, J. H. (1985) Mortality of lead smelter workers. Am. J. Epidemiol. 122: 673-683.

Selevan, S. G.; Rice, D. C.; Hogan, K. A.; Euling, S. Y.; Pfahles-Hutchens, A.; Bethel, J. (2003) Blood lead concentration and delayed puberty in girls. N. Engl. J. Med. 348: 1527-1536.

Selvester, R. H. S.; Ahmed, J.; Tolan, G. D. (1996) Asymptomatic coronary artery disease detection: update 1996: a screening protocol using 16-lead high-resolution ECG, ultrafast CT, exercise testing, and radionuclear imaging. J. Electrocardiol. 29(suppl.) 135-144.

Seshadri, S.; Wolf, P. A.; Beiser, A.; Vasan, R. S.; Wilson, P. W. F.; Kase, C. S.; Kelly-Hays, M.; Kannel, W. B.; D'Agostino, R. B. (2001) Elevated midlife blood pressure increases stroke risk in elderly persons: the Framingham Study. Arch. Intern. Med. 161: 2343-2350.

Shadick, N. A.; Kim, R.; Weiss, S.; Liang, M. H.; Sparrow, D.; Hu, H. (2000) Effect of low level lead exposure on hyperuricemia and gout among middle aged and elderly men: the normative aging study. J. Rheumatol. 27: 1708-1712.

Shannon, M.; Graef, J. W. (1996) Lead intoxication in children with pervasive developmental disorders. J. Toxicol. Clin. Toxicol. 34: 177-181.

Shannon, M.; Woolf, A.; Binns, H. (2001) Chelation therapy in children exposed to lead [comment]. N. Engl. J. Med. 345: 1212-1213.

Shapiro, I. M.; Dobkin, B.; Tuncay, O. C.; Needleman, H. L. (1973) Lead levels in dentin and circumpulpal dentin of deciduous teeth of normal and lead poisoned children. Clin. Chimica. Acta. 46: 119-23.

Shapiro, I. M.; Burke, A.; Mitchell, G.; Bloch, P. (1978) X-ray fluorescence analysis of lead in teeth of urban children in situ: correlation between the tooth lead level and the concentration of blood lead and free erythroporphyrins. Environ. Res. 17: 46-52.

Sharma, K.; Reutergardh, L. B. (2000) Exposure of preschoolers to lead in the Makati area of Metro Manila, the Philippines. Environ. Res. A 83: 322-332.

Sharp, D. S.; Benowitz, N. L.; Osterloh, J. D.; Becker, C. E.; Smith, A. H.; Syme, S. L. (1990) Influence of race, tobacco use, and caffeine use on the relation between blood pressure and blood lead concentration. Am. J. Epidemiol. 131: 845-854.

Sheffet, A.; Thind, I.; Miller, A. M.; Louria, D. B. (1982) Cancer mortality in a pigment plant utilizing lead and zinc chromates. Arch. Environ. Health 37: 44-52.

Shen, X.-M.; Yan, C.-H.; Guo, D.; Wu, S.-M.; Li, R.-Q.; Huang, H.; Ao, L.-M.; Zhou, J.-D.; Hong, Z.-Y.; Xu, J.-D.; Jin, X.-M.; Tang, J.-M. (1998) Low-level prenatal lead exposure and neurobehavioral development of children in the first year of life: a prospective study in Shanghai. Environ. Res. 79: 1-8.

Shen, X.-M.; Wu, S.-H.; Yan, C.-H.; Zhao, W.; Ao, L.-M.; Zhang, Y.-W.; He, J.-M.; Ying, J.-M.; Li, R.-Q.; Wu, S.-M.; Guo, D. (2000) Delta-aminolevulinate dehydratase polymorphism and blood lead levels in Chinese children. Environ. Res. 85: 185-190.

Sherins, R. J. (1995) Are semen quality and male fertility changing? N. Engl. J. Med. 332: 327-328.

Sherlock, J. C.; Quinn, M. J. (1986) Relationship between blood and lead concentrations and dietary lead intake in infants: the Glasgow Duplicate Diet Study 1979-1980. Food Addit. Contam. 3: 167-176.

Sherlock, J.; Smart, G.; Forbes, G. I.; Moore, M. R.; Patterson, W. J.; Richards, W. N.; Wilson, T. S. (1982) Assessment of lead intakes and dose-response for a population in Ayr exposed to a plumbosolvent water supply. Hum. Toxicol. 1: 115-122.

Sherlock, J. C.; Ashby, D.; Delves, H. T.; Forbes, G. I.; Moore, M. R.; Patterson, W. J.; Pocock, S. J.; Quinn, M. J.; Richards, W. N.; Wilson, T. S. (1984) Reduction in exposure to lead from drinking water and its effect on blood lead concentrations. Hum. Toxicol. 3: 383-392.

Shiau, C.-Y.; Wang, J.-D.; Chen, P.-C. (2004) Decreased fecundity among male lead workers. Occup. Environ. Med. 61: 915-923.

Shukla, H.; Atakent, Y. S.; Ferrara, A.; Topsis, J.; Antoine, C. (1987) Postnatal overestimation of gestational age in preterm infants. Am. J. Dis. Child. 141: 1106-1107.

Shukla, R.; Bornschein, R. L.; Dietrich, K. N.; Buncher, C. R.; Berger, O. G.; Hammond, P. B.; Succop, P. A. (1989) Fetal and infant lead exposure: effects on growth in stature. Pediatrics 84: 604-612.

Shukla, V. K.; Prakash, A.; Tripathi, B. D.; Reddy, D. C.; Singh, S. (1998) Biliary heavy metal concentrations in carcinoma of the gall bladder: case-control study. Br. Med. J. 317: 1288-1289.

Siddiqui, M. K.; Srivastava, S.; Mehrotra, P. K. (2002) Environmental exposure to lead as a risk for prostate cancer. Biomed. Environ. Sci. 15: 298-305.

Siegel, M.; Forsyth, B.; Siegel, L.; Cullen, M. R. (1989) The effect of lead on thyroid function in children. Environ. Res. 49: 190-196.

Siemiatycki, J.; Gerin, M.; Stewart, P.; Nadon, L.; Dewar, R.; Richardson, L. (1988) Associations between several sites of cancer and ten types of exhaust and combustion products: results from a case-referent study in Montreal. Scand. J. Work Environ. Health 14: 79-90.

Siemiatycki, J.; Gerin, M.; Dewar, R.; Nadon, L.; Lakhani, R.; Begin, D.; Richardson, L. (1991) Associations between occupational circumstances and cancer. In: Siemiatycki, J., ed. Risk factors for cancer in the workplace. Boca Raton, FL: CRC Press; pp. 141-145.

Silbergeld, E. K. (1991) Lead in bone: implications for toxicology during pregnancy and lactation. Environ. Health Perspect. 91: 63-70.

Silbergeld, E. K.; Schwartz, J.; Mahaffey, K. (1988) Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. Environ. Res. 47: 79-94.

Silbergeld, E. K.; Sauk, J.; Somerman, M.; Todd, A.; McNeill, F.; Fowler, B.; Fontaine, A.; van Buren, J. (1993) Lead in bone: storage site, exposure source, and target organ. Presented at: Ninth international neurotoxicology conference; October 1991; Little Rock, AR. Neurotoxicology 14(2-3): 225-236.

Silbergeld, E. K.; Waalkes, M.; Rice, J. M. (2000) Lead as a carcinogen: experimental evidence and mechanisms of action. Am. J. Ind. Med. 38: 316-323.

Silva, P. A.; Hughes, P.; Williams, S.; Faed, J. M. (1988) Blood lead, intelligence, reading attainment, and behaviour in eleven year old children in Dunedin, New Zealand. J. Child Psychol. Psychiatr. Allied Discipl. 29: 43-52.

Singh, B.; Chandran, V.; Bandhu, H. K.; Mittal, B. R.; Bhattacharya, A.; Jindal, S. K.; Varma, S. (2000) Impact of lead exposure on pituitary-thyroid axis in humans. BioMetals 13: 187-192.

Sirivarasai, J.; Kaojarern, S.; Wananukul, W.; Deechakwan, W.; Srisomerarn, P. (2004) Non-occupational lead and cadmium exposure and blood pressure in Thai men. Asia Pac. J. Public Health 16: 133-137.

Skerfving, S. (1988) Biological monitoring of exposure to inorganic lead. In: Clarkson, T. W.; Friberg, L.; Nordberg, G. F.; Sager, R. P., eds. Biological monitoring of toxic metals. New York, NY: Plenum Press; pp. 169-197.

Skerfving, S.; Ahlgren, L.; Christoffersson, J.-O.; Haeger-Aronsen, B.; Mattsson, S.; Schutz, A. (1983) Metabolism of inorganic lead in occupationally exposed humans. Arh. Hig. Rada Toksikol. 34: 341-350.

Skerfving, S.; Nilsson, U.; Schutz, A.; Gerhardsson, L. (1993) Biological monitoring of inorganic lead. Scand. J. Work Environ. Health 19(suppl. 1): 59-64.

Slobozhanina, E. I.; Kozlova, N. M.; Lukyanenko, L. M.; Oleksiuk, O. B.; Gabbianelli, R.; Fedeli, D.; Caulini, G. C.; Falcioni, G. (2005) Lead-induced changes in human erythrocytes and lymphocytes. J. Appl. Toxicol. 25: 109-114.

Smith, F. L., 2nd; Rathmell, T. K.; Marcil, G. E. (1938) The early diagnosis of acute and latent plumbism. Am. J. Clin. Pathol. 8: 471-508.

Smith, C. M.; Wang, X.; Hu, H.; Kelsey, K. T. (1995) A polymorphism in the "delta"-aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead. Environ. Health Perspect. 103: 248-253.

Smith, D. R.; Osterloh, J. D.; Flegal, A. R. (1996) Use of endogenous, stable lead isotopes to determine release of lead from the skeleton. Environ. Health Perspect. 104: 60-66.

Smith, D.; Hernandez-Avila, M.; Tellez-Rojo, M.M.; Mercado, A.; Hu, H. (2002) The relationship between lead in plasma and whole blood in women. Environ. Health Perspect. 110: 263-268.

Sokas, R. K.; Simmens, S.; Sophar, K.; Welch, L. S.; Liziewski, T. (1997) Lead levels in Maryland construction workers. Am. J. Ind. Med. 31: 188-194.

Soldin, O. P.; Pezzullo, J. C.; Hanak, B.; Miller, M.; Soldin, S. J. (2003) Changing trends in the epidemiology of pediatric lead exposure: interrelationship of blood lead and ZPP concentrations and a comparison to the US population. Ther. Drug Monit. 25: 415-420.

Solliway, B. M.; Schaffer, A.; Pratt, H.; Yannai, S. (1996) Effects of exposure to lead on selected biochemical and haematological variables. PharmacoI. ToxicoI. 78: 18-22.

Somervaille, L. J.; Chettle, D. R.; Scott, M. C.; Tennant, D. R.; McKiernan, M. J.; Skilbeck, A.; Trethowan, W. N. (1988) In vivo tibia lead measurements as an index of cumulative exposure in occupationally exposed subjects. Br. J. Ind. Med. 45: 174-181.

Somervaille, L. J.; Nilsson, U.; Chettle, D. R.; Tell, I.; Scott, M. C.; Schutz, A.; Mattsson, S.; Skerfving, S. (1989) In vivo measurements of bone lead--a comparison of two x-ray fluorescence techniques used at three different bone sites. Phys. Med. Biol. 34: 1833-1845.

Sonmez, F.; Donmez, O.; Sonmez, H. M.; Keskinoglu, A.; Kabasakal, C.; Mir, S. (2002) Lead exposure and urinary N-acetyl "beta" D glucosaminidase activity in adolescent workers in auto repair workshops. J. Adolesc. Health 30: 213-216.

Sorel, J. E.; Heiss, G.; Tyroler, H. A.; Davis, W. B.; Wing, S. B.; Ragland, D. R. (1991) Black-white differences in blood pressure among participants in NHANES II: the contribution of blood lead. Epidemiology 2: 348-352.

Sorrell, M.; Rosen, J. F.; Roginsky, M. (1977) Interactions of lead, calcium, vitamin D, and nutrition in lead-burdened children. Arch. Environ. Health 32: 160-164.

Sowers, M.; Jannausch, M.; Scholl, T.; Li, W.; Kemp, F. W.; Bogden, J. D. (2002) Blood lead concentrations and pregnancy outcomes. Arch. Environ. Health 57: 489-495.

Spencer, H.; O'Sullivan, V.; Sontag, S. J. (1992) Does lead play a role in Paget's disease of bone? A hypothesis. J. Lab. Clin. Med. 120: 798-800.

Spencer, H.; O'Sullivan, V.; Sontag, S. J. (1994) Occupational exposure to lead: preliminary observations in Paget's disease of bone in women and in family members of affected patients. J. Trace Elem. Exp. Med. 7: 53-58.

Spencer, H.; O'Sullivan, V.; Sontag, S. J. (1995) Exposure to lead, a potentially hazardous toxin - Paget's disease of bone. J. Trace Elem. Exp. Med. 8: 163-171.

Spinnato, J. A.; Sibai, B. M.; Shaver, D. C.; Anderson, G. D. (1984) Inaccuracy of Dubowitz gestational age in low birth weight infants. Obstet. Gynecol. 63: 491-495.

Spivey, G. H.; Baloh, R. W.; Brown, C. P.; Browdy, B. L.; Campion, D. S.; Valentine, J. L.; Morgan, D. E.; Culver, B. D. (1980) Subclinical effects of chronic increased lead absorption--a prospective study. III. Neurologic findings at follow-up examination. J. Occup. Med. 22: 607-612.

Spreen, O.; Risser, A. T.; Edgell, D. (1995) Developmental neuropsychology. New York, NY: Oxford University Press.

Srivastava, S.; Mehrotra, P. K.; Srivastava, S. P.; Tandon, I.; Siddiqui, M. K. J. (2001) Blood lead and zinc in pregnant women and their offspring in intrauterine growth retardation cases. J. Anal. Toxicol. 25: 461-465.

Staessen, J. (1995) Low-level lead exposure, renal function and blood pressure. Verh.-K. Acad. Geneeskd. Belg. 57: 527-574.

Staessen, J.; Yeoman, W. B.; Fletcher, A. E.; Markowe, H. L.; Marmot, M. G.; Rose, G.; Semmence, A.; Shipley, M. J.; Bulpitt, C. J. (1990) Blood lead concentration, renal function, and blood pressure in London civil servants. Br. J. Ind. Med. 47: 442-447.

Staessen, J.; Amery, A.; Bernard, A.; Bruaux, P.; Buchet, J. P.; Bulpitt, C. J.; Claeys, F.; De Plaen, P.; Ducoffre, G.; Fagard, R.; Lauwerys, R. R.; Lijnen, P.; Nick, L.; Saint Remy, A.; Roels, H.; Rondia, D.; Sartor, F.; Thijs, L. (1991) Blood pressure, the prevalence of cardiovascular diseases, and exposure to cadmium: a population study. Am. J. Epidemiol. 134: 257-267.

Staessen, J. A.; Lauwerys, R. R.; Buchet, J.-P.; Bulpitt, C. J.; Rondia, D.; Van Renterghem, Y.; Amery, A. (1992) Impairment of renal function with increasing blood lead concentrations in the general population. N. Engl. J. Med. 327: 151-156.

Staessen, J. A.; Dolenc, P.; Amery, A.; Buchet, J. P.; Claeys, F.; Fayard, R.; Lauwerys, R.; Lijnen, P.; Roels, H.; Rondia, D.; Sartor, F.; Thijs, L.; Vyncke, G. (1993) Environmental lead exposure does not increase blood pressure in the population at large: evidence from the Cadmibel study. J. Hypertens. 11(suppl. 2): S35-S41.

Staessen, J. A.; Bulpitt, C. J.; Fagard, R.; Lauwerys, R. R.; Roels, H.; Thijs, L.; Amery, A. (1994) Hypertension caused by low-level lead exposure: myth or fact? J. Cardiovasc. Risk 1: 87-97.

Staessen, J. A.; Roels, H.; Lauwerys, R. R.; Amery, A. (1995) Low-level lead exposure and blood pressure. J. Hum. Hypertens. 9: 303-328.

Staessen, J. A.; Buchet, J.-P.; Ginucchio, G.; Lauwerys, R. R.; Lijnen, P.; Roels, H.; Fagard, R. (1996) Public health implications of environmental exposure to cadmium and lead: an overview of epidemiological studies in Belgium. J. Cardiovasc. Risk 3: 26-41.

Staessen, J. A.; Roels, H.; Fagard, R. (1996) Lead exposure and conventional and ambulatory blood pressure: a prospective population study. JAMA J. Am. Med. Assoc. 275: 1563-1570.

Staessen, J. A.; Nawrot, T.; Den Hond, E.; Thijs, L.; Fagard, R.; Hoppenbrouwers, K.; Koppen, G.; Nelen, V.; Schoeters, G.; Vanderschueren, D.; Van Hecke, E.; Verschaeve, L.; Vlietinck, R.; Roels, H. A. (2001) Renal function, cytogenetic measurements, and sexual developments in adolescents in relation to environmental pollutants: a feasibility study of biomarkers. Lancet 357: 1660-1669.

Steele, G.; Kattouf, V. (2000) Blood lead levels and vision. Optometry 71: 217-220.

Steenhout, A.; Pourtois, M. (1981) Lead accumulation in teeth as a function of age with different exposures. Br. J. Ind. Med. 38: 297-303.

Steenland, K.; Boffetta, P. (2000) Lead and cancer in humans: where are we now? Am. J. Ind. Med. 38: 295-299.

Steenland, K.; Thun, M. J.; Ferguson, C. W.; Port, F. K. (1990) Occupational and other exposures associated with male end-stage renal disease: a case/control study. Am. J. Public Health. 80: 153-157.

Steenland, K.; Selevan, S.; Landrigan, P. (1992) The mortality of lead smelter workers: an update. Am. J. Public Health 82: 1641-1644.

Steenland, K.; Loomis, D.; Shy, C.; Simonsen, N. (1996) Review of occupational lung carcinogens. Am. J. Ind. Med. 29: 474-490.

Steenland, K.; Mannetje, A.; Boffetta, P.; Stayner, L.; Attfield, M.; Chen, J.; Dosemeci, M.; DeKlerk, N.; Hnizdo, E.; Koskela, R.; Checkoway, H. (2002) Pooled exposure-response analyses and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multi-centric study (vol 12, pg 773, 2001). Cancer Causes Control 13: 777.

Stefanak, M. A.; Bourguet, C. C.; Benzies-Styka, T. (1996) Use of the Centers for Disease Control and Prevention childhood lead poisoning risk questionnaire to predict blood lead elevations in pregnant women. Obstet. Gynecol. 87: 209-212.

Stevens, L. A.; Levey, A. S. (2005a) Measurement of kidney function. Med. Clin. N. Am. 89: 457-473.

Stevens, L. A.; Levey, A. S. (2005b) Chronic kidney disease in the elderly -- how to assess risk. N. Engl. J. Med. 352: 2122-2124.

Stewart, W. F.; Schwartz, B. S.; Simon, D.; Bolla, K. I.; Todd, A. C.; Links, J. (1999) Neurobehavioral function and tibial and chelatable lead levels in 543 former organolead workers. Neurology 52: 1610-1617.

Stewart, W. F.; Schwartz, B. S.; Simon, D.; Kelsey, K.; Todd, A. C. (2002) ApoE genotype, past adult lead exposure, and neurobehavioral function. Environ. Health Perspect. 110: 501-505.

Stiefel, Th.; Schulze, K.; Zorn, H.; Toelg, G. (1980) Toxicokinetic and toxicodynamic studies of beryllium. Arch. Toxicol. 45: 81-92.

Stiles, K. M.; Bellinger, D. C. (1993) Neuropsychological correlates of low-level lead exposure in school-age children: a prospective study. Neurotoxicol. Teratol. 15: 27-35.

Stojek, E.; Skoczynska, A. (2003) Oddzialywanie olowiu na srodblonek naczyniowy [The effect of lead on vascular endothelium]. Med. Pr. 54: 87-93.

Stokes, L.; Letz, R.; Gerr, F.; Kolczak, M.; McNeill, F. E.; Chettle, D. R.; Kaye, W. E. (1998) Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience. Occup. Environ. Med. 55: 507-516.

Stollery, B. T. (1996) Reaction time changes in workers exposed to lead. Neurotoxicol. Teratol. 18: 477-483.

Stollery, B. T.; Banks, H. A.; Broadbent, D. E.; Lee, W. R. (1989) Cognitive functioning in lead workers. Br. J. Ind. Med. 46: 698-707.

Stollery, B. T.; Broadbent, D. E.; Banks, H. A.; Lee, W. R. (1991) Short term prospective study of cognitive functioning in lead workers. Br. J. Ind. Med. 48: 739-749.

Stone, B. M.; Reynolds, C. R. (2003) Can the National Health and Nutrition Examination Survey III (NHANES III) data help resolve the controversy over low blood lead levels and neuropsychological development in children? Arch. Clin. Neuropsychol. 18: 219-244.

Stretesky, P. B.; Lynch, M. J. (2001) The relationship between lead exposure and homicide. Arch. Pediatr. Adolesc. Med. 155: 579-582.

Succop, P.; Bornschein, R.; Brown, K.; Tseng, C.-Y. (1998) An empirical comparison of lead exposure pathway models. Environ. Health Perspect. Suppl. 106(6): 1577-1583.

Sugawara, E.; Nakamura, K.; Miyake, T.; Fukumura, A.; Seki, Y. (1991) Lipid peroxidation and concentration of glutathione in erythrocytes from workers exposed to lead. Br. J. Ind. Med. 48: 239-242.

Sun, C. A.; Chang, Y. C.; Liou, S. H.; Yang, G. Y.; Wu, T. N.; Ko, Y. C.; Lee, C. C.; Ho, S. T.; Lai, J. M.; Wu, Y. Q.; Chiang, H. C.; Ko, K. N.; Chang, P. Y. (1997) Test reliability of blood lead levels in a multicenter epidemiological study: the Taiwan experience. Am. J. Epidemiol. 145(11 suppl.): S48.

Sun, L.; Hu, J.; Zhao, Z.; Li, L.; Cheng, H. (2003) Influence of exposure to environmental lead on serum immunoglobulin in preschool children. Environ. Res. 92: 124-128.

Susser, M. (1991) What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am. J. Epidemiol. 133: 635-648.

Suzen, H. S.; Duydu, Y.; Aydin, A.; Isimer, A; Vural, N. (2003) Influence of the delta-aminolevulinic acid dehydratase (ALAD) polymorphism on biomarkers of lead exposure in Turkish storage battery manufacturing workers. Am. J. Ind. Med. 43: 165-171.

Symanski, E.; Hertz-Picciotto, I. (1995) Blood lead levels in relation to menopause, smoking, and pregnancy history. Am. J. Epidemiol. 141: 1047-1058.

Syracuse Research Corporation. (2003) Evaluation of the ICRP lead biokinetics model: empirical comparisons with observations of plasma-blood lead concentration relationships in humans [draft final]. Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response; contract no. GS-10F-0137K; SRC no. FA332.

Tabacova, S.; Balabaeva, L. (1993) Environmental pollutants in relation to complications of pregnancy. Environ. Health Perspect. 101(suppl. 2): 27-31.

Tang, N.; Zhu, Z. Q. (2003) Adverse reproductive effects in female workers of lead battery plants. Int. J. Occup. Med. Environ. Health 16: 359-361.

Tang, H.-W.; Liang, Y.-X.; Hu, X.-H.; Yang, H.-G. (1995) Alterations of monoamine metabolites and neurobehavioral function in lead-exposed workers. Biomed. Environ. Sci. 8: 23-29.

Taskinen, H. (1988) Spontaneous abortions among women occupationally exposed to lead. In: Hogstedt, C.; Reuterwall, C., eds. Progress in occupational epidemiology. New York, NY: Elsevier Science Publishers; pp. 197-200.

Tassler, P.; Schwartz, B. S.; Coresh, J.; Stewart, W.; Todd, A. (2001) Associations of tibia lead, DMSA-Chelatable lead, and blood lead with measures of peripheral nervous system function in former organolead manufacturing workers. Am. J. Ind. Med. 39: 254-261.

Taupeau, C.; Poupon, J.; Treton, D.; Brosse, A.; Richard, Y.; Machelon, V. (2003) Lead reduces messenger RNA and protein levels of cytochrome P450 aromatase and estrogen receptor "Beta" in human ovarian granulosa cells. Biol. Reprod. 68: 1982-1988.

Telisman, S.; Cvitkovic, P.; Jurasovic, J.; Pizent, A.; Favella, M.; Rocic, B. (2000) Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. Environ. Health Perspect. 108: 45-53.

Telisman, S.; Pizent, A.; Jurasovic, J.; Cvitkovic, P. (2004) Lead effect on blood pressure in moderately lead-exposed male workers. Am. J. Ind. Med. 45: 446-454.

Tellez-Rojo, M. M.; Hernandez-Avila, M.; Gonzalez-Cossio, T.; Romieu, I.; Aro, A.; Palazuelos, E.; Schwartz, J.; Hu, H. (2002) Impact of reastfeeding on the mobilization of lead from bone. Am. J. Epidemiol. 155: 420-428.

Tellez-Rojo, M. M.; Hernandez-Avila, M.; Lamadrid-Figueroa, H.; Smith, D.; Hernandez-Cadena, L.; Mercado, A.; Aro, A.; Schwartz, J.; Hu, H. (2004) Impact of bone lead and bone resorption on plasma and whole blood lead levels during pregnancy. Am. J. Epidemiol. 160: 668-678.

Tepper, A.; Mueller, C.; Singal, M.; Sagar, K. (2001) Blood pressure, left ventricular mass, and lead exposure in battery manufacturing workers. Am. J. Ind. Med. 40: 63-72.

TerraGraphics Environmental Engineering, Inc. (2001) Final human health risk assessment for the Coeur d'Alene Basin extending from Harrison to Mullan on the Coeur d'Alene River and tributaries remedial investigation/feasibility study. Washington, DC: U.S. Environmental Protection Agency, prepared for the Idaho Department of Health and Welfare, Idaho Department of Environmental Quality.

Teruya, K.; Sakurai, H.; Omae, K.; Higashi, T.; Muto, T.; Kaneko, Y. (1991) Effect of lead on cardiac parasympathetic function. Int. Arch. Occup. Environ. Health 62: 549-553.

Thacker, S. B.; Hoffman, D. A.; Smith, J.; Steinberg, K.; Zack, M. (1992) Effect of low-level body burdens of lead on the mental development of children: limitations of meta-analysis in a review of longitudinal data. Arch. Environ. Health 47: 336-346.

Thacker, S. B.; Hoffman, D. A.; Smith, J.; Steinberg, K.; Zack, M. (1993) [Untitled author response to letters concerning "Effect of low-level body burdens of lead on the mental development of children: limitations of meta-analysis in a review of longitudinal data." Arch. Environ. Health 48: 126-127.

Theppeang, K.; Schwartz, B. S.; Lee, B.-K.; Lustberg, M. E.; Silbergeld, E. K.; Kelsey, K. T.; Parsons, P. J.; Todd, A. C. (2004) Associations of patella lead with polymorphisms in the vitamin D receptor, "delta"-aminolevulinic acid dehydratase and endothelial nitric oxide synthase genes. J. Occup. Environ. Med. 46: 528-537.

Thompson, S. G.; Pocock, S. J. (1992) Can meta-analysis be trusted? Lancet 338: 1127-1130.

Thomson, G. O. B.; Raab, G. M.; Hepburn, W. S.; Hunter, R.; Fulton, M.; Laxen, D. P. H. (1989) Blood-lead levels and children's behaviour - results from the Edinburgh lead study. J. Child Psychol. Psychiatr. 30: 515-528.

Todd, A. C.; McNeill, F. E.; Palethorpe, J. E.; Peach, D. E.; Chettle, D. R.; Tobin, M. J.; Strosko, S. J.; Rosen, J. C. (1992) In vivo X-ray fluorescence of lead in bone using K X-ray excitation with 109Cd sources: radiation dosimetry studies. Environ. Res. 57: 117-132.

Todd, A. C.; Carroll, S.; Godbold, J. H.; Moshier, E. L.; Khan, F. A. (2000) Variability in XRF-measured tibia lead levels. Phys. Med. Biol. 45: 3737-3748.

Todd, A. C.; Buchanan, R.; Carroll, S.; Moshier, E. L.; Popovac, D.; Slavkovich, V.; Graziano, J. H. (2001) Tibia lead levels and methodological uncertainty in 12-year-old children. Environ. Res. 86: 60-65.

Todd, A. C.; Spencer, C.; Geraghty, C.; Khan, F. A.; Moshier, E. L.; Tang, S.; Parsons, P. J. (2002) L-shell x-ray fluorescence measurements of lead in bone: accuracy and precision. Phys. Med. Biol. 47: 1399-1419.

Tollestrup, K.; Daling, J. R.; Allard, J. (1995) Mortality in a cohort of orchard workers exposed to lead arsenate pesticide spray. Arch. Environ. Health 50: 221-229.

Tomatis, L. (1990) Cancer: causes, occurrence, and control. Lyon, France: International Agency for Research on Cancer. (IARC scientific publications: v. 100).

Tong, S. (1998) Lead exposure and cognitive development: persistence and a dynamic pattern. J. Paediatr. Child Health 34: 114-118.

Tong, I. S.; Lu, Y. (2001) Identification of confounders in the assessment of the relationship between lead exposure and child development. Ann. Epidemiol. 11: 38-45.

Tong, S.; Baghurst, P.; McMichael, A.; Sawyer, M.; Mudge, J. (1996) Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study. Br. Med. J. 312: 1569-1575.

Tong, S.; Baghurst, P. A.; Sawyer, M. G.; Burns, J.; McMichael, A. J. (1998) Declining blood lead levels and changes in cognitive function during childhood: the Port Pirie cohort study. JAMA J. Am. Med. Assoc. 280: 1915-1919.

Tong, S.; McMichael, A. J.; Baghurst, P. A. (2000) Interactions between environmental lead exposure and sociodemographic factors on cognitive development. Arch. Environ. Health 55: 330-335.

Torres-Sanchez, L. E.; Berkowitz, G.; Lopez-Carrillo, L.; Torres-Arreola, L.; Rios, C.; Lopez-Cervantes, M. (1999) Intrauterine lead exposure and preterm birth. Environ. Res. 81: 297-301.

Trope, I.; Lopez-Villegas, D.; Lenkinski, R. E. (1998) Magnetic resonance imaging and spectroscopy of regional brain structure in a 10-year-old boy with elevated blood lead levels. Pediatrics 101(6): E7.

Trope, I.; Lopez-Villegas, D.; Cecil, K. M.; Lenkinski, R. E. (2001) Exposure to lead appears to selectively alter metabolism of cortical gray matter. Pediatrics 107: 1437-1443.

Tsaih, S. W.; Schwartz, J.; Ting Lee, M. L.; Amarasiriwardena, C.; Aro, A.; Sparrow, D.; Hu, H. (1999) The independent contribution of bone and erythrocyte lead to urinary lead among middle-aged and elderly men: the normative aging study. Environ. Health Perspect. 107:391-396.

Tsaih, S.-W.; Korrick, S.; Schwartz, J.; Lee, M.-L. T.; Amarasiriwardena, C.; Aro, A.; Sparrow, D.; Hu, H. (2001) Influence of bone resorption on the mobilization of lead from bone among middle-aged and elderly men: the Normative Aging Study. Environ. Health Perspect. 109: 995-999.

Tsaih, S.-W.; Korrick, S.; Schwartz, J.; Amarasiriwardena, C.; Aro, A.; Sparrow, D; Hu, H. (2004) Lead, diabetes, hypertension, and renal function: the normative aging study. Environ. Health Perspect. 112: 1178-1182.

Tuppurainen, M.; Wagar, G.; Kurppa, K.; Sakari, W.; Wambugu, A.; Froseth, B.; Alho, J.; Nykyri, E. (1988) Thyroid function as assessed by routine laboratory tests of workers with long-term lead exposure. Scand. J. Work Environ. Health 14: 175-180.

Tuthill, R. W. (1996) Hair lead levels related to children's classroom attention-deficit behavior. Arch. Environ. Health 51: 214-220.

Tvinnereim, H. M.; Eide, R.; Riise, T.; Wesenberg, G. R.; Fosse, G.; Steinnes, E. (1997) Lead in primary teeth from Norway: changes in lead levels from the 1970s to the 1990s. Sci. Total Environ. 207: 165-177.

Tvinnereim, H. M.; Eide, R.; Riise, T. (2000) Heavy metals in human primary teeth: some factors influencing the metal concentrations. Sci. Total Environ. 255: 21-27.

U.S. Environmental Protection Agency. (1986a) Air quality criteria for lead. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-83/028aF-dF. 4v. Available from: NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency. (1986b) Lead effects on cardiovascular function, early development, and stature: an addendum to U.S. EPA Air Quality Criteria for Lead (1986). In: Air quality criteria for lead, v. 1. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; pp. A1-A67; EPA report no. EPA-600/8-83/028aF. Available from: NTIS, Springfield, VA; PB87-142378.

U.S. Environmental Protection Agency. (1990) Air quality criteria for lead: supplement to the 1986 addendum. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; report no. EPA/600/8-89/049F. Available from: NTIS, Springfield, VA; PB91-138420.

U.S. Environmental Protection Agency. (2001) Final human health risk assessment for the Coeur d'Alene Basin extending from Harrison to Mullan on the Coeur d'Alene River and Tributaries remedial investigation/feasibility study. Washington, DC: U.S. Environmental Protection Agency, Idaho Department of Environmental Quality.

U.S. Environmental Protection Agency. (2003) Evaluation of the ICRP Lead Biokinetics Model: Empirical Comparisons with Observations of Plasma-Blood Lead Concentration Relationships in Humans. Prepared for U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC. Syracuse Research Corporation under Contract No. GS-10F-0137K, FEDSIM Order No. DABT63-01-F-0133-00.

U.S. Environmental Protection Agency. (2004) Air quality criteria for particulate matter. Research Triangle Park, NC: National Center for Environmental Assessment; report no. EPA/600/P-99/002aF-bF. 2v. Available: http://cfpub.epa.gov/ncea/ [9 November, 2004].

U.S. Environmental Protection Agency. (2005) Guidelines for carcinogen risk assessment. Washington, DC: Risk Assessment Forum; report no. EPA/630/P-03/001F. Available: http://cfpub.epa.gov/ncea/index.cfm [30 November, 2005].

U.S. Renal Data System. (2004) Outcomes: hospitalization & mortality. In: Annual data report. Minneapolis, MN: USRDS Coordinating Center; pp. 118-138. Available: http://www.usrds.org/2004/pdf/06_hosp_morte_04.pdf [21 November, 2005].

Undeger, U.; Basaran, N.; Canpinar, H.; Kansu, E. (1996) Immune alterations in lead-exposed workers. Toxicology 109: 167-172.

Vacca, C. V.; Hines, J. D.; Hall, P. W., III. (1986) The proteinuria of industrial lead intoxication. Environ. Res. 41: 440-446.

Valciukas, J. A.; Lilis, R.; Eisinger, J.; Blumberg, W. E.; Fischbein, A.; Selikoff, I. J. (1978) Behavioral indicators of lead neurotoxicity: results of a clinical field survey. Int. Arch. Occup. Environ. Health 41: 217-236.

Valentine, J. L.; Baloh, R. W.; Browdy, B. L.; Gonick, H. C.; Brown, C. P.; Spivey, G. H.; Culver, B. D. (1982) Subclinical effects of chronic increased lead absorption--a prospective study. J. Occup. Med. 24: 120-125.

Valentino, M.; Governa, M.; Marchiseppe, I.; Visona, I. (1991) Effects of lead on polymorphonuclear leukocyte (PMN) functions in occupationally exposed workers. Arch. Toxicol. 65: 685-688.

Van De Vyver, F. L.; D'Haese, P. C.; Visser, W. J.; Elseviers, M. M.; Knippenberg, L. J.; Lamberts, L. V.; Wedeen, R. P.; De Broe, M. E. (1988) Bone lead in dialysis patients. Kidney Int. 33: 601-607.

Van Den Berg, B; Oechsli, F. (1984) Prematurity. In: Bracken, M., ed. Perinatal Epidemiology. New York, NY: Oxford University Press; pp. 69-85.

Van Den Hoogen, P.; Seidell, J. Nagelkerke, N.; Menotti, A.; Kromhout, D. (2001) Relation between blood pressure and mortality: is there a threshold? Eur. Heart J. 22: 2132-2133.

Van Larebeke, N.; Koppen, G.; Nelen, V.; Schoeters, G.; Van Loon H, Albering H, Riga L, Vlietinck, R.; Kleinjans, J.; Flemish Environment and Health Study Group. (2004) Differences in HPRT mutant frequency among middle-aged Flemish women in association with area of residence and blood lead levels. Biomarkers 9: 71-84.

Vaziri, N. D.; Sica, D. A. (2004) Lead-induced hypertension: role of oxidative stress. Curr. Hypertens. Rep. 6: 314-320.

Verberk, M. M.; Willems, T. E. P.; Verplanke, A. J. W.; De Wolff, F. A. (1996) Environmental lead and renal effects in children. Arch. Environ. Health 51: 83-87.

Verschoor, M.; Wibowo, A.; Herber, R.; van Hemmen, J.; Zielhuis, R. (1987) Influence of occupational low-level lead exposure on renal parameters. Am. J. Ind. Med. 12: 341-351.

Vig, E.; Hu, H. (2000) Lead toxicity in older adults. J. Am. Geriatr. Soc. 48: 1501-1506.

Vijayalakshhmi, P.; Serrano, J.; Sparrow, D.; Hu, H. (1999) Relationship of lead in drinking water to bone lead levels twenty years later in Boston men: The Normative Aging Study. J. Occup. Environ. Med. 41: 349-355.

Vimpani, G. V.; Wigg, N. R.; Robertson, E. F.; McMichael, A. J.; Baghurst, P. A.; Roberts, R. J. (1985) The Port Pirie cohort study: blood lead concentration and childhood developmental assessment. In: Goldwater, L. J.; Wysocki, L. M.; Volpe, R. A., eds. Edited proceedings: Lead environmental health - the current issues; May; Durham, NC. Durham, NC: Duke University; pp. 139-146.

Vinceti, M.; Guidetti, D.; Bergomi, M.; Caselgrandi, E.; Vivoli, R.; Olmi, M.; Rinaldi, L.; Rovesti, S.; Solime, F. (1997) Lead, cadmium, and selenium in the blood of patients with sporadic amyotrophic lateral sclerosis. Ital. J. Neurol. Sci. 18: 87-92.

Vupputuri, S.; He, J.; Muntner, P.; Bazzano, L. A.; Whelton, P. K.; Batuman, V. (2003) Blood lead level is associated with elevated blood pressure in blacks. Hypertension 41: 463-468.

Wagnerova, M.; Wagner, V.; Madlo, Z.; Zavazal, Y.; Wokounova, D.; Kriz, J.; Mohyla, O. (1986) Seasonal variations in the level of immunoglobulins and serum proteins of children differing by exposure to air-borne lead. J. Hyg. Epidemiol. Microbiol. Immunol. 30(2): 127-138.

Walkowiak, J.; Altmann, L.; Kramer, U.; Sveinsson, K.; Turfeld, M.; Weishoff-Houben, M.; Winneke, G. (1998) Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. Neurotoxicol. Teratol. 20: 511-521.

Wang, S. T.; Pizzolato, S.; Demshar, H. P.; Smith, L. F. (1997) Decline in blood lead in Ontario children correlated to decreasing consumption of leaded gasoline, 1983-1992 [letter]. Clin. Chem. 43: 1251-1252.

Wang, C.-L.; Chuang, H.-Y.; Ho, C.-K.; Yang, C.-Y.; Tsai, J.-L.; Wu, T.-S.; Wu, T.-N. (2002) Relationship between blood lead concentrations and learning achievement among primary school children in Taiwan. Environ. Res. 89: 12-18.

Wang, V.-S.; Lee, M.-T.; Chiou, J.-Y.; Guu, C.-F.; Wu, C.-C.; Wu, T.-N.; Lai, J.-S. (2002) Relationship between blood lead levels and renal function in lead battery workers. Int. Arch. Occup. Environ. Health 75: 569-575.

Ward, N. I.; Watson, R.; Bryce-Smith, D. (1987) Placental element levels in relation to fetal development for obstetrically 'normal' births: a study of 37 elements. Evidence for effects of cadmium, lead and zinc on fetal growth, and for smoking as a source of cadmium. Int. J. Biosoc. Res. 9: 63-81.

Wasserman, G. A. (1995) Effects of early lead exposure: time to integrate and broaden our efforts. Neurotoxicol. Teratol. 17: 243-244.

Wasserman, G. A.; Factor-Litvak, P. (2001) Methodology, inference and causation: environmental lead exposure and childhood intelligence. Arch. Clin. Neurospychol. 16: 343-352.

Wasserman, G.; Graziano, J. H.; Factor-Litvak, R.; Popovac, D.; Morina, N.; Musabegovic, A.; Vrenezi, N.; Capuni-Paracka, S.; Lekic, V.; Preteni-Redjepi, E.; Hadzialjevic, S.; Slavkovich, V.; Kline, J.; Shrout, P.; Stein, Z. (1992) Independent effects of lead exposure and iron deficiency anemia on developmental outcome at age 2 years. J. Pediatr. 121: 695-703.

Wasserman, G. A.; Graziano, J. H.; Factor-Litvak, P.; Popovac, D.; Morina, N.; Musabegovic, A.; Vrenezi, N.; Capuni-Paracka, S.; Lekic, V.; Preteni-Redjepi, E.; Hadzialjevic, S.; Slavkovich, V.; Kline, J.; Shrout, P.; Stein, Z. (1994) Consequences of lead exposure and iron supplementation on childhood development at age 4 years. Neurotoxicol. Teratol. 16: 233-240.

Wasserman, G. A.; Liu, X.; Lolacono, N. J.; Factor-Litvak, P.; Kline, J. K.; Popovac, D.; Morina, N.; Musabegovic, A.; Vrenezi, N.; Capuni-Paracka, S.; Lekic, V.; Preteni-Redjepi, E.; Hadzialjevic, S.; Slavkovich, V.; Graziano, J. H. (1997) Lead exposure and intelligence in 7-year-old children: the Yugoslavia prospective study. Environ. Health Perspect. 105: 956-962.

Wasserman, G. A.; Graziano, J.; Factor-Litvak, P. (1998) Lead effects research [response]. Am. J. Pub. Health 88: 1879-1880.

Wasserman, G. A.; Staghezza-Jaramillo, B.; Shrout, P.; Popovac, D.; Graziano, J. (1998) The effect of lead exposure on behavior problems in preschool children. Am. J. Pub. Health 88 (3): 481-486.

Wasserman, G. A.; Musabegovic, A.; Liu, X.; Kline, J.; Factor-Litvak, P.; Graziano, J. H. (2000a) Lead exposure and motor functioning in 4 1/2-year-old children: the Yugoslavia prospective study. J. Pediatr. 137: 555-561.

Wasserman, G. A.; Liu, X.; Popovac, D.; Factor-Litvak, P.; Kline, J.; Waternaux, C.; LoIacono, N.; Graziano, J. H. (2000b) The Yugoslavia prospective lead industry study: contributions of prenatal and postnatal lead exposure to early intelligence. Neurotoxicol. Teratol. 22: 811-818.

Wasserman, G. A.; Liu, X.; Pine, D. S.; Graziano, J. H. (2001) Contribution of maternal smoking during pregnancy and lead exposure to early child behavior problems. Neurotoxicol. Teratol. 23: 13-21.

Wasserman, G. A.; Factor-Litvak, P.; Liu, X.; Todd, A. C.; Kline, J. K.; Slavkovich, V.; Popovac, D.; Graziano, J. H. (2003) The relationship between blood lead, bone lead and child intelligence. Child Neuropsychol. 9: 22-34.

Watt, G. C. M.; Britton, A.; Gilmore, W. H.; Moore, M. R.; Murray, G. D.; Robertson, S. J.; Womersley, J. (1996) Is lead in tap water still a public health problem? An observational study in Glasgow. Br. Med. J. 313: 979-981.

Weaver, V. M.; Lee, B.-K.; Ahn, K.-D.; Lee, G.-S.; Todd, A. C.; Stewart, W. F.; Wen, J.; Simon, D. J.; Parsons, P. J.; Schwartz, B. S. (2003a) Associations of lead biomarkers with renal function in Korean lead workers. Occup. Environ. Med. 60: 551-562.

Weaver, V. M.; Schwartz, B. S.; Ahn, K.-D.; Stewart, W. F.; Kelsey, K. T.; Todd, A. C.; Wen, J.; Simon, D. J.; Lustberg, M. E.; Parsons, P. J.; Silbergeld, E. K.; Lee, B.-K. (2003b) Associations of renal function with polymorphisms in the "delta"-aminolevulinic acid dehydratase, vitamin D receptor, and nitric oxide synthase genes in Korean lead workers. Environ. Health Perspect. 111: 1613-1619.

Weaver, V. M.; Jarr, B. G.; Schwartz, B. S.; Todd, A. C.; Ahn, K.-D.; Lee, S.-S.; Wen, J.; Parsons, P. J.; Lee, B.-K. (2005a) Associations among lead dose biomarkers, uric acid, and renal function in Korean lead workers. Environ. Health Perspect. 113: 36-42.

Weaver, V. M.; Lee, B.-K.; Todd, A. C.; Jaar, B. G.; Ahn, K.-D.; Wen, J.; Shi, W.; Parsons, P. J.; Schwartz, B. S. (2005b) Associations of patella lead and other lead biomarkers with renal function in lead workers. J. Occup. Environ. Med. 47: 235-243.

Weaver, V. M.; Schwartz, B. S.; Jaar, B. G.; Ahn, K.-D.; Todd, A. C.; Lee, S.-S.; Kelsey, K. T.; Silbergeld, E. K.; Lustberg, M. E.; Parsons, P. J.; Wen, J.; Lee-B.-K. (2005c) Associations of uric acid with polymorphisms in the "delta"-aminolevulinic acid dehydratase, vitamin D receptor, and nitric oxide synthase genes in Korean lead workers. Environ. Health Perspect. 113: 1509-1515.

Webber, C. E.; Chettle, D. R.; Bowins, R. J.; Beaumont, L. F.; Gordon, C. L.; Song, X.; Blake, J. M.; McNutt, R. H. (1995) Hormone replacement therapy may reduce the return of endogenous lead from bone to the circulation. Environ. Health Perspect. 103: 1150-1153.

Wedeen, R. P. (1992) Removing lead from bone: clinical implications of bone lead stores. Neurotoxicology 13: 843-852.

Wedeen, R. P.; Maesaka, J. K.; Weiner, B.; Lipat, G. A.; Lyons, M. M.; Vitale, L. F.; Joselow, M. M. (1975) Occupational lead nephropathy. Am. J. Med. 59: 630-641.

Wedeen, R. P.; Mallik, D. K.; Batuman, V. (1979) Detection and treatment of occupational lead nephropathy. Arch. Intern. Med. 139: 53-57.

Wedeen, R. P.; Batuman, V.; Landy, E. (1983) The safety of the EDTA lead-mobilization test. Environ. Res. 30: 58-62.

Weinberg, C. R.; Baird, D. D.; Rowland, A. S. (1993) Pitfalls inherent in retrospective time-to-event studies: the example of time to pregnancy. Stat. Med. 12: 867-879.

Weinberg, C. R.; Baird, D. D.; Wilcox, A. J. (1994) Sources of bias in studies of time to pregnancy. Stat. Med. 13: 671-681.

Weiss, B. (1988) Neurobehavioral toxicity as a basis for risk assessment. Trends Pharmacol. Sci. 9: 59-62.

Weiss, B. (1990) Risk assessment: the insidious nature of neurotoxicity and the aging brain. Neurotoxicology 11: 305-314.

Weiss, B. (2000) Vulnerability of children and the developing brain to neurotoxic hazards. Environ. Health Perspect. Suppl. 108(3): 375-381.

Weiss, S. T.; Munoz, A.; Stein, A.; Sparrow, D.; Speizer, F. E. (1986) The relationship of blood lead to blood pressure in a longitudinal study of working men. Am. J. Epidemiol. 123: 800-808.

Weisskopf, M. G.; Wright, R. O.; Schwartz, J.; Spiro, A., III; Sparrow, D.; Aro, A.; Hu, H. (2004) Cumulative lead exposure and prospective change in cognition among elderly men. The VA Normative Aging Study. Am. J. Epidemiol. 160: 1184-1193.

West, W. L.; Knight, E. M.; Edwards, C. H.; Manning, M.; Spurlock, B.; James, H.; Johnson, A. A.; Oyemade, U. J.; Cole, O. J.; Westney, O. E.; Laryea, H.; Jones, S.; Westney, L. S. (1994) Maternal low level lead and pregnancy outcomes. J. Nutr. 124(suppl.): 981S-986S.

Wetmur, J. G.; Lehnert, G.; Desnick, R. J. (1991) The "delta"-aminolevulinate dehydratase polymorphism: higher blood lead levels in lead workers and environmentally exposed children with the 1-2 and 2-2 isozymes. Environ. Res. 56: 109-119.

Weyermann, M.; Brenner, H. (1998) Factors affecting bone demineralization and blood lead levels of postmenopausal women--a population-based study from Germany. Environ. Res. 76: 19-25.

Wibberley, D. G.; Khera, A. K.; Edwards, J. H.; Rushton, D. I. (1977) Lead levels in human placentae from normal and malformed births. J. Med. Genet. 14: 339-345.

Wigg, N. R. (2001) Low-level lead exposure and children. J. Paediatr. Child Health 37: 423-425.

Wigg, N. R.; Vimpani, G. V.; McMichael, A. J.; Baghurst, P. A.; Robertson, E. F.; Roberts, R. J. (1988) Port Pirie cohort study: childhood blood lead and neuropsychological development at age two years. J. Epidemiol. Community Health 42: 213-219.

Wildt, K.; Berlin, M.; Isberg, P. E. (1987) Monitoring of zinc protoporphyrin levels in blood following occupational lead exposure. Am. J. Ind. Med. 12: 385-398.

Wilhelm, M.; Lombeck, I.; Hafner, D.; Ohnesorge, F. K. (1989) Hair lead levels in young children from the F.R.G. J. Trace Elem. Electrolytes Health Dis. 3: 165-170.

Wilhelm, M.; Pesch, A.; Rostek, U.; Begerow, J.; Schmitz, N.; Idel, H.; Ranft, U. (2002) Concentrations of lead in blood, hair and saliva of German children living in three different areas of traffic density. Sci. Total Environ. 297: 109-118.

Wingren, G.; Axelson, O. (1985) Mortality pattern in a glass producing area in SE Sweden. Br. J. Ind. Med. 42: 411-414.

Wingren, G.; Axelson, O. (1987) Mortality in the Swedish glassworks industry. Scand. J. Work Environ. Health 13: 412-416.

Wingren, G.; Axelson, O. (1993) Epidemiologic studies of occupational cancer as related to complex mixtures of trace elements in the art glass industry. Scand. J. Work Environ. Health 19(suppl. 1): 95-100.

Wingren, G. Englander, V. (1990) Mortality and cancer morbidity in a cohort of Swedish glassworkers. Int. Arch. Occup. Environ. Health 62: 253-257.

Winkelstein, W.; Balfour, J. L. (1996) [Untitled letter concerning bone lead levels and antisocial and delinquent behavior]. JAMA J. Am. Med. Assoc. 275: 1727-1728.

Winneke, G. (1992) Cross species extrapolation in neurotoxicology: neurophysiological and neurobehavioral aspects. Neurotoxicology 13: 15-25.

Winneke, G. (1995) Lead and child development: uncertainties, possibilities, and explanations. Neurotoxicol. Teratol. 17: 245-247.

Winneke, G. (1995) Endpoints of developmental neurotoxicity in environmentally exposed children. Toxicol. Lett. 77: 127-136.

Winneke, G.; Kraemer, U. (1984) Neuropsychological effects of lead in children: interactions with social background variables. Neuropsychobiology 11: 195-202.

Winneke, G.; Kramer, U. (1997) Neurobehavioral aspects of lead neurotoxicity in children. Cent. Eur. J. Public Health 5: 65-69.

Winneke, G.; Collet, W.; Lilienthal, H. (1988) The effects of lead in laboratory animals and environmentally-exposed children. Toxicology 49: 291-298.

Winneke, G.; Brockhaus, A.; Collet, W.; Kramer, U. (1989) Modulation of lead-induced performance deficit in children by varying signal rate in a serial choice reaction task. Neurotoxicol. Teratol. 11: 587-592.

Winneke, G.; Brockhaus, A.; Ewers, U.; Kramer, U.; Neuf, M. (1990) Results from the European multicenter study on lead neurotoxicity in children: implications for risk assessment. Neurotoxicol. Teratol. 12: 553-559.

Winneke, G.; Altmann, L.; Kramer, U.; Turfeld, M.; Behler, R.; Gutsmuths, F. J.; Mangold, M. (1994) Neurobehavioral and neurophysiological observations in six year old children with low lead levels in East and West Germany. Neurotoxicology 15: 705-713.

Winterberg, B.; Korte, R.; Bertram, H. P. (1991) Response: bone lead is elevated in renal failure [letter]. Nephron 58: 496-497.

Wittmers, L. E.; Aufderheide, A. C.; Wallgren, J.; Rapp, G.; Alich, A. (1988) Lead in bone. IV. Distribution of lead in the human skeleton. Arch. Environ. Health 43: 381-391.

Wolf, A. W.; Ernhart, C. B.; White, C. S. (1985) Intrauterine lead exposure and early development. In: Lekkas, T. D., ed. International conference: heavy metals in the environment, v. 2; September; Athens, Greece. Edinburgh, United Kingdom: CEP Consultants, Ltd.; pp. 153-155.

Wolf, C.; Wallnofer, A.; Waldhoer, T.; Vutuc, C.; Meisinger, V.; Rudiger, H. W. (1995) Effect of lead on blood pressure in occupationally nonexposed men. Am. J. Ind. Med. 27: 897-903.

Wong, O.; Harris, F. (2000) Cancer mortality study of employees at lead battery plants and lead smelters, 1947-1955. Am. J. Ind. Med. 38: 255-270.

World Health Organization. (1977) Lead. Geneva, Switzerland: World Health Organization. (Environmental health criteria: v.3). Available: http://www.inchem.org/documents/ehc/ehc/ehc003.htm [11 March, 2005].

World Health Organization. (1992) International statistical classification of diseases and related health problems: tenth revision (ICD-10). World Health Organization, Geneva. pp. 369-370.

World Health Organization. (1995) Inorganic lead. Geneva, Switzerland: World Health Organization, International Programme on Chemical Safety. (Environmental health criteria 165).

Wright, R. O.; Hu, H.; Silverman, E. K.; Tsaih, S. W.; Schwartz, J.; Bellinger, D.; Palazuelos, E.; Weiss, S. T.; Hernandez-Avila, M. (2003) Apolipoprotein E genotype predicts 24-month bayley scales infant development score. Pediatr. Res. 54: 819-825.

Wright, R. O.; Silverman, E. K.; Schwartz, J.; Tsaih, S.-W.; Senter, J.; Sparrow, D.; Weiss, S. T.; Aro, A.; Hu, H. (2004) Association between hemochromatosis genotype and lead exposure among elderly men: the Normative Aging Study. Environ. Health Perspect. 112: 746-750.

Wu, M. T.; Kelsey, K.; Schwartz, J.; Sparrow, D.; Weiss, S.; Hu, H. (2003) A "delta"-aminolevulinic acid dehydratase (ALAD) polymorphism may modify the relationship of low-level lead exposure to uricemia and renal function: the normative aging study. Environ. Health Perspect. 111: 335-341.

Wu, T.-N.; Shen, C.-Y.; Ko, K.-N.; Guu, C.-F.; Gau, H.-J.; Lai, J.-S.; Chen, C.-J.; Chang, P.-Y. (1996) Occupational lead exposure and blood pressure. Int. J. Epidemiol. 25: 791-796.

Wu, T.; Buck, G. M.; Mendola, P. (2003) Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988-1994. Environ. Health Perspect. 111: 737-741.

Yagoda, B.; Miller, S. A. (1987) Lead in calcium supplements [letter and answer]. JAMA J. Am. Med Assoc. 257: 1810.

Yankel, A. J.; Von Lindern, I. H.; Walter, S. D. (1977) The Silver Valley lead study: the relationship between childhood blood lead levels and environmental exposure. J. Air Pollut. Control Assoc. 27: 763-767.

Yassin, A. S.; Martonik, J. F.; Davidson, J. L. (2004) Blood lead levels in U.S. workers, 1988-1994. J. Occup. Environ. Med. 46: 720-728.

Ye, X. B.; Wu, C. E.; Fu, H.; Yang, S.-L.; Lu, Y.-W.; Ni, W.-M. (2003) Associations of blood lead levels, kidney function, and blood pressure with "delta"-aminolevulinic acid dehydratase and vitamin D receptor gene polymorphisms. Toxicol. Mech. Methods 13: 139-146.

Yokoyama, K.; Araki, S.; Murata, K.; Morita, Y.; Katsuno, N.; Tanigawa, T.; Mori, N.; Yokota, J.; Ito, A.; Sakata, E. (1997) Subclinical vestibulo-cerebellar, anterior cerebellar lobe and spinocerebellar effects in lead workers in relation to concurrent and past exposure. Neurotoxicology 18: 371-380.

Yokoyama, K.; Araki, S.; Aono, H.; Murata, K. (1998) Calcium disodium ethylenediaminetetraacetate-chelated lead as a predictor for subclinical lead neurotoxicity: follow-up study on gun-metal foundry workers. Int. Arch. Occup. Environ. Health 71: 459-464.

Yokoyama, K.; Araki, S.; Yamashita, K.; Murata, K.; Nomiyama, K.; Nomiyama, H.; Tao, Y.-X.; Liu, S.-J. (2002) Subclinical cerebellar anterior lobe, vestibulocerebellar and spinocerebellar afferent effects in young female lead workers in China: computerized posturography with sway frequency analysis and brainstem auditory evoked potentials. Ind. Health 40: 245-253.

Younes, B.; Al-Meshari, A. A.; Al-Hakeem, A.; Al-Saleh, S.; Al-Zamel, F.; Al-Shammari, F.; Alwarthan, A. (1995) Lead concentration in breast milk of nursing mothers living in Riyadh. Ann. Saudi Med. 15: 249-251.

Young, S. S.; Hawkins, D. M. (1988) Using recursive partitioning to analyze a large SAR data set. Struct.-Act. Relat. Quant. Struct.-Act. Relat. 8: 183-193.

Young, B. A.; Boyko, E. J.; Ross, H. J.; Fihn, S.; Bryson, C. L. (2004) Association of urine cadmium with hypertension, microalbuminuria and reduced renal function: results from the NHANES III study [abstract]. J. Am. Soc. Nephrol. 15: 146A.

Yu, C.-C.; Lin, J.-L.; Lin-Tan, D.-T. (2004) Environmental exposure to lead and progression of chronic renal diseases: a four-year prospective longitudinal study. J. Am. Soc. Nephrol. 15: 1016-1022.

Yule, W.; Lansdown, R.; Millar, I. B.; Urbanowicz, M.-A. (1981) The relationship between blood lead concentrations, intelligence and attainment in a school population: a pilot study. Dev. Med. Child Neurol. 23: 567-576.

Yule, W.; Urbanowicz, M.-A.; Lansdown, R.; Millar, I. B. (1984) Teachers' ratings of children's behaviour in relation to blood lead levels. Br. J. Dev. Psychol. 2: 295-305.

Yucesoy, B.; Turhan, A.; Ure, M.; Imir, T.; Karakaya, A. (1997a) Effects of occupational lead and cadmium exposure on some immunoregulatory cytokine levels in man. Toxicology 123: 143-147.

Yucesoy, B.; Turhan, A.; Ure, M.; Imir, T.; Karakaya, A. (1997b) Simultaneous effects of lead and cadmium on NK cell activity and some phenotypic parameters. Immunopharmacol. Immunotoxicol. 19: 339-348.

Zentner, L. E. A.; Rondo, P. H. C. (2004) Lead contamination among pregnant Brazilian women living near a lead smelter. Int. J. Gynecol. Obstet. 87: 147-148.

Zhang, Z.-W.; Shimbo, S.; Ochi, N.; Eguchi, M.; Watanabe, T.; Moon, C.-S.; Ikeda, M. (1997) Determination of lead and cadmium in food and blood inductively coupled plasma mass spectrometry: a comparison with graphite furnace atomic adsorption spectrometry. Sci. Total Environ. 205: 179-187.

Zhao, Z. Y.; Li, R.; Sun, L.; Li, Z. Y.; Yang, R. L. (2004) Effect of lead exposure on the immune function of lymphocytes and erythrocytes. in preschool children. J. Zhejiang Univ. Sci. 5(8): 1001-1004.

Zheng, W.; Lu, Y. M.; Lu, G. Y.; Zhao, Q.; Cheung, 0.; Blaner, W. S. (2001) Transthyretin, thyroxine, and retinol-binding protein in human cerebrospinal fluid: effect of lead exposure. Toxicol. Sci. 61(1): 107-114.

Zimmermann-Tansella, C.; Campara, P.; Andrea, F. D.; Savontto, C.; Tansella, m. (1983) Psychological and physical complaints of subjects with low exposure to lead. Hum. Toxicol. 2: 615-623.

Zuckerman, B.; Amaro, H.; Cabral, H. (1989) Validity of self-reporting of marijuana and cocaine use among pregnant adolescents. J. Pediatr. (St. Louis) 115: 812-815.

5A.2 Ecological Effects

When lead is released in an uncontrolled manner into the environment, whether indoors or outdoors, it ultimately becomes a part of the larger environment in which humans, animals and plants live. In the case of renovation work, the immediate concern is primarily with releases occurring outdoors due to exterior RRP events that do not follow the work practices specified in the proposed regulations. Interior releases, however, can eventually be washed, swept, or disposed of into outdoor environments. When lead-paint dust and debris are disposed of responsibly, the impact may be minimal. However, in the absence of the proposed regulations, it is anticipated that lead will ultimately enter the environment and thereby provide a source of exposure to aquatic or terrestrial receptors.

Lead can affect biota in various ways. Plants are exposed to lead both through their foliage (through atmospheric deposits) and their roots. The extent to which plants uptake lead from the soil depends on various factors, including "cation exchange capacity, soil composition (e.g., organic matter component, calcium content)… [and] is favored at lower pH values and in soils with low organic carbon content" (U.S. EPA 2005b). In plants, exposure to lead can result in decreased photosynthesis, transpiration, water absorption and growth (U.S. EPA 1986, 2005b). Soil microorganisms (decomposers) appear to be more sensitive to lead than higher plants (U.S. EPA 1986).

Avian and mammalian species are exposed to lead primarily through food. Exposure may take place through direct ingestion of soil or through the ingestion of lead-contaminated plants or prey. Effects of lead on avian and mammalian species include increased mortality, adverse effects on growth and reproduction, as well as developmental and behavioral changes. Effects on soil invertebrates include decreased growth and reproduction as well as increased mortality (U.S. EPA 1986).

One benchmark indicator of the toxicity of lead to plants and animals is the Ecological Soil Screening Levels (Eco-SSLs) developed by the U.S. EPA's Office of Emergency and Remedial Response. These contaminant concentration levels are intended for use in identifying contaminants of potential concern (COPCs) during the screening stage of an ecological risk assessment. Eco-SSLs are derived separately for plants, soil invertebrates, birds and mammals and represent conservative estimates of contaminant concentrations that may pose a risk to each group of species (U.S. EPA 2005b). Table 5A-1 presents current Eco-SSLs for lead (as of March 2005).

Table 5A-1: Eco-SSLs for Lead (mg/kg dry weight in soil)

Plants	Invertebrates	Wildlife	
		Avian	Mammal
120	1,700	11	56

Source: U.S. EPA 2005b

In addition to terrestrial species, lead is also highly toxic to aquatic life. The Agency has established both acute and chronic fresh and saltwater criteria for lead. Because the effects threshold increases with water hardness, these criteria vary depending upon the hardness of the water for a given area. The higher the hardness, the higher the criterion. (U.S. EPA 1985).

The impacts of lead on domestic animals have been well-documented. Lead-based paint is the most commonly reported source of lead exposure for household cats and dogs. According to Jill E. Madison, "Renovations of older houses involving sanding or scraping lead-based paint is believed to be the major origin of the lead-based paint in [paint ingestion] instances" (Madison 2005). Lead poisoning symptoms in dogs include GI abnormalities, such as anorexia or colic, and behavioral changes, including anxiety, salivation, blindness and muscular spasms (Merck & Co. 2003). Lead poisoning in dogs may also cause seizures (Thomas 2005). Cats are less likely to be exposed to lead because they are less likely to chew on lead-containing surfaces. Because of their grooming habits, however, they may ingest lead particles. Food avoidance is one of the major symptoms of lead poisoning in cats (Madison 2005). Similarly to dogs and cats, birds may also be exposed to lead through lead-based paint. According to Merck & Co., "in avian species, anorexia, ataxia, loss of condition, wing and leg weakness and anemia are the most notable signs" (Merck & Co. 2003).

Although specific economic benefits to ecological components have not been quantified in this rule, it is reasonable to assume that proposed rule is likely to reduce the amount of lead released from renovation activities, thereby reducing the lead body burdens to plants and animals.

Appendix 5B: Adult Health Benefits Calculations

5B.1 Health Benefits to Men

Lead exposure has also been shown to adversely affect adults. The epidemiological data on the effects of lead in adults are discussed in Appendix 5A. The health effects in adults that are quantified and included in the benefits analysis are all related to the effects of lead on blood pressure.[18] The estimated relationships between these health effects and lead exposure differ between men and women. The quantified health effects include increased incidence of hypertension, initial coronary heart disease (CHD), strokes (initial cerebrovascular accidents and atherothrombotic brain infarctions) and increased mortality. This section describes the methods for quantifying health effects for men; the next section describes the health effects for women. Note that the dose-response functions noted below rely on older published data; not all of these data are included in the review in Appendix 5A. EPA intends to perform an expanded risk assessment for this rulemaking and plans on examining the more recent data discussed in Appendix 5A on the blood-lead-blood pressure relationship, as well as more recent data on the relationship of blood pressure to the risk of cardiovascular disease, as part of that effort. The uncertainties in the quantification of adult effects compared to children's IQ effects is discussed in Section 5.5.5.

5B.1.1 Changes in Hypertension

Quantifying the relationship between blood-lead levels and hypertension

Increased blood-lead (PbB) has been linked to increased blood pressure (BP) in adult males, especially men aged 40-59 years (Pirkle 1985). Further studies have demonstrated a dose-response relationship for hypertension (defined as diastolic blood pressure above 90 mm Hg for this model) in males aged 20-74 years (Schwartz 1988). This relationship is:

$$\Delta \Pr(Hyp) = \frac{1}{1+e^{2.744-0.793*(\ln PbB_1)}} - \frac{1}{1+e^{2.744-0.793*(\ln PbB_2)}} \qquad (1)$$

where:

ΔPr(HYP) = the change in the probability of hypertension;
PbB_1 = PbB level in the control scenario; and
PbB_2 = PbB level in the no-control scenario.

Quantifying the relationship between blood-lead and blood pressure

Because PbB has been identified as a risk factor in a number of cardiovascular effects (Shurtleff 1974, McGee and Gordon 1976, PPRG 1978), it is useful to quantify the effect of changes in PbB levels on changes in blood pressure for reasons other than predicting the probability of hypertension. Based on results of a meta-analysis of several studies, Schwartz (1992a,b) estimated a relationship between a change in blood pressure associated with a decrease in PbB from 10 µg/dL to 5 µg/dL. The coefficient

[18] Citing laboratory studies with rodents, U.S. EPA (1990) also presents evidence of the genotoxicity and/or carcinogenicity of lead compounds. While such animal toxicological evidence suggests that human cancer effects are possible, dose-response relationships are not currently available.

reported by Schwartz (1992 a,b) leads to the following function relating blood pressure to blood-lead for men:

$$\Delta DBP_{men} = 1.4 \times \ln(\frac{PbB_1}{PbB_2}) \qquad (2)$$

where:

ΔDBP_{men} = the change in men's diastolic blood pressure expected from change in PbB;
PbB_1 = PbB level in the control scenario (in μg/dL); and
PbB_2 = PbB level in the no-control scenario (in μg/dL).

This PbB to blood pressure relationship is used to estimate the incidence of initial coronary heart disease, strokes (atherothrombotic brain infarctions and initial cerebrovascular accidents) and premature mortality in men.

5B.1.2 Changes In Coronary Heart Disease

Quantifying the relationship between blood pressure and coronary heart disease

Estimated blood pressure changes can be used to predict the increased probability of the initial occurrence of CHD and stroke (EPA 1987). Increased blood pressure would also increase the probability of reoccurrence of CHD and stroke, but these quantified relationships are not available. First-time CHD events in men can be predicted using an equation with different coefficients for each of three age groups. For men between 40 and 59 years old, information from a 1978 study by the Pooling Project Research Group (PPRG) was used. PPRG (1978) presents a multivariate model (controlling for smoking and serum cholesterol) that relates the probability of CHD to blood pressure. The model used data from five different epidemiological studies. From this study, the equation for the change in 10-year probability of the occurrence of a CHD event is:

$$\Delta \Pr(CHD_{40-59}) = \frac{1}{1+e^{4.996-0.030365*(DBP_1)}} - \frac{1}{1+e^{4.996-0.030365*(DBP_2)}} \qquad (3)$$

where:

$\Delta \Pr(CHD_{40\text{-}59})$ = change in 10-year probability of occurrence of a CHD event for men between 40-59 years old;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

The relationship between BP and first-time CHD in older men was determined from information presented in Shurtleff (1974, Table 1-2). This study also uses data from the Framingham Study (McGee and Gordon 1976) to estimate univariate relationships between blood pressure and a variety of health effects by sex and for each of the following age ranges: 45-54, 55-64 and 65-74 years. Single composite analyses for ages 45-74 were also performed for each sex. For every equation, t-statistics on the variable blood pressure are significant at the 99th percent confidence interval. For men aged 60 to 64 years old, the first-time CHD event can be predicted from the following equation:

$$\Delta \Pr(CHD_{60-64}) = \frac{1}{1+e^{5.19676-0.02351*(DBP_1)}} - \frac{1}{1+e^{5.19676-0.02351*(DBP_2)}} \qquad (4)$$

where:

$\Delta\Pr(CHD_{60\text{-}64})$ = change in 2 year probability of occurrence of a CHD event for men between 60-64 years old;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

For men aged 65 to 74 years old, the following equation uses data from Shurtleff (1974, Table 1-2) to predict the probability of a first-time CHD event:

$$\Delta \Pr(CHD_{65-74}) = \frac{1}{1+e^{4.90723-0.02031*(DBP_1)}} - \frac{1}{1+e^{4.90723-0.02031*(DBP_2)}} \qquad (5)$$

where:

$\Delta\Pr(CHD_{65\text{-}74})$ = change in 2 year probability of occurrence of a CHD event for men between 65-74 years old;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

The probability changes calculated using the functions above are used to estimate the number of CHD events avoided in a given year. The resulting CHD incidence estimates include both fatal and non-fatal events. However, because mortality benefits are independently estimated in this analysis, it is important to capture only the non-fatal CHD events. Shurtleff (1974) reported that two-thirds of all CHD events were non-fatal. This factor was therefore applied to the estimate of avoided CHD events for each age category.

5B.1.3 Changes in Initial Cerebrovascular Accidents and Initial Atherothrombotic Brain Infarctions

Quantifying the relationship between blood pressure and first-time stroke

Two types of health events are categorized as strokes: initial cerebrovascular accidents (CA) and initial atherothrombotic brain infarctions (BI). The risk has been quantified for the male population between 45 and 74 years old (Shurtleff 1974, Tables 8-2 and 9-2). For initial cerebrovascular accidents, the logistic equation is:

$$\Delta \Pr(CA_{men}) = \frac{1}{1+e^{8.58889-0.04066*(DBP_1)}} - \frac{1}{1+e^{8.58889-0.04066*(DBP_2)}} \qquad (6)$$

where:

$\Delta\Pr(CA_{men})$ = change in 2 year probability of cerebrovascular accidents in men;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

For initial atherothrombotic brain infarctions, the logistic equation is:

$$\Delta \Pr(BI_{men}) = \frac{1}{1+e^{9.9516-0.04840*(DBP_1)}} - \frac{1}{1+e^{9.9516-0.04840*(DBP_2)}} \quad (7)$$

where:

$\Delta\Pr(BI_{men})$ = change in 2 year probability of brain infarctions in men;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

Similar to CHD events, this analysis estimates only non-fatal strokes (to avoid double-counting with premature mortality). Shurtleff (1974) reported that 70 percent of strokes were non-fatal. This factor was applied to the estimates of both CA and BI.

5B.1.4 Changes in Premature Mortality

Quantifying the relationship between blood pressure and premature mortality

Information also exists to predict the increased probability of premature death from all causes as a function of increased blood pressure. U.S. EPA (1987) used population mean values for serum cholesterol and smoking to reduce results from a 12-year follow-up of men aged 40-54 years old in the Framingham Study (McGee and Gordon 1976) to an equation in one explanatory variable:

$$\Delta \Pr(MORT_{40-54}) = \frac{1}{1+e^{5.3158-0.03516*(DBP_1)}} - \frac{1}{1+e^{5.3158-0.03516*(DBP_2)}} \quad (8)$$

where:

$\Delta\Pr(MORT_{40-54})$ = the change in 12 year probability of death for men 40-54 years old;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

Information from Shurtleff (1974, Table 12-2) can be used to estimate the probability of premature death in men older than 54 years old. This study has a 2-year follow-up period, so a 2-year probability is estimated. For men aged 55 to 64 years old, mortality can be predicted by the following equation:

$$\Delta \Pr(MORT_{55-64}) = \frac{1}{1+e^{4.89528-0.01866*(DBP_1)}} - \frac{1}{1+e^{4.89528-0.01866*(DBP_2)}} \quad (9)$$

where:

$\Delta\Pr(MORT_{55-64})$ = the change in 2 year probability of death in men 55-64 years old;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

For men aged 65 to 74 years old, premature mortality can be predicted by the following equation:

$$\Delta \Pr(MORT_{65-74}) = \frac{1}{1+e^{3.05723-0.00547*(DBP_1)}} - \frac{1}{1+e^{3.05723-0.00547*(DBP_2)}} \quad (10)$$

where:

$\Delta Pr(MORT_{65\text{-}74})$= the change in 2 year probability of death in men 65-74 years old;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

5B.2 Health Benefits to Women

5B.2.1 Blood Lead-Blood Pressure Relationship

Analysis of data from the second National Health and Nutrition Examination Survey[19] (NHANES II) by Schwartz (1991) indicates a significant association between blood pressure and blood-lead in women. The effect of lead exposure on the blood pressure of women, relative to the effect on men, is examined in a review of ten published studies (Schwartz 1992). All of the reviewed studies included data for men, and some included data for women. The results of this study suggest that the effect on blood pressure for women of this decrease was less than the effect of the same change observed in men. However, a recent study by Nash et al. (2003) examined the relationship between blood lead and changes in blood pressure and hypertension in peri- and post- menopausal women ages 40-59. The study found small but statistically significant changes in both systolic and diastolic blood pressure when comparing the highest and lowest exposure quartiles. Women in the highest exposure quartile also had a higher risk of diastolic (>90 mm Hg) hypertension. The overall mean blood lead among these women was 2.9 mg/dL but the lowest quartile mean was 1.0 while the highest quartile mean was 6.3 mg/dL. The difference in mean systolic and diastolic blood pressure between these two groups was 1.7 and 1.4 mm Hg, respectively. While the grouping of exposures into quartiles makes the use of the data for dose-response somewhat difficult, the difference between mean blood lead in the lowest quartile and highest quartiles was about 5.3 mg/dL while the difference in mean diastolic blood pressure between these two quartiles was 1.4 mm Hg. This compares to an estimated change of 1 mm Hg diastolic blood pressure for a change from 10 mg/dL to 5 mg/dL blood lead, reported for men in Schwartz 1992b (p. 227). While the figures are not directly comparable, it suggests that the effect in women 40-59 may be similar to the effect in men. The Nash study also found that the adjusted odds ratios for diastolic hypertension (using the lowest quartile as the reference group) showed a strong dose-response relationship (that is, the odds ratio increase for each quartile of blood lead level).

Appendix 5A discusses the data on the relationship between blood lead and blood pressure effects in women. The Appendix concludes that "although females often show lower lead coefficients than males, … where these differences have been formally tested, they are usually not statistically significant. The tendencies may well arise in the differential lead exposure …lower in women than in men …. The same sex … differential is found with blood pressure."

Based on this information, the same equations were used to calculate the change in blood pressure in women as in men.

$$\Delta DBP_{women} = (1.4) \times \ln(\frac{PbB_1}{PbB_2}) \qquad (11)$$

[19] The Second National Health and Nutrition Examination Survey (NHANES II) was conducted by the U.S. Department of Health and Human Services from 1976 to 1980 and provides researchers with a comprehensive set of nutritional, demographic and health data for the U.S. population (NHANES 2005).

where:

ΔDBP_{women} = the change in women's diastolic blood pressure expected from a change in PbB;
PbB_1 = PbB level in the control scenario; and
PbB_2 = PbB level in the no-control scenario.

Although women are at risk of having lead-induced hypertension, there is not a dose-response function for hypertension in women available at this time. Thus, the hypertension dose response for men was used to make an estimate of hypertension cases among women.

5B.2.2 Changes in Coronary Heart Disease

Quantifying the relationship between blood pressure and coronary heart disease

Increased blood pressure in women results in the same effects as for men (the occurrence of CHD, two types of stroke and premature death). However, the general relationships between blood pressure and these health effects are not identical to the dose-response functions estimated for men. All relationships presented here have been estimated for women aged 45 to 74 years old using information from Shurtleff (1974). First-time CHD events in women can be estimated from the following equation (Shurtleff 1974, Table 1-2):

$$\Delta \Pr(CHD_{women}) = \frac{1}{1+e^{6.9401-0.03072*(DBP_1)}} - \frac{1}{1+e^{6.9401-0.03072*(DBP_2)}} \qquad (12)$$

where:

$\Delta Pr(CHD_{women})$ = change in 2 year probability of occurrence of CHD event for women 45-74 years of age;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

Again, non-fatal CHD events were estimated by assuming that two-thirds of the estimated events were not fatal (Shurtleff 1974).

5B.2.3 Changes in Atherothrombotic Brain Infarctions and Initial Cerebrovascular Accidents

Quantifying the relationship between blood pressure and first-time stroke

For initial atherothrombotic brain infarctions in women, the logistic equation is (Shurtleff 1974, Table 9-2):

$$\Delta \Pr(BI_{women}) = \frac{1}{1+e^{10.6716-0.0544*(DBP_1)}} - \frac{1}{1+e^{10.6716-0.0544*(DBP_2)}} \qquad (13)$$

where:

$\Delta Pr(BI_{women})$ = change in 2 year probability of brain infarction in women 45-74 years of age;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

The relationship between blood pressure and initial cerebrovascular accidents can be predicted by the following logistic equation (Shurtleff 1974, Table 8-2):

$$\Delta \Pr(CA_{women}) = \frac{1}{1+e^{9.07737-0.04287*(DBP_1)}} - \frac{1}{1+e^{9.07737-0.04287*(DBP_2)}} \quad (14)$$

where:

$\Delta \Pr(CA_{women})$ = change in 2 year probability of cerebrovascular accident in women 45-74 years of age;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

The predicted incidences of avoided atherothrombotic brain infarctions and cerebrovascular accidents were multiplied by 70 percent to estimate only non-fatal strokes (Shurtleff 1974).

5B.2.4 Changes in Premature Mortality

Quantifying the relationship between blood pressure and premature mortality

The risk of premature mortality in women can be estimated by the following equation (Shurtleff, 1974, Table 12-2):

$$\Delta \Pr(MORT_{women}) = \frac{1}{1+e^{5.40374-0.01511*(DBP_1)}} - \frac{1}{1+e^{5.40374-0.01511*(DBP_2)}} \quad (15)$$

where:

$\Delta \Pr(MORT_{women})$ = the change in 2 year probability of death for women 45-74 years of age;
DBP_1 = mean diastolic blood pressure in the control scenario; and
DBP_2 = mean diastolic blood pressure in the no-control scenario.

Appendix 5C: Identifying and Characterizing Lead Loadings for Interior Renovation, Repair and Painting Tasks

5C.1 Renovation, Repair, and Painting Tasks, Work Components, and Estimated Time Requirements

Dust loading levels for RRP tasks can be estimated using the 1997 EPA Lead Exposure Associated with Renovation and Remodeling Activities: Environmental Field Sampling Study (EFSS). (U.S. EPA 1997a). The 1997 study measured lead levels in dust and air, primarily in the rooms where the renovation work was performed. The levels measured in the work area were extrapolated to adjacent rooms for this analysis because the lead dust levels in adjacent rooms provide an estimate for the average lead dust level in a home. In the 1997 study, lead loadings were quantified for specific work components (e.g., drilling, sawing, HVAC work) rather than for a task as defined by the POMS and AHS (e.g., replacing a sink). Consequently, it was necessary to match the work components described in the 1997 study to the renovation and remodeling tasks described in the POMS and AHS.

Table 5C-1 lists the work components for which lead loading data were provided in the renovation and remodeling study. The exhibit provides a brief description of the activity summarized from the renovation study (1997). The components are followed in parentheses by the units of measure (e.g., carpet one home, replace 3 windows, carry out one hour of work) used to evaluate lead loadings in the EPA study. These units are either time or activities.

There were differences in the conditions under which different work components were carried out. Carpet removal and window replacement were each self-contained observational phases of the study, where only the types and locations of the samples were specified in the sampling design. Housing style, lead levels and other factors varied. The remainder of the work components was carried out in the "controlled, experimentally-designed (CED) phase," with observations and measurements made for one hour of work in controlled environments. The type and conduct of the renovation activity, as well as the type and location of samples, were controlled (U.S. EPA 1997a, pg 8-45) in the CED phase.

Table 5C-1: Work Components Listed in the 1997 EPA Renovation Study with Lead Loading Data[a]		
Activity		**Description**
A	Carpet removal (1 house or apartment)	Removal of 2 to 5 rooms of carpeting from 8 units (1 apartment, 1 duplex and 6 single-family homes) of various sizes (pgs. 8-6 and 8-7). The quantity of carpet removed ranged from 246 to 732 ft^2 per unit and was not related to the size of the unit. The geometric mean (pg A-5) was used in this analysis.
B	Windows (3 units)	Removal and replacement of 3 windows each in 4 structures. Windows were selected to represent all approaches to window replacement, all types of windows and the various lead levels that could be encountered in this type of work (pg 8-22). The geometric mean (pg. A-23) was used in this analysis.
C	Paint removal/sanding (time)	In each unit, paint was removed in one area. Paint was removed in half of the area by hand scraping and sanding and the other half by power sanding. No vacuum attachments or dust reduction methods were used (pg 8-48).
D	Demolition (time)	In each unit, three large structure removal activities were carried out involving the demolition of one or more walls, usually a single plaster wall. Removal involved removing the surface of the wall, and NOT the underlying structure, so that an exposed wall structure was available for installation of new drywall (pg 8-46).
E	HVAC (time)	One HVAC repair/replacement activity was carried out in each unit, involving removal of several sections of the HVAC ductwork (pg 8-46).
F	Door modification (time)	This work involved trimming wood from the edge of an existing door, sanding it smooth and drilling a hole for installation of a doorknob, characterized as a small surface disruption. The work involved primarily sawing and sanding (pgs 8-46-47).
G	Power drilling (time)	A lattice of holes was drilled into either plaster walls or wood doors or walls (pg 8-47)
H	Sawing (time)	A series of 15 parallel cuts, 5 feet in length, were made into either plaster walls or wood baseboards using either a rough or fine blade (pg 8-47).
I	Component removal (time)	The following were removed in one unit: lead-painted wood trim, baseboards, doors, and door-jambs (pg 8-47).
a. Page numbers where data are located in the 1997 renovation document are listed in parenthesis.		

This analysis estimated the number of work hours, or the number of alternative units (such as windows replaced) required for each component of each renovation, repair, and painting task expected to generate lead dust detailed in the POMS and AHS. The activities typically required in each RRP task were analyzed using a normative approach due to the wide variability in homes, materials and the way that work is carried out. This approach used assumptions about what a professional would reasonably do in the process of carrying out a specific task in an average home (average homes are defined in Chapter 4). For example, replacing plumbing fixtures in a home is likely to require a small amount of two activities - sawing and drilling into wood or plaster. The number of fixtures replaced is not specified in the AHS. The work was estimated to require an hour or less of each work component. Although the full work of replacing plumbing fixtures is likely to require more time than this, the work involves many other activities that do not cause lead disruption. For example, the estimated time to complete tasks did not include the actual plumbing activities that would not generate lead paint dust, such as sawing new copper pipe.

The process of estimating time and work components for RRP tasks involves uncertainty. The AHS remodeling statistics report the types of renovation activities but not the extent of work. This analysis uses reasonable assumptions regarding task size. For example, EPA assumed that one-half of the windows in an average size house would be replaced when the survey respondent said windows were

replaced. As noted above, when plumbing fixtures were replaced in a home, it was assumed that two major fixtures were replaced (e.g., a toilet and sink), and EPA estimated that one hour each was spent on drilling and sawing. Time units were measured in hours with the smallest unit of time for any task being one hour. For example, tasks figured to involve drilling were estimated to generate at least one hour worth of lead (18 $\mu g/ft^2$; see Table 5C-3) in the room adjacent to the workroom.

An argument could be made that of the work components included in the analysis, power drilling and sawing may not occur continuously for the duration of an hour. However, in calculating the amount of lead generated by a unit of either component, it was assumed that the work occurs uninterrupted for an entire hour. This could have resulted in an over estimate of the number of households with increased lead levels due to RRP. Households that conducted only one renovation or repair task comprised of power drilling were not included in the analysis since the expected lead generation was below the EPA floor lead dust hazard level of 40 $\mu g/ft^2$. Conversely, households that conducted renovation or repair tasks comprised of power drilling and sawing or just sawing were included in the analysis as the expected lead generation was above the EPA floor lead dust hazard level.

Some tasks posed more difficult estimation problems. For example, carpet replacement, which is a very common renovation activity, can be carried out in one or most rooms in a house. Carpet replacement was measured in the renovation study on a per-home basis, in homes ranging from a single apartment to a multi-story house. The number of rooms of carpet replaced and the square footage did not appear to be correlated to home size. The lack of correlation is not unexpected due to the very small sample size in the study (8 homes) and because the number of rooms needing carpet removal varies within a home and does not include the entire house.

In the analysis, EPA assumed that the amount of carpet replaced in the study is representative of carpet reported in the 2003 AHS. This was based on a review of home types and sizes. Although carpet replacement in the renovation study cannot be specifically matched to its national occurrence and scope, the renovation study probably provides a reasonable approximation of the types of units, amount replaced, and resulting lead loadings from replacement, based on the information available for review. In addition, the amount of lead released during carpet replacement is quite high, so that if less carpet were replaced, the lead contamination threshold of 40 $\mu g/ft^2$ would still likely be exceeded.

Variability in the amount of work required for a particular task is an uncertainty for most tasks. The variability may be due to the type of materials involved, their age, their condition, etc, as well as the scope of work (e.g., number or size of units). For example, replacing a free-standing bathroom sink may involve minimal carpentry and focus solely on plumbing, while replacing a sink in a vanity may involve removing the cabinet, re-cutting the counter area, etc. The wood may have many coats of paint or none, and the materials may have other variations that alter the work component time required and the amount of lead paint released. Estimates of the work components carried out and the number of units of work (e.g., hours) required was made considering a pre-1978 housing stock, but work on individual homes will vary.

5C.2 Work Component Lead Loading Levels

The renovation study (U.S. EPA 1997a) provides both airborne (workers' breathing zone) and floor lead loading measurements for each component, following a specific increment of work (e.g., 102 minutes of sanding) or a particular activity (e.g., replacing 3 windows). EPA chose to use floor lead loadings as the relevant contamination measure in this analysis because they could be matched to the selected benchmarks. Floor lead loading measurements ranged mostly from 1 to 6 feet away from the actual work site in most study evaluations. The 6-foot location was used for estimating loadings in this analysis. The relationship between lead loadings and distance from the worksite declines steeply over the first few feet and then tapers off more gradually. The goal in using these loadings is to estimate contamination levels throughout the work area. Consequently, the most distant measurement is more appropriate for estimating lead loadings in other locations. The workroom lead loadings at 6 feet were subsequently scaled to adjacent room lead loadings for this analysis.

All floor measurements used in this analysis were taken one hour post-activity. These were available for all activities, unlike some of the longer post-activity measurements, and so provide consistency in deposition time. However, the use of these data will likely underestimate lead loadings because airborne lead can continue to settle for many hours after work is completed. This was illustrated in the 1997 renovation study, where some measurements were taken both one and two hours post-activity. The study found that deposition continued to occur through the second hour, although at a lower rate (pg A-31 in U.S. EPA 1997a shows lead loadings for the carpet removal work component for one and two hours post-activity). This observation indicates that floor loadings at one hour post-activity are a low estimate of potential lead loadings.

Table 5C-2 lists the contaminant levels measured in the 1997 renovation study for each renovation, repair, and painting task. For activities quantified on the basis of work duration, the contaminant levels are presented first as they were reported in the 1997 renovation report. This is followed by the levels standardized to one hour of work. The standardized value was calculated by proportionally scaling the contaminant levels to one hour of work. For example, it was assumed that if 150 $\mu g/ft^2$ resulted from 1.5 hours of work, then 100 $\mu g/ft^2$ would result from 1.0 hour of work.

The 1997 EPA study reports a distribution of contamination levels for each task at the 6-foot distance (U.S. EPA 1997a). For purposes of this analysis, the 50^{th} percentile values were chosen as most representative of the "average" levels that may occur as a result of the work. They are listed under "measured levels" in Table 5C-2. Maximum or upper 95^{th} percentile airborne lead contaminant values were not used in this analysis directly; however, they are included in the exhibit as an indication of the potential range of exposures that may occur as a result of RRP activities.

As shown in Table 5C-2, measurements of contamination resulting from two different types of materials (i.e., wood and plaster) were made for some work components and yielded different lead releases and lead loadings. Because the proportion of work to be carried out in a typical task on each type of material cannot be estimated, EPA calculated an average lead loading level for the two media. For paint removal, drilling, sawing and clean-up, one half hour of work on each type of media was assumed to occur and contamination from the two half hours were added to yield an average hourly lead loading. For example, floor lead loadings for drilling wood and plaster were 3.61 $\mu g/ft^2$ and 0.1025 $\mu g/ft^2$ per minute, respectively. When these are each multiplied by 30 minutes and added together, the resulting average (18

$\mu g/ft^2$) represents one half-hour of work on each media. This value was used in the analysis as a representative of the floor lead loading generated by one hour of drilling.

Lead concentration in household paint varies considerably. The 1997 renovation analysis does not include a quantitative evaluation of the percent of lead in paint, the thickness of the paint or the number of layers of paint that was present in the structural materials. Data are also not available on those characteristics for the national housing stock. Because EPA designed its 1997 study to capture the spectrum of housing types and ages, the study housing units are likely to have similar lead concentrations to those throughout the country. However, the lack of information is a source of uncertainty in the analysis.

5C.3 Estimated Contamination Levels Throughout the House

The 1997 renovation study included measurements of lead concentrations in air and dust floor loadings in work areas, as shown in Table 5C-2. The measured levels in the work area are not a good measure of residents' exposure for two reasons:

- Clean-up always takes place in the work area after task completion, so that residents are not exposed to pre-clean-up levels (i.e., the primary measurement in the U.S. EPA 1997a study). Although some data on post-clean-up levels exist, they are limited. Contractors usually broom-clean or vacuum (frequently using a shop vac) the work area and remove debris.

- Lead dispersion is airborne and the heaviest particles settle within a short distance from the worksite. This causes adjacent rooms to have a lower lead loading than that found in the work area, and these adjacent rooms are a better measure of lead loadings occurring throughout the house.

Lacking direct lead loading measurements in rooms adjacent to where most RRP activities occurred, EPA estimated these loadings. The estimates are based on the observed relationships between the workroom and adjacent room contamination for window replacement. Adjacent room levels were available only for airborne samples, not for floor samples. It is reasonable to use airborne levels because the lead that settles to the floor results from airborne particles moving through the home. The airborne lead levels in adjacent rooms contribute directly to the floor levels in those rooms. Of the two work components for which adjacent room data are available, window replacement and carpet removal, window replacement is most similar to other work components. It involves working with wood, plaster, and other structural materials, as do the other components. Carpet removal is a unique activity and carpeting is also a unique material known to be a "sink" for lead.

Table 5C-2: Renovation, Repair, and Painting Work Components and Related Floor Lead Loadings and Air Concentrations (Based on data from U.S. EPA, 1996. All measurements are in the work room unless noted as "adjacent.")

Renovation Task		Time (minutes or units)	Floor Lead Loading (µg/ft^2) [a]		Air Concentrations (µg/m^3)			
			Average lead loading measured	Average lead loading per unit or hour	Average personal concentration measured	Average concentration for one unit or hour (See Column 2)	Maximum[b] measured	Maximum concentration for one unit or hour
Carpet	Work room	Rooms needing re-carpeting (see text)	N/A because floor replaced		8.4	8.4	221.3	221.3
	Adjacent room		130.4	130[c]	0.3	0.3	13.4	13.4
Window	Work room	3 windows	878.4	878[d]	7.5	7.5	44.3	44.3
	Adjacent room		not available	not available	1.2	not available	4.2	not available
Paint Removal via sanding	*Hand*	63			254	242	1,410	1,343
	Power	39			571	879	3,170	4,877
	Both methods (1/2 hour each)	102	15,500[e]	9,118	413	561	2,290	3,110
Demolition		61	1,530	1,505	108	107	403	396
HVAC		48	414	518	50	63	66.6	83
Door		68	6,700	5,912	590	521	4,480	3,953
Drilling	*Wood*	36	130	217	15	25	16.3	27
	Plaster	40	4.1	6	7	11	127	191
	Both methods (1/2 hour each)			112				
Sawing	*Wood*	41	7,900	11,561	546	799	1,020	1,493
	Plaster	19	480	1,516	110	347	681	2,151
	Both methods (1/2 hour each)			6,539				
Component Removal		160	1,464	549	344	129	370	139

a. Measurements taken one hour after work was completed. No maximums were available for floor lead loadings other than window and carpet removal (see text).

b. All but carpet and window data are 95th percentiles. See U.S. EPA 1997a for a description of the maximum levels estimated for carpet and window replacement.

c. Maximum was reported as 6135 µg/ft^2 for the floor in the adjacent room.

d. Maximum was reported as 54.515 µg/ft^2 for the floor in the adjacent room.

e. A single value was reported for 102 minutes (hand and power sanding not measured separately).

The airborne window replacement lead concentrations shown in Table 5C-2 for the same room (7.5 $\mu g/m^3$) and the adjacent room (1.2 $\mu g/m^3$) were used to obtain a ratio that is expected to be characteristic of the "workroom-adjacent room" floor lead loadings relationship for other work components. This ratio between the workroom and the adjacent room was calculated as:

$$1.2\ \mu g/m^3 / 7.5\ \mu g/m^3 = 0.16 \text{ (a dimensionless value)}$$

EPA multiplied this ratio (0.16) times the workroom floor lead loadings for each activity shown in Table 5C-2 to estimate the floor lead loadings in an adjacent room for one unit of work. For example, one hour of demolition results in 1,505 $\mu g/ft^2$ in the workroom. This is multiplied by 0.16 to obtain an estimate of the floor lead loadings in the adjacent rooms of 241 $\mu g/ft^2$. Table 5C-3 contains the estimated floor lead loadings in adjacent rooms for all the work components after applying the 0.16 scaling factor to each task shown in Table 5C-2.

Table 5C-3: Work Components, Unit/Time of Measurement, Measured and Estimated Floor Lead Loadings and a Comparison to the Proposed EPA Floor Standard (40 $\mu g/ft^2$)

Work Component[a]	I.D. Code[b]	Measured Level in Work Room ($\mu g/ft^2$)[c]	Estimated Levels in Adjacent Rooms ($\mu g/ft^2$)[d]	One Unit Exceeds Proposed EPA Standard
Carpet removal	A	Not available	130[e]	Yes
Window replacement	B	878	141	Yes
Paint removal	C	9118	1459	Yes
Demolition	D	1505	241	Yes
HVAC	E	518	83	Yes
Door removal	F	5912	946	Yes
Drilling	G	112	18	No
Sawing	H	6539	1046	Yes
Component removal	I	549	88	Yes

a. See definitions in Table 5C-1.
b. Identification codes that were used to assign specific work components to each task are listed in Table 5C-4 and Table 5C- 5.
c. Measurements in the work room are taken from
d. A multiplier of 0.16 was used to estimate floor lead loading in adjacent rooms. See text for discussion.
e. The value for carpet replacement is an actual measurement, as opposed to an estimated value.

Adjacent room loadings are assumed to be reasonably representative of lead loadings throughout the house. However, lead loadings will vary in a home and also vary over time. In the absence of clean-up, the lead loadings in rooms nearest the workroom will initially be the highest. The levels will decline as activities and physical processes cause lead to be moved to other rooms. Consequently, although the loading estimates in this analysis are relevant for an extended period after the RRP work, the specific dynamics of the very long-term loadings are not known. Actual levels in homes depend on a variety of factors including home size, airflow, resident behavior, the paint's lead concentration and thickness, and other factors. In a very large house, there would likely be some rooms with lower lead loadings than those near the workroom. In the absence of specialized clean-up, however, the lead would eventually be distributed to all rooms in the house. Based on available data, it was not possible to determine the

distribution of lead loadings in the various rooms of a home over the long term. The most relevant rooms are those where residents (especially children) spend most of their time.

5C.4 Renovation, Repair, and Painting Tasks and Lead Loading Estimates

This analysis uses the 1995 *Property Owners and Managers Survey* (POMS) (U.S. Census 1995) and the 1997 and 2003 *American Housing Survey* (AHS) (U.S. Census 1997 and 2003) to characterize the different RRP tasks that households perform and the lead loadings that result from performing these tasks. The AHS and the POMS provide data on the type of housing unit (e.g., single-family homes, apartment buildings, the age of the structure) and other critical features of the housing stock (e.g., number of rooms, type of interior RRP). The AHS also describes the residents of homes in which these tasks take place, including whether there are children under the age of 6, the size of families and other demographic features.

In 1997, the AHS provided detailed survey information on renovation and repair tasks performed in homes from a panel of residents living in over 50,000 housing units. In 2003, the AHS continued to cover renovation and repair activities, but reported the data in less detail, combining the 1997 AHS tasks into a smaller number of tasks. As a result, EPA uses the 2003 AHS for characterizing some RRP tasks and 1997 AHS data to characterize RRP tasks where the level of detail in the 2003 survey is not sufficient. The survey results are extrapolated to the national population using weighting factors that adjusted the survey housing stock to match the national housing stock.[20] From the three data sources mentioned above, those tasks likely to generate some lead dust in homes built prior to 1978 were identified. Because it is not known which respondents to the AHS live in structures that actually have lead paint, data from the 2000 HUD National Survey of Lead and Allergens in Housing was used to estimate the number of RRP events occurring in homes that contain lead-based paint and to estimate the number of homes with a pre-existing lead hazard.

To determine the estimated exposure to lead dust resulting from an RRP event, EPA estimated the total floor lead loadings for the RRP tasks where painted surfaces are likely to be disturbed. Table 5C-4 shows the RRP tasks that are reported in the 2003 AHS (owner-occupied RRP) and the 1995 POMS (rental unit RRP), the work components associated with each task, and the estimated household dust loadings (outside work area) resulting from the work components. Since some tasks are too general to assign work components to, 1997 AHS data are used to estimate the work components and resulting household lead loadings for these tasks. In these cases, Table 5C-4 lists the 1997 tasks and Table 5C- 5 shows the work components and lead loadings associated with these tasks. An average weighted by the relative frequencies observed in the 1997 AHS data is used to estimate the lead loading associated with the more general task used in the analysis. For example, the lead loading associated with 2003 AHS task 45, *Added/Replaced Doors Or Windows In Home* (1,991 $\mu g/ft^2$) is estimated as the weighted average of 5,492 (loading for 1997 AHS Task 45) and 1,599 (loading for 1997 AHS Task 46); 1997 tasks 45 and 46 are weighted based on the relative frequency of their occurrence in the 1997 AHS.

Using the task definitions in the AHS, EPA estimated the amount of time each component would typically be employed for each task. While the actual amount of each component used may vary widely within a task, data are not available to provide a distribution of values. Further data collection would be necessary to improve this effort. The number of units of each work component was multiplied by the

[20] For this analysis, sample weights developed by the Harvard University Joint Center for Housing were used to develop national estimates.

expected household dust loading resulting from one unit of each activity. The totals for each component were summed to get an overall estimate of the floor loading outside the work area for each task. For example, replacing plumbing fixtures in a home (task #47 listed in Table 5C-4) was estimated to require one hour each of drilling and sawing. Drilling results in 18 $\mu g/ft^2$ and sawing 1,046 $\mu g/ft^2$ (from Table 5C-3) with a summed estimate of 1,064 $\mu g/ft^2$. All tasks shown exceed EPA's proposed standard of 40 $\mu g/ft^2$ of lead on floors.

Table 5C-4: RRP Tasks and Their Associated Lead Loadings

2003 AHS Task Description (Owner-Occupied Units)	2003 AHS Task ID	POMS Task Description (Rental Units)	1997 AHS Task ID or 2003 Work Components[a]	Resulting Lead Loading Outside Work Area[b] (µg/ft^2)
Remodeled Bathroom	71	Renovation Of Bathroom	1997 Task 16	5,701
			1997 Task 17	
			1997 Task 18	
			1997 Task 19	
			1997 Task 21	
			1997 Task 25	
Remodeled Kitchen	72	Replacement Of Kitchen	1997 Task 26	10,874
			1997 Task 27	
			1997 Task 29	
			1997 Task 30	
			1997 Task 32	
			1997 Task 33	
			1997 Task 34	
Added Room, Or Room Created Through Structural Changes	8, 9, 10, 26, 35, 36	N.A.	4D, 2G, 2H, 4I, F, 4C	10,226
Added/Replaced Internal Water Pipes In Home	40	Upgrading Plumbing System	1997 Task 40	288
			1997 Task 41	
Added/Replaced Electrical Wiring To Home	42	Unit Rewired	1997 Task 42	746
			1997 Task 43	
Added/Replaced Doors Or Windows In Home	45	N.A.	1997 Task 45	1,991
			1997 Task 46	
Added/Replaced Plumbing Fixtures In Home	47	N.A.	G, H	1,064
Installed Paneling Or Ceiling Tiles	55	N.A.	1997 Task 55	3,433
			1997 Task 56	
Added/Replaced Central Air Conditioning	57	Upgrading Heating System; Heating/AC Unit Repaired; Add Or Upgrade AC.[c]	2G, 2H, 8E	2,792
Added/Replaced Built-In Heating Equipment	58		G, H, 2I	1,240
Other Major Improvements Or Repairs Inside Home	64	Other Major Repairs Or Capital Improvement	2G, 2H, 2C, 2I	5,222
Added/Replaced Security System In Home	74	Addition of Security System	G, C	1,477
Interior Painting	N.A.	Interior Painting	4C	5,836

a. See Table 5C-5 for the work component key, 1997 task descriptions, and lead loadings associated with the 1997 tasks.

b. Loadings shown are the estimated loadings for the room adjacent to the work area. Loading estimated based on 1997 tasks are calculated as the weighted average loading according to the 1997 AHS.

c. The loading associated with rental units reporting any of these tasks is estimated as the weighted average loading observed for owner-occupants reporting task 57 and/or task 58 (a loading of 3,226). Note that these tasks are frequently performed together.

Source: EPA Calculations

Table 5C- 5: Work Components Assigned to each Interior Renovation Task and Expected Lead Loadings			
AHS Task ID	**Task Name**	**Work Components (listed in Key) and number of units of each component (see text).**	**Estimated Household Levels (µg/ft^2)**
16	Moved Walls In Bathroom	2D, 2I, G, H, F, 4C	8,504
17	Added/Replaced Cabinets In Bathroom	G, H, I, C	2,611
18	Added/Replaced Flooring In Bathroom	I	88
19	Added/Replaced Counter Tops In Bathroom	G, H, I, C	2,611
21	Added/Replaced Tub/Shower In Bathroom	G, C	1,477
25	Painted/Papered/Wall Tiles Bathroom	2C	2,918
26	Moved Walls In Kitchen	4D, 2G, 2H, 4I, F, 4C	10,226
27	Added/Replaced Cabinets In Kitchen	2G, 2H, 2I, 2C	5,222
29	Added/Replaced Counter Tops In Kitchen	2G, 2H, 2I, C	3,763
30	Added/Replaced Other Built-In Appliances In Kitchen	G, H, I	1,152
32	Added/Replaced Lighting Fixtures In Kitchen	G, C	1,477
33	Added/Replaced Other Electrical Items In Kitchen	G, H, I	1,152
34	Painted/Papered/Wall Tiles Kitchen	4C	5,836
40	Added Internal Water Pipes To Home	2G, 2H	2,128
41	Replaced Internal Water Pipes In Home	3G	54
42	Added Electrical Wiring To Home	G, C	1,477
43	Completely Rewired The Electrical Wiring In Home	4G, I	160
45	Added Doors/Windows To Home	2H, 2D, 2C	5,492
46	Replaced Door/Windows To Home	B, C	1,599
55	Installed New Paneling/Ceiling Tiles	G, C	1,477
56	Replaced Existing Paneling/Ceiling Tiles	8I, 2C, G, H	4,686

Key:

A = carpet removal	(See text)	B = replace windows	(3 windows)
C = paint removal	(1 hour)	D = interior demolitions	(1 hour)
E = HVAC	(1 hour)	F = door removal	(1 hour)
G = drilling	(1 hour)	H = sawing	(1 hour)
I = remove trim	(1 hour)		

5C.5 Interior Painting

5C.5.1 Number of Homes Painted

This analysis identified the number of homes performing an interior painting event using the 1997 AHS. This is described in more detail in Chapter 4 of this document.

5C.6 Background Lead Loadings in Homes

Background lead levels existing in homes prior to RRP work have not been added to the loading levels resulting from RRP events in this analysis, although they may have an impact on one task: carpet

removal.[21] The lead loadings reported in the renovation study (U.S. EPA 1997a) include only post-activity levels on floors for most tasks and involved a sampling method that started with a clean, smooth floor surface at the outset of the task (window and carpet replacement did not take this approach and include pre-existing levels). In actual practice any RRP event will add to the background level.

[21] The high lead levels generated by carpet replacement are assumed to be due to the presence of accumulated lead (Yiin 2002). The levels reported in EPA's renovation study reflect carpet removal from a home with lead-based paint.

Appendix 5D: Distributions of Inputs and Results

As described in section 5.5, the estimation of benefits uses a Monte Carlo approach to reflect the uncertainties inherent in the available data. Several of the inputs used in the analysis are described as distributions, and the results are expressed as a distribution of estimates. This appendix supplements section 5.5 by providing additional details on the various distributions.

5D.1 Custom Distributions for Input Parameters

Four of the input parameters are in the form of custom distributions. These are: Soil Lead Concentrations, Frequency of Household Cleaning, Percent of House Represented by Work Room Area, and Initial Interior Lead Levels.

The distribution of soil lead concentrations due to exterior painting events is shown in Table 5D-1. There are five paint-removal techniques. Within a housing type, the likelihood of occurrence for each of the five techniques is assumed to be the same. But the number of exterior paint removal events varies across housing types based on the number of housing units of each type. Thus the percentage of exterior paint removal events by technique varies across housing types. Also, the lead concentration for a particular paint removal approach varies across housing types because the relationship of the perimeter area to the rest of the yard area also varies across housing types.[22].

[22] For each housing type, the analysis assumes that one-quarter of the exterior paint removal events encompass the entire exterior, one-quarter encompass only one side of the home and the other one-half encompass some thing in between.

Table 5D-1: Custom Distribution Values for Input Parameter: Soil Lead Concentration Outdoors without Rule		
	Whole House Event Soil Conc. (µg/g)	**Probability of Occurrence /Percent of Households**
Single Family Owner		
Exterior paint – alkaline	577	0.031
Exterior paint - heat gun	1,166	0.031
Exterior paint - paint shaver	575	0.031
Exterior paint - safe stripper	1,023	0.031
Exterior paint – wet scrape	983	0.031
Single Family Renter		
Exterior paint – alkaline	565	0.085
Exterior paint - heat gun	1070	0.085
Exterior paint - paint shaver	563	0.085
Exterior paint - safe stripper	947	0.085
Exterior paint – wet scrape	913	0.085
Multi-Family Unit		
Exterior paint – alkaline	559	0.085
Exterior paint - heat gun	1028	0.085
Exterior paint - paint shaver	558	0.085
Exterior paint - safe stripper	914	0.085
Exterior paint – wet scrape	883	0.085
Source: See Section 5.2.3 for development of the lead concentrations. See Section 4.2.5 for development of probabilities.		

The second custom distribution is represents the frequency of household cleaning. In estimating benefits, households are assumed to clean their house immediately following the contractor cleaning at the end of the RRP project. After that cleaning, the household is assumed to clean the house on a regular basis, with the frequency drawn from the distribution shown in Table 5D- 2.

Table 5D- 2: Custom Distribution Values for Input Parameter: Frequency of Household Cleaning per Year		
	Frequency of Cleaning Per Year	**Probability of Occurrence**
Greater than Weekly	104	40%
Weekly	52	45%
Less than Weekly	26	15%
Source: Simcox, 1995		

The house-wide average interior lead loadings are calculated using the lead loadings in the workroom and in the adjacent room, weighted by the percent of house the workroom and the adjacent room represent. These percentages are shown in Table 5D-3 (and as Table 5-8 in this report). These values are not used by them selves, but are combined with the lead loading likelihood values, as shown in Table 5D-4 below.

Table 5D-3: Work Area Size by Event Type (Percent of Housing Unit)	
Event Type	**Work Area Size**
Kitchen	6%
Bathroom	3%
Addition	5%
Non-Room-Specific	30%
Interior Painting	16%
Average Household Work Area	**24%**
Source: Calculated from the American Housing Survey, see Chapter 4 for details.	

Each combination of RRP events yields a specific lead loading in the workroom. A "combination of RRP events" refers to the event or events performed in a single housing unit in one year. This may be a single event (e.g., renovating a kitchen), or it may be a several events involving multiple rooms (e.g., a kitchen and a bathroom). In addition, RRP events where the type of activity is reported but not the location with in the home. Examples are: added or replaced doors or windows, internal water pipes or electrical wiring, other major improvements or repairs. These events are referred to as Non-Room Specific events. Associated with each of the workroom lead loadings is an adjacent room lead loading, equal to 16 percent of the workroom lead load.

Each combination of RRP events has a particular probability of occurring, based on the American Housing Survey data and likelihood of lead. Because the category called Non-Room Specific RRP events contains so many different RRP activities (See Table 4-2) and each combination of activities has its own estimated lead loading, the most commonly reported Percent of Home that is Work Area is 29.9 percent. The final column in Table 5D-4 presents the probability that the particular RRP event and associated lead loadings will occur. The most commonly occurring single RRP event is interior painting. Combinations shown with a 0.0% probability on the table have a positive but very small likelihood (less than 0.05%) of occurring.

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
36475	5836	16.0%	23.2%
12443.75	1991	29.9%	8.4%
32637.5	5222	29.9%	6.9%
67962.5	10874	5.6%	5.5%
103593.75	16575	8.9%	4.0%
20162.5	3226	29.9%	3.2%
6650	1064	29.9%	3.0%
110243.75	17639	29.9%	2.3%
69112.5	11058	29.9%	2.2%
35631.25	5701	3.3%	1.8%
104437.5	16710	21.6%	1.7%
100600	16096	29.9%	1.4%
42281.25	6765	29.9%	1.3%
4662.5	746	29.9%	1.3%
68268.75	10923	29.9%	1.1%
43125	6900	29.9%	1.1%
136231.25	21797	29.9%	1.1%
56637.5	9062	29.9%	1.1%
74612.5	11938	29.9%	1.1%
140068.75	22411	24.9%	1.1%
72106.25	11537	19.3%	1.0%
48918.75	7827	29.9%	1.0%
9231.25	1477	29.9%	0.8%
114906.25	18385	29.9%	0.7%
48075	7692	29.9%	0.7%
80406.25	12865	29.9%	0.7%
19093.75	3055	29.9%	0.6%
88125	14100	29.9%	0.6%
146718.75	23475	29.9%	0.5%
39287.5	6286	29.9%	0.5%
116037.5	18566	29.9%	0.5%
17106.25	2737	29.9%	0.5%
142881.25	22861	29.9%	0.4%
55793.75	8927	29.9%	0.4%
41137.5	6582	29.9%	0.4%
40293.75	6447	29.9%	0.4%
108256.25	17321	29.9%	0.4%
151381.25	24221	29.9%	0.4%
74918.75	11987	29.9%	0.4%
32606.25	5217	29.9%	0.4%
137075	21932	29.9%	0.3%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
172706.25	27633	29.9%	0.3%
52800	8448	29.9%	0.3%
78756.25	12601	29.9%	0.3%
46943.75	7511	29.9%	0.3%
130406.25	20865	29.9%	0.3%
111087.5	17774	29.9%	0.3%
21675	3468	29.9%	0.3%
104743.75	16759	29.9%	0.3%
123756.25	19801	29.9%	0.3%
147543.75	23607	29.9%	0.3%
26812.5	4290	29.9%	0.2%
41868.75	6699	29.9%	0.2%
140893.75	22543	29.9%	0.2%
62443.75	9991	29.9%	0.2%
54725	8756	29.9%	0.2%
122687.5	19630	29.9%	0.2%
37300	5968	29.9%	0.2%
75762.5	12122	29.9%	0.2%
1800	288	29.9%	0.2%
63912.5	10226	5.2%	0.2%
144731.25	23157	29.9%	0.2%
77193.75	12351	29.9%	0.2%
92268.75	14763	29.9%	0.2%
76768.75	12283	29.9%	0.2%
21456.25	3433	29.9%	0.2%
119475	19116	29.9%	0.2%
184018.75	29443	29.9%	0.2%
79581.25	12733	29.9%	0.2%
84550	13528	29.9%	0.2%
11312.5	1810	29.9%	0.2%
177368.75	28379	29.9%	0.2%
152512.5	24402	29.9%	0.1%
116881.25	18701	29.9%	0.1%
33900	5424	29.9%	0.1%
107250	17160	29.9%	0.1%
179356.25	28697	29.9%	0.1%
89275	14284	29.9%	0.1%
88431.25	14149	29.9%	0.1%
83418.75	13347	29.9%	0.1%
111393.75	17823	29.9%	0.1%
127350	20376	29.9%	0.1%
63287.5	10126	29.9%	0.1%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
59387.5	9502	29.9%	0.1%
73775	11804	29.9%	0.1%
94775	15164	29.9%	0.1%
38562.5	6170	29.9%	0.1%
52737.5	8438	29.9%	0.1%
124600	19936	29.9%	0.1%
79275	12684	29.9%	0.1%
120700	19312	29.9%	0.1%
44862.5	7178	29.9%	0.1%
120762.5	19322	29.9%	0.1%
156393.75	25023	29.9%	0.1%
68237.5	10918	29.9%	0.1%
72931.25	11669	29.9%	0.1%
80425	12868	29.9%	0.1%
135068.75	21611	29.9%	0.1%
72625	11620	29.9%	0.1%
45706.25	7313	29.9%	0.1%
23756.25	3801	29.9%	0.1%
47787.5	7646	29.9%	0.1%
43950	7032	29.9%	0.1%
109831.25	17573	29.9%	0.1%
145462.5	23274	29.9%	0.1%
87056.25	13929	29.9%	0.1%
55568.75	8891	29.9%	0.1%
109406.25	17505	29.9%	0.1%
163825	26212	29.9%	0.1%
69081.25	11053	29.9%	0.1%
25556.25	4089	29.9%	0.1%
25200	4032	29.9%	0.1%
116056.25	18569	29.9%	0.1%
78343.75	12535	29.9%	0.1%
157175	25148	29.9%	0.1%
160231.25	25637	29.9%	0.1%
111912.5	17906	29.9%	0.1%
24825	3972	29.9%	0.1%
98918.75	15827	29.9%	0.1%
171543.75	27447	29.9%	0.1%
61300	9808	29.9%	0.1%
91200	14592	29.9%	0.1%
45081.25	7213	29.9%	0.1%
159162.5	25466	29.9%	0.1%
163043.75	26087	29.9%	0.1%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
113668.75	18187	29.9%	0.1%
109100	17456	29.9%	0.1%
174837.5	27974	29.9%	0.1%
143725	22996	29.9%	0.0%
110925	17748	29.9%	0.0%
105262.5	16842	29.9%	0.0%
53581.25	8573	29.9%	0.0%
157237.5	25158	29.9%	0.0%
39256.25	6281	29.9%	0.0%
100568.75	16091	29.9%	0.0%
17450	2792	29.9%	0.0%
152112.5	24338	29.9%	0.0%
124906.25	19985	29.9%	0.0%
112825	18052	29.9%	0.0%
6462.5	1034	29.9%	0.0%
166881.25	26701	29.9%	0.0%
91718.75	14675	29.9%	0.0%
59450	9512	29.9%	0.0%
131918.75	21107	29.9%	0.0%
30687.5	4910	29.9%	0.0%
95862.5	15338	29.9%	0.0%
85587.5	13694	29.9%	0.0%
136200	21792	29.9%	0.0%
50368.75	8059	29.9%	0.0%
161056.25	25769	29.9%	0.0%
83843.75	13415	29.9%	0.0%
192868.75	30859	29.9%	0.0%
102475	16396	29.9%	0.0%
14243.75	2279	29.9%	0.0%
89212.5	14274	29.9%	0.0%
125268.75	20043	29.9%	0.0%
210468.75	33675	29.9%	0.0%
13893.75	2223	29.9%	0.0%
278431.25	44549	29.9%	0.0%
15881.25	2541	29.9%	0.0%
160593.75	25695	29.9%	0.0%
156775	25084	29.9%	0.0%
60231.25	9637	29.9%	0.0%
167706.25	26833	29.9%	0.0%
181937.5	29110	29.9%	0.0%
293600	46976	29.9%	0.0%
58150	9304	29.9%	0.0%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
221343.75	35415	29.9%	0.0%
99543.75	15927	8.5%	0.0%
409031.25	65445	29.9%	0.0%
114493.75	18319	29.9%	0.0%
149300	23888	29.9%	0.0%
61187.5	9790	29.9%	0.0%
111987.5	17918	29.9%	0.0%
68575	10972	29.9%	0.0%
139637.5	22342	29.9%	0.0%
76412.5	12226	29.9%	0.0%
29393.75	4703	29.9%	0.0%
106193.75	16991	29.9%	0.0%
104712.5	16754	29.9%	0.0%
148387.5	23742	29.9%	0.0%
7750	1240	29.9%	0.0%
26118.75	4179	29.9%	0.0%
123531.25	19765	29.9%	0.0%
37643.75	6023	29.9%	0.0%
115750	18520	29.9%	0.0%
89637.5	14342	29.9%	0.0%
186600	29856	29.9%	0.0%
48518.75	7763	29.9%	0.0%
13112.5	2098	29.9%	0.0%
197531.25	31605	29.9%	0.0%
178887.5	28622	29.9%	0.0%
238681.25	38189	29.9%	0.0%
45212.5	7234	29.9%	0.0%
67950	10872	29.9%	0.0%
51512.5	8242	29.9%	0.0%
95081.25	15213	29.9%	0.0%
137043.75	21927	29.9%	0.0%
95925	15348	29.9%	0.0%
100950	16152	29.9%	0.0%
131250	21000	29.9%	0.0%
28325	4532	29.9%	0.0%
84993.75	13599	29.9%	0.0%
193250	30920	29.9%	0.0%
199518.75	31923	29.9%	0.0%
204181.25	32669	29.9%	0.0%
96287.5	15406	29.9%	0.0%
85068.75	13611	29.9%	0.0%
142850	22856	29.9%	0.0%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
57306.25	9169	29.9%	0.0%
31475	5036	29.9%	0.0%
93093.75	14895	29.9%	0.0%
140862.5	22538	29.9%	0.0%
238750	38200	29.9%	0.0%
127825	20452	10.4%	0.0%
128418.75	20547	29.9%	0.0%
66537.5	10646	29.9%	0.0%
89418.75	14307	29.9%	0.0%
172675	27628	29.9%	0.0%
117487.5	18798	29.9%	0.0%
147512.5	23602	29.9%	0.0%
32768.75	5243	29.9%	0.0%
200275	32044	29.9%	0.0%
67106.25	10737	29.9%	0.0%
129568.75	20731	29.9%	0.0%
77500	12400	29.9%	0.0%
28106.25	4497	29.9%	0.0%
325712.5	52114	29.9%	0.0%
72900	11664	29.9%	0.0%
146306.25	23409	29.9%	0.0%
300512.5	48082	29.9%	0.0%
117743.75	18839	29.9%	0.0%
74887.5	11982	29.9%	0.0%
23256.25	3721	29.9%	0.0%
20893.75	3343	29.9%	0.0%
70531.25	11285	29.9%	0.0%
91875	14700	29.9%	0.0%
138162.5	22106	29.9%	0.0%
20543.75	3287	29.9%	0.0%
52356.25	8377	29.9%	0.0%
339131.25	54261	29.9%	0.0%
177337.5	28374	29.9%	0.0%
144143.75	23063	29.9%	0.0%
113975	18236	29.9%	0.0%
164643.75	26343	29.9%	0.0%
155950	24952	29.9%	0.0%
192287.5	30766	29.9%	0.0%
366575	58652	29.9%	0.0%
133500	21360	29.9%	0.0%
42093.75	6735	29.9%	0.0%
105606.25	16897	29.9%	0.0%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
191262.5	30602	29.9%	0.0%
48743.75	7799	29.9%	0.0%
74425	11908	29.9%	0.0%
209856.25	33577	29.9%	0.0%
153962.5	24634	29.9%	0.0%
183987.5	29438	29.9%	0.0%
136581.25	21853	29.9%	0.0%
94731.25	15157	29.9%	0.0%
75731.25	12117	29.9%	0.0%
161743.75	25879	29.9%	0.0%
69531.25	11125	29.9%	0.0%
94300	15088	29.9%	0.0%
109375	17500	29.9%	0.0%
31850	5096	29.9%	0.0%
97356.25	15577	29.9%	0.0%
93937.5	15030	29.9%	0.0%
58887.5	9422	29.9%	0.0%
179325	28692	29.9%	0.0%
100587.5	16094	29.9%	0.0%
34056.25	5449	29.9%	0.0%
103581.25	16573	29.9%	0.0%
62031.25	9925	29.9%	0.0%
186625	29860	29.9%	0.0%
141737.5	22678	29.9%	0.0%
164893.75	26383	29.9%	0.0%
128193.75	20511	29.9%	0.0%
62662.5	10026	29.9%	0.0%
37268.75	5963	29.9%	0.0%
188587.5	30174	29.9%	0.0%
146556.25	23449	29.9%	0.0%
57462.5	9194	29.9%	0.0%
338293.75	54127	29.9%	0.0%
172425	27588	29.9%	0.0%
132312.5	21170	29.9%	0.0%
208056.25	33289	29.9%	0.0%
172275	27564	29.9%	0.0%
165625	26500	29.9%	0.0%
269981.25	43197	29.9%	0.0%
225637.5	36102	29.9%	0.0%
53312.5	8530	29.9%	0.0%
132987.5	21278	29.9%	0.0%
64800	10368	29.9%	0.0%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading (μg/ft²)	**Adjacent Room Loading (μg/ft²)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
43918.75	7027	29.9%	0.0%
173056.25	27689	29.9%	0.0%
62537.5	10006	29.9%	0.0%
41837.5	6694	29.9%	0.0%
24100	3856	29.9%	0.0%
37337.5	5974	29.9%	0.0%
57837.5	9254	29.9%	0.0%
15693.75	2511	29.9%	0.0%
63737.5	10198	29.9%	0.0%
327862.5	52458	29.9%	0.0%
127675	20428	29.9%	0.0%
104006.25	16641	29.9%	0.0%
302662.5	48426	29.9%	0.0%
99437.5	15910	29.9%	0.0%
38906.25	6225	29.9%	0.0%
64112.5	10258	29.9%	0.0%
127412.5	20386	29.9%	0.0%
127650	20424	29.9%	0.0%
11031.25	1765	29.9%	0.0%
121275	19404	29.9%	0.0%
263950	42232	29.9%	0.0%
18906.25	3025	29.9%	0.0%
29862.5	4778	29.9%	0.0%
123681.25	19789	29.9%	0.0%
26337.5	4214	29.9%	0.0%
98481.25	15757	29.9%	0.0%
41081.25	6573	29.9%	0.0%
108325	17332	29.9%	0.0%
126112.5	20178	29.9%	0.0%
119693.75	19151	29.9%	0.0%
73743.75	11799	29.9%	0.0%
70562.5	11290	29.9%	0.0%
169462.5	27114	29.9%	0.0%
80393.75	12863	29.9%	0.0%
93162.5	14906	29.9%	0.0%
135912.5	21746	29.9%	0.0%
43006.25	6881	29.9%	0.0%
19250	3080	29.9%	0.0%
93781.25	15005	29.9%	0.0%
8450	1352	29.9%	0.0%
70762.5	11322	29.9%	0.0%
34568.75	5531	29.9%	0.0%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
71675	11468	29.9%	0.0%
200037.5	32006	29.9%	0.0%
89112.5	14258	29.9%	0.0%
73143.75	11703	29.9%	0.0%
118675	18988	29.9%	0.0%
46656.25	7465	29.9%	0.0%
59768.75	9563	29.9%	0.0%
42306.25	6769	29.9%	0.0%
145100	23216	29.9%	0.0%
132075	21132	29.9%	0.0%
56012.5	8962	29.9%	0.0%
68681.25	10989	29.9%	0.0%
70412.5	11266	29.9%	0.0%
256200	40992	29.9%	0.0%
137650	22024	29.9%	0.0%
121543.75	19447	29.9%	0.0%
60456.25	9673	29.9%	0.0%
20193.75	3231	29.9%	0.0%
168393.75	26943	29.9%	0.0%
9550	1528	29.9%	0.0%
69762.5	11162	29.9%	0.0%
88012.5	14082	29.9%	0.0%
97662.5	15626	29.9%	0.0%
34437.5	5510	29.9%	0.0%
29906.25	4785	29.9%	0.0%
152081.25	24333	29.9%	0.0%
145431.25	23269	29.9%	0.0%
55887.5	8942	29.9%	0.0%
202100	32336	29.9%	0.0%
110225	17636	29.9%	0.0%
72518.75	11603	29.9%	0.0%
48487.5	7758	29.9%	0.0%
92787.5	14846	29.9%	0.0%
96931.25	15509	29.9%	0.0%
46875	7500	29.9%	0.0%
134137.5	21462	29.9%	0.0%
125425	20068	29.9%	0.0%
168550	26968	29.9%	0.0%
176937.5	28310	29.9%	0.0%
107218.75	17155	29.9%	0.0%
176112.5	28178	29.9%	0.0%
99743.75	15959	29.9%	0.0%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading ($\mu g/ft^2$)	**Adjacent Room Loading ($\mu g/ft^2$)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
60487.5	9678	29.9%	0.0%
127731.25	20437	29.9%	0.0%
102531.25	16405	29.9%	0.0%
33306.25	5329	29.9%	0.0%
174125	27860	29.9%	0.0%
82362.5	13178	29.9%	0.0%
29893.75	4783	29.9%	0.0%
133831.25	21413	29.9%	0.0%
123850	19816	29.9%	0.0%
14400	2304	29.9%	0.0%
35350	5656	29.9%	0.0%
125931.25	20149	29.9%	0.0%
246431.25	39429	29.9%	0.0%
121043.75	19367	29.9%	0.0%
98650	15784	29.9%	0.0%
100731.25	16117	29.9%	0.0%
105156.25	16825	29.9%	0.0%
45775	7324	29.9%	0.0%
65868.75	10539	29.9%	0.0%
38343.75	6135	29.9%	0.0%
131556.25	21049	29.9%	0.0%
54093.75	8655	29.9%	0.0%
12412.5	1986	29.9%	0.0%
136218.75	21795	29.9%	0.0%
129262.5	20682	29.9%	0.0%
287431.25	45989	29.9%	0.0%
36043.75	5767	29.9%	0.0%
161900	25904	29.9%	0.0%
24856.25	3977	29.9%	0.0%
208750	33400	29.9%	0.0%
213412.5	34146	29.9%	0.0%
85412.5	13666	29.9%	0.0%
92062.5	14730	29.9%	0.0%
81362.5	13018	29.9%	0.0%
128375	20540	29.9%	0.0%
151893.75	24303	29.9%	0.0%
99625	15940	29.9%	0.0%
51318.75	8211	29.9%	0.0%
77468.75	12395	29.9%	0.0%
111881.25	17901	29.9%	0.0%
81187.5	12990	29.9%	0.0%
35856.25	5737	29.9%	0.0%

Table 5D-4: Custom Distribution Values for Input Parameters: Initial Lead Dust Level in Work Area After Indoor Work, and Percentage of Area of the Home That is a Work Area			
Work Area Loading (µg/ft^2)	**Adjacent Room Loading (µg/ft^2)**	**Percent of Home that is Work Area**	**Probability of Occurrence[1]**
49843.75	7975	29.9%	0.0%
217606.25	34817	29.9%	0.0%
51350	8216	29.9%	0.0%
28643.75	4583	29.9%	0.0%
79550	12728	29.9%	0.0%
181906.25	29105	29.9%	0.0%
105231.25	16837	29.9%	0.0%
66637.5	10662	29.9%	0.0%
113943.75	18231	29.9%	0.0%
148356.25	23737	29.9%	0.0%
156743.75	25079	29.9%	0.0%
29425	4708	29.9%	0.0%
246500	39440	29.9%	0.0%
84962.5	13594	29.9%	0.0%
208025	33284	29.9%	0.0%
233387.5	37342	29.9%	0.0%
29206.25	4673	29.9%	0.0%
111362.5	17818	29.9%	0.0%
116025	18564	29.9%	0.0%
141706.25	22673	29.9%	0.0%
188556.25	30169	29.9%	0.0%
193218.75	30915	29.9%	0.0%
16981.25	2717	29.9%	0.0%
22112.5	3538	29.9%	0.0%
43381.25	6941	29.9%	0.0%
42187.5	6750	29.9%	0.0%
45050	7208	29.9%	0.0%
20862.5	3338	29.9%	0.0%

1.Probabilities shown as 0.0% have a positive but very small values.

Source: See Appendix 5C for development of lead loadings. See Chapter 4 for development of probabilities

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR). 1999. Toxicological profile for lead. U.S. Department of Health and Human Services, Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/tp13.html

Apostoli, P., et al. 2004. Lead and cardiopathy. Medicina del Lavoro, 95(2): 124-132.

Bagchi, D. and H.G. Preuss. 2005. Effects of acute and chronic oval exposure of lead on blood pressure and bone mineral density in rats. Journal of Inorganic Biochemistry, 99(5): 1155-1164.

Baghurst, P. A., et al. 1992. Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study. New England Journal of Medicine, 327: 1279-1284.

Battelle. 2005. Using the IEUBK Model to Predict Geometric Mean Blood-Lead Concentration in Children Aged 1-2 Years as a Function of Hand Dust-Lead Concentration.

Bellinger, D., et al. 1991. Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics, 87: 219-227.

Bellinger, D. C., et al. 1992. Low-Level Lead Exposure, Intelligence and Academic Achievement: A Long-term Follow-up Study. Pediatrics, 90(6): 855-861.

Bellinger, D. C. and H. L. Needleman. 2003. Intellectual Impairment and Blood Lead Levels. New England Journal of Medicine, 349(5): 500.

Bernard, S. M. 2003. Should the Centers for Disease Control and Prevention's childhood lead poisoning intervention level be lowered? American Journal of Public Health, 93(8): 1253-1260.

Brown, R. T. 2001. Behavioral teratology/toxicology: How do we know what we know? Archives of Clinical Neuropsychology, 16: 389-402.

California Air Resources Board (CARB). 1996. Proposed Identification of Inorganic Lead as a Toxic Air Contaminant. California Environmental Protection Agency, Stationary Source Division, Sacramento, California. http://www.arb.ca.gov/regact/lead/isor2.pdf

Canadian Mortgage and Housing Corporation (CMHC). 1992. Effectiveness of Clean-up Techniques for Leaded Paint Dust. Canadian Mortgage and Housing Corporation, Research Division. Research Highlights Technical; Series Number 92-203. http://www.cmhc.ca/publications/en/rh-pr/tech/92-203.pdf

Canfield, R. L., et al. 2003. Intellectual Impairment in Children with Blood Lead Concentrations below 10μg per Deciliter. New England Journal of Medicine, 348(16): 1517-1526.

Canfield, R. L., et al. 2004. Impaired neuropsychological functioning in lead-exposed children. Developmental Neuropsychology, 26: 513-540

Centers for Disease Control (CDC). 1997. Children with Elevated Blood Lead Levels Attributed to Home Renovation and Remodeling Activities – New York, 1993-1994, Morbidity and Mortality Weekly Report, 45(51-52): 1120-3. http://www.cdc.gov/mmwr/PDF/wk/mm4551.pdf

Centers for Disease Control and Prevention (CDC). 2005a. Lead Poisoning in Young Children: A Statement by the Centers for Disease Control and Prevention, Appendix, August 2005. http://www.cdc.gov/nceh/lead/Publications/PrevLeadPoisoning.pdf

Centers for Disease Control and Prevention (CDC). 2005b. Blood Lead Levels – United States, 1999-2002. Morbidity and Mortality Weekly Report, 54(20): 513-516.

Chen, A., et al. 2005. IQ and blood lead from 2 to 7 years of age: Are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environmental Health Perspectives, 113(5): 597-601.

Clark, C. S., et al. 1985. Condition and Type of Housing as an Indicator of Potential Environmental Lead Exposure and Pediatric Blood Lead Levels. Environmental Research, 38: 46-53.

Clemson Environmental Technologies Laboratory (CETL). 2001. A Comparison of Post-Renovation and Remodeling Surface Cleaning Techniques (Unpublished grant report). EPA Grant Agreement Reference No. 82844901.

Cropper, Maureen L. and Alan J. Krupnick. 1990. The Social Costs of Chronic Heart and Lung Disease (Discussion Paper QE89-16-REV). Resources for the Future, Quality of the Environment Division. June 1990.

Department of Health and Human Services (DHHS). 1986. Blood Pressure Levels in Persons 18-74 Years of Age in 1976-1980 and Trends in Blood Pressure from 1960 to 1980 in the United States. DHHS Publication (PHS), 86-1684, July 1986. http://www.cdc.gov/nchs/data/series/sr_11/sr11_234.pdf

Dietrich, K. M., et al. 1993. The Development Consequences of Low to Moderate Prenatal and Postnatal Lead Exposure: Intellectual Attainment in the Cincinnati Lead Study Cohort Following School Entry. Neurotoxicology and Teratology, 15: 37-44.

Dietrich, K. M. 1995. A higher level of analysis: Bellinger's, Interpreting the literature on lead and child development (Commentary). Neurotoxicology and Teratology, 17(3): 223-225.

Dietrich, K. M., et al. 2004. Effect of Chelation Therapy on the Neuropsychology and Behavioral Development of Lead-Exposed Children After School Entry. Pediatrics, 114(1): 19-26.

Dixon, S., et al. 1999. Achieving dust lead clearance standards after lead hazard control projects: An evaluation of the HUD-recommended cleaning procedure and an abbreviated alternative. Applied Occupational and Environmental Hygiene, 14: 339–344.

Durnsun, N., et al. 2005. Blood pressure relationship to nitric oxide, lipid peroxidation, renal function, and renal blood flow in rats exposed to low lead levels. Biological Trace Element Research, 104(2): 141-149.

Efroymson, R. A. et al. 1997. Toxicological benchmarks for screening potential contaminants of concern for effects on terrestrial plants: 1997 Revision, ES/ER/TM-85/R3, Oak Ridge National Laboratory, Oak Ridge, TN. http://www.esd.ornl.gov/programs/ecorisk/documents/tm85r3.pdf

Ettinger, A. S., et al. 2002. Assessment of Cleaning to Control Lead Dust in Homes of Children with Moderate Lead Poisoning: Treatment of Lead-Exposed Children Trial. Environmental Health Perspectives, 110(12): A773-779.

Ewers, L., et al. 1994. Clean-up of Lead in Household Carpet and Floor Dust. American Industrial Hygiene Association Journal, 55(7): 650-657.

Farfel, M. R. and J. J. Chisolm, Jr. 1991. An Evaluation of Experimental Practices for Abatement of Residential Lead-Based Paint: Report on a Pilot Project. Environmental Research, 55: 199-212.

Farfel, M. R., et al. 1994. The Lead Paint Abatement and Repair and Maintenance Study in Baltimore. Lead in Paint, Soil and Dust: Health Risks, Exposure Studies, Control Measures, Measurement Methods, and Quality Assurance, ASTM 1226, Michael E. Beard and S. D. Allen Iske, Eds, American Society for Testing and Materials, Philadelphia, PA.

Farmand, F., et al. 2005. Lead-induced dysregulation of superoxide dismutases, catalase, glutathione peroxidase, and guanylate cyclase. Environmental Research, 98(1): 33-39.

Goch, A. and J.H. Goch. 2005. Lead-induced pathomechanisms of hypertension. Polski Merkuriusz Lekarski, 18(105): 351-353.

Grinshpun, S. A., et al. 2002. Efficiency of final cleaning for lead-based paint abatement in indoor environments. Applied Occupational and Environmental Hygiene, 17(3): 222-34.

Hartunian, N. et al. 1981. The Incidence and Economic Costs of Major Health Impairments. Lexington, MA: Lexington Books.

Hawley, J. 1985. Assessment of Health Risk from Exposure to Contaminated Soil. Risk Analysis, 5(4): 289-302.

Hebben, N. 2001. Low lead levels and neuropsychological assessment: let us not be misled (Commentary). Archives of Clinical Neuropsychology, 16: 353-357.

Hilts, S.R., et al. 1995. A Controlled Trial of the Effect of HEPA Vacuuming on Childhood Lead Exposure. Canadian Journal of Public Health, 86: 345-350.

Hilts S. R., et al. 1998. Effect of Interventions on Children's Blood Lead Levels. Environmental Health Perspectives, 106(2): 79-83.

IRIS Database for Risk Assessment. Updated July 8, 2004. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment. http://www.epa.gov/iriswebp/iris/index.html

Jacobs, D. E., et al. 2002. The prevalence of lead-based paint hazards in U.S. housing. Environmental Health Perspectives, 110(10): A599-606.

Jones, D. S. et. al. 1997. Toxicological benchmarks for screening potential contaminants of concern for effects on sediment-associated biota: 1997 Revision, ES/ER/TM-95/R4, Oak Ridge National Laboratory, Oak Ridge, TN. http://www.esd.ornl.gov/programs/ecorisk/documents/tm95r4.pdf

Lange, J. H., et al. 1997. Personal sample measurements of airborne lead during abatement procedures. Bulletin of Environmental Contamination and Toxicology, 58: 659-666.

Lanphear, B. P., 1996. Lead-Contaminated House Dust and Urban Children's Blood Lead Levels, American Journal of Public Health, 86(10): 1416-1421.

Lanphear, B. P., et al. 1998a. Environmental Exposures to Lead and Urban Children's Blood Lead Levels. Environmental Research, Section A, 76: 120-130.

Lanphear, B. P., et al. 1998b. The Contribution of Lead-Contaminated House Dust and Residential Soil to Children's Blood Lead Levels. Environmental Research,(4) Section A, 79: 51-68.

Lanphear, B. P., et al. 2000. Cognitive deficits associated with blood lead concentrations < 10 "mu"g/dL in U.S. children and adolescents. Public Health Reports, 115: 521-529.

Lanphear, B. P., et al. 2005. Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis. Environmental Health Perspectives, 113(7): 894-899.

Liu, X., et al. 2002. Do Children with Falling Blood Lead Levels Have Improved Cognition? Pediatrics, 110(4): 787-791.

Lustberg, M.E., et al. 2004. The G(894)-T(894) polymorphism in the gene for endothelial nitric oxide synthase and blood pressure in lead-exposed workers from Korea. Journal of Occupational and Environmental Medicine, 46(6): 584-590.

Madison, Jill E. and Christine G. Hawk. 2005. Lead Poisoned Pets and Your Family. Lead Advisory Service Australia. http://www.lead.org.au/fs/fst9.html.

Merck & Co. 2003. Lead Poisoning: Introduction. The Merck Veterinary Manual. http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/211700.htm

McGee and Gordon. 1976. The Results of the Framingham Study Applied to Four Other U.S.-based Epidemiologic Studies of Coronary Heart Disease. The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. Section 31, April.

Nash, D, et al. 2003. Blood Lead, Blood Pressure, and Hypertension in Perimenopausal and Postmenopausal Women. Journal of the American Medical Association, 289(12): 1523-1532.

Nation, J. R. and D. H. Greaves. 2001. Low-level lead exposure and intelligence in children. Archives of Clinical Neuropsychology, 16: 375-388.

Needleman, H. L. et al. 1996. Bone lead levels and delinquent behavior. Journal of the American Medical Association, 275(5): 363-9.

Needleman, H. L. and D. Bellinger. 2001. Studies of lead exposure and the developing central nervous system: a reply to Kaufman. Archives of Clinical Neuropsychology, 16: 359-374.

Ni, Z., et al. 2004. Lead exposure raises superoxide and hydrogen peroxide in human endothelial and vascular smooth muscle cells. Kidney International, 66(6): 2329-2336.

Pirkle, J. L., et al. 1985. The Relationship Between Blood Lead Levels and Blood Pressure and its Cardiovascular Risk Implications. American Journal of Epidemiology 121(2): 246-258.

Pocock, S. J. et al. 1983. Effects of tap water lead, water hardness, alcohol, and cigarettes on blood lead concentrations. Journal of Epidemiology and Community Health, 37(1): 1-7.

Pooling Project Research Group (PPRG). 1978. Relationship of Blood Pressure, Serum Cholesterol, Smoking Habit, Relative Weight and ECG Abnormalities to Incidence of Major Coronary Events: Final Report of the Pooling Project. Journal of Chronic Disease, 31: 201-306.

Potula V. et al. 2001. Blood Lead Levels in Relation to Paint and Dust Lead Levels: The Lead-Safe Cambridge Program. American Journal of Public Health, 91(12): 1973-1974.

Reissman, D. et al. 2002. Is Home Renovation or Repair a Risk Factor for Exposure to Lead Among Children Residing in New York City? Journal of Urban Health: Bulletin of the New York Academy of Medicine, 79(4): 502-511.

Rice D. C. 1996. Behavioral Effects of Lead: Commonalities between Experimental and Epidemiologic Data. Environmental Health Perspectives, 104(S2): 337-51.

Rice, D. and S. Barone, Jr. 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environmental Health Perspectives, Supplement. 108(3): 511-533.

Rich, D. Q. 2002. Comparison of Home Lead Dust Reduction Techniques on Hard Surfaces: The New Jersey Assessment of Cleaning Techniques Trial. Environmental Health Perspectives, 110(9): 889-893.

Rogan, W. J., et al. 2001. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. New England Journal of Medicine, 344(19): 1421-1426.

Rogan, W. J. and J. H. Ware. 2003. Exposure to lead in children – how low is low enough? (Perspective) New England Journal of Medicine, 348(16): 1515-1516.

Ruff, H. A., et al. 1993. Declining blood lead levels and cognitive changes in moderately lead-poisoned children. The Journal of the American Medical Association, 269(13): 1641-1646.

Salkever, D. S. 1995. Updated estimates of earnings benefits from reduced exposure of children to environmental lead. Environmental Research, 70(1): 1-6.

Schnaas, L., et al. 2000. Temporal pattern in the effect of postnatal blood lead level on intellectual development of young children. Neurotoxicology and Teratology, 22: 805-810.

Schwartz, J. 1988. The Relationship Between Blood Lead and Blood Pressure in the NHANES II Survey. Environmental Health Perspectives, 78: 15-22.

Schwartz, J. 1991. Lead, Blood Pressure, and Cardiovascular Disease in Men and Women. Environmental Health Perspectives, 91: 71-75.

Schwartz, J. 1992. Chapter 13: Lead, Blood Pressure and Cardiovascular Disease. Human Lead Exposure, H. L. Needleman, Ed. CRC Press.

Schwartz, J. 1994. Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environmental Research, 65(1): 42-55.

Sharifi, A.M., et al. 2004. Investigation of circulatory and tissue ACE activity during development of lead-induced hypertension. Toxicology Letters, 153(2): 233-238.

Shurtleff, D. 1974. Some Characteristics Related to the Incidence of Cardiovascular Disease and Death. The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease. Section 30, February.

Simcox, N. J., et al. 1995. Pesticides in Household Dust and Soil: Exposure Pathways for Children of Agricultural Families. Environmental Health Perspectives, 103(12): 1126-1134.

Staes, C. and Rinehart, R. 1995. Does Residential Lead-Based Paint Hazard Control Work? A Review of the Scientific Evidence. The National Center for Lead-Safe Housing. http://www.hud.gov/offices/lead/reports/Leastudy.pdf

Stokes, L., et al. 1998. Neurotoxicity in young adults 20 years after childhood exposure to lead: the Bunker Hill experience. Occupational Environmental Medicine, 55: 507-516.

Taylor, T.N. et al. 1996. Lifetime Cost of Stroke in the United States. Stroke, 27(9): 1459-1466.

Thomas, WB. 2005. Lead Poisoning and Seizures. Canine Epilepsy Resource Center. http://www.canine-epilepsy.com/Lead.html.

Tong, S., et al. 1996. Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study. British Medical Journal, 312: 1569-1575.

Tong, S. et al. 2000. Interactions between environmental lead exposure and sociodemographic factors on cognitive development. Archives of Environmental Health, 55: 330-335.

Tong, S. and A.Y. Lu. 2001. Identification of confounders in the assessment of the relationship between exposure and child development. Annals of Epidemiology, 11: 38-45.

U.S. Census Bureau. 1997 and 2003. American Housing Survey (AHS). http://www.census.gov/hhes/www/housing/ahs/ahs.html

U.S. Census Bureau. 1995. Property Owners and Managers Survey (POMS). http://www.census.gov/hhes/www/housing/poms/poms.html

U.S. Department of Health and Human Services (HHS). 1986. Blood pressure levels in persons 18-74 years of age in 1976-1980 and trends in blood pressure from 1960 to 1980 in the United States. In: United States Vital and Health Statistics, Series II, No. 234, DHHS Publication No. (PHS) 86-1684, National Center for Health Statistics, July 1986. (NHANES II study). http://www.cdc.gov/nchs/data/series/sr_11/sr11_234.pdf

U.S. Department of Housing and Urban Development (HUD). 2000. National Survey of Lead and Allergens in Housing. http://www.hud.gov/offices/lead/techstudies/survey.cfm#natsurvey

U.S. Environmental Protection Agency (U.S. EPA). 1985. Ambient water quality criteria for lead - 1984. Washington, DC: Office of Water Regulations and Standards, Criteria and Standards Division; report no. EPA/440/5-84/027. Available: http://www.epa.gov/npdes/pubs/owm586.pdf [25October, 2005]

U.S. Environmental Protection Agency (U.S. EPA). 1986. Air Quality Criteria for Lead, Volumes 1-4 and Supplement. Research Triangle Park, N.C., EPA 600/8-83-028AF. http://cfpub.epa.gov/ncea/cfm/nceapublication.cfm?ActType=PublicationTopics&detype=DOCUMENT&subject=LEAD&subjtype=TITLE&excCol=Archive

U.S. Environmental Protection Agency (U.S. EPA). 1987. Methodology for Valuing Health Risks of Ambient Lead Exposure. Prepared by Mathtech, Inc. for U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Ambient Standards Branch, Contract No. 68-02-4323.

U.S. Environmental Protection Agency (U.S. EPA). 1989. Air Quality Criteria for Lead: Supplement to the 1986 Addendum. EPA/600/8-89/049F (NTIS PB91138420). http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=45189

U.S. Environmental Protection Agency (U.S. EPA). 1990. Review of the National Ambient Air Quality Standards for Lead: Assessment of Scientific and Technical Information. Office of Air Quality Planning and Standards Staff Paper, Air Quality Management Division, Research Triangle Park,

NC. EPA-450/2-89-022, December.
http://www.epa.gov/ttn/naaqs/standards/pb/data/rnaaqsl_asti.pdf

U.S. Environmental Protection Agency (U.S. EPA). 1996. TSCA Title IV, Sections 402(a) and 404: Target Housing and Child Occupied Facilities Final Rule, Regulatory Impact Analysis. http://yosemite.epa.gov/ee/epa/ria.nsf/vwRef/P.96.1+A?OpenDocument

U.S. Environmental Protection Agency (U.S. EPA). 1997a. Lead Exposure Associated with Renovation and Remodeling Activities: Environmental Field Sampling Study (EFSS). EPA 747-R-96-007, May 1997. http://www.epa.gov/lead/pubs/r96-007.pdf

U.S. Environmental Protection Agency (U.S. EPA). 1997b. Exposure Factors Handbook. Office of Research and Development. http://www.epa.gov/ncea/pdfs/efh/front.pdf

U.S. Environmental Protection Agency (U.S. EPA). 1997c. The Benefits and Costs of the Clean Air Act: 1970 to 1990. U.S. EPA, Office of Air and Radiation.
http://www.epa.gov/oar/sect812/contsetc.pdf

U.S. Environmental Protection Agency (U.S. EPA). 1999. Cost of Illness Handbook. U.S. EPA, Office of Pollution, Prevention and Toxics. http://www.epa.gov/oppt/coi/

U.S. Environmental Protection Agency (U.S. EPA). 2000a. Hazard Standard Risk Analysis Supplement – TSCA Section 403. Risk Analysis to Support Standards for Lead in Paint, Dust, and Soil, Supplemental Report, Volume 1. EPA 747-R-00-004. December 2000.
http://www.epa.gov/lead/403risksupp.htm

U.S. Environmental Protection Agency (U.S. EPA). 2000b. Guidelines for Preparing Economic Analyses, p. 90, September.
http://yosemite.epa.gov/ee/epa/eed.nsf/webpages/Guidelines.html/$file/Guidelines.pdf

U.S. Environmental Protection Agency (U.S. EPA). 2001. Economic Analysis of Toxic Substances Control Act Section 403: Lead-Based Paint Hazard Standards. USEPA, Office of Pollution, Prevention and Toxics. http://www.epa.gov/lead/403_ea_d21.pdf

U.S. Environmental Protection Agency (U.S. EPA). 2003. Recommendations of the Technical Review Workgroup for Lead for an Approach to Assessing Risks Associated with Adult Exposures to Lead in Soil. EPA-540-R-03-001. January.
http://www.epa.gov/superfund/lead/products/adultpb.pdf

U.S. Environmental Protection Agency (U.S. EPA). 2005. Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead in Children, Windows® version (IEUBKwin v1.0 build 262) (September, 2005) 32-bit version. http://www.epa.gov/superfund/programs/lead/products.htm

U.S. Environmental Protection Agency (U.S. EPA). 2005b. *Ecological Soil Screening Levels for Lead. Interim Final.* OSWER Directive 9285.7-70. Available at: http://www.epa.gov/ecotox/ecossl/pdf/eco-ssl_lead.pdf.

U.S. Environmental Protection Agency (EPA). 2005c. Air Quality Criteria for Lead (First

External Review Draft). EPA/600/R-05/144aA-bA. December. http://cfpub2.epa.gov/ncea/cfm/recordisplay.cfm?deid=141779

University of Illinois at Urbana-Champaign. 2002. Comparative Analysis of Exterior Paint Removal Methods: Lead Exposures and Production When Preparing Exterior Clapboard Siding. University of Illinois at Urbana-Champaign, Building Research Council, School of Architecture. EPA Grant Agreement. (Unpublished grant report).

University of Rochester School of Medicine (URSM) and National Center for Lead-Safe Housing (NCLSH). 1995. The Relationship of Lead-Contaminated House Dust and Blood-Lead Levels Among Urban Children. Prepared for the U.S. Department of Housing and Urban Development. Grant # MLDP T0001-93. November 15, 1994.

Vaziri, N.D. and D.A. Sica. 2004. Lead-induced hypertension: role of oxidative stress. Current Hypertension Reports, 6(4): 314-320.

Walkowiak, J., et al. 1998. Cognitive and sensorimotor functions in 6-year-old children in relation to lead and mercury levels: adjustment for intelligence and contrast sensitivity in computerized testing. Neurotoxicology and Teratology, 20(5): 511-521.

Wasserman, G. A., et al. 2000. The Yugoslavia Prospective Lead Study: contributions of prenatal and postnatal lead exposure to early intelligence. Neurotoxicology and Teratology, 22: 811-818.

Wasserman, G. A. and P. Factor-Litvak. 2001. Methodology, inference and causation: Environmental lead exposure and childhood intelligence. Archives of Clinical Neuropsychology, 16: 343-352.

Wittels, E. H., et al. 1990. Medical Costs of Coronary Artery Disease in the United States. American Journal of Cardiology, 65: 432-440.

Yiin, L. M., et al. 2002. Comparison of Techniques to Reduce Residential Lead Dust on Carpet and Upholstery: The New Jersey Assessment of Cleaning Techniques Trial. Environmental Health Perspectives, 110(12): 1233-1237.

Yiin, L. M., et al. 2004. Evaluation of cleaning methods applied in home environments after renovation and remodeling activities. Environmental Research, 96(2): 156-62.

Zysko, D., et al. 2004. Effect of lead on the cardiovascular system. Polski Merkuriusz Lekarski, 17(101): 512-515.

6. Comparison of Benefits to Costs

This chapter evaluates the various regulatory options under consideration in terms of their net benefits (i.e. benefits minus costs). Because there is a range of estimated IQ points gained for each option, net benefits are presented as a range of the estimates for each option. It is important to remember that these estimates only partially account for the benefits of the rule; some important groups of benefits are excluded from monetization.

Four regulatory options are analyzed in this report – three allow for flexibility in applying the specific work practices and one is prescriptive. The options also differ in terms of the age of housing covered in the first year. By the second year they all cover the same housing stock. The regulatory options cover the following housing units:

Table 6- 1: Definitions of Regulatory Options

	First Year – Phase 1	Second Year – Phase 2
Option A	All renter-occupied target housing units built before 1978, and owner-occupied target housing units built before 1978 where a child under the age of six resides. Flexible application of work practices	All renter-occupied target housing built before 1978, and owner-occupied target housing units built before 1978 where a child under the age of six resides. Flexible application of work practices
Option B	All renter-occupied target housing units built before 1960, and owner-occupied target housing units built before 1960 where a child under the age of six resides, plus all target housing units built before 1978 where a child with an increased blood-lead level resides.[a] Flexible application of work practices	Same as Option A.
Option C	All renter-occupied target housing units built before 1950, and owner-occupied target housing units built before 1950 where a child under the age of six resides, plus all target housing units built before 1978 where a child with an increased blood-lead level resides.[a] Flexible application of work practices	Same as Option A.
Option D	The prescriptive option. Covers the same housing units as Option B – but requires specific work practices.	The prescriptive option. Covers the same housing units as Option B – but requires specific work practices.

[a] Where increased is defined as greater than or equal to 10 µg/dL or a State or local government level of concern, if lower.
The proposed rule is Option B.

The costs for these four options are estimated in Chapter 4 and summarized in Table 6-2. In terms of first year costs, the regulatory options display a wide range, from $924 million down to $393 million. The range is much narrower in terms of annualized costs, from $588 million down to $488 million when calculated with a three percent discount rate and from $629 million down to $518 million when calculated with a seven percent discount rate. First year costs are much higher, in part because the lead-based paint test kits used in the first year to determine if lead is present are assumed to have a much higher false

positive rate, as compared to the improved tests anticipated to be available after the first year. Work practice costs are higher in the first year because the less accurate lead-based paint test kits result in more cases where a false positive test results in the unnecessary use of the rule'swork practices. The regulatory options that phase in housing units (Options B, C and D) have higher training and certification costs than Option A in the second year because some of the initial training and certification costs are incurred in the second year under these options (when the regulated universe is expanded).

Table 6-2: Comparison of Options – Cost per Individual Protected[a]

	Annual Cost (millions 2005$)			Annual Number of At-Risk Individuals Protected[b] (millions)			Annual Cost per At-Risk Individual Protected		
	Year 1	Year 2	Annual-ized	Year 1	Year 2	Annual Average	Year 1	Year 2	Annual-ized
	3 Percent Discount Rate								
Option A	$924	$495	$505	5.31	5.29	4.81	$174	$94	$105
Option B	$531	$552	$492	4.53	5.29	4.79	$117	$104	$103
Option C	$393	$572	$488	3.66	5.29	4.78	$107	$108	$102
Option D	$645	$649	$588	4.53	5.29	4.79	$142	$123	$123
	7 Percent Discount Rate								
Option A	$924	$476	$551	5.31	5.29	4.81	$174	$90	$115
Option B	$531	$532	$526	4.53	5.29	4.79	$117	$101	$110
Option C	$393	$551	$518	3.66	5.29	4.78	$107	$104	$108
Option D	$645	$625	$629	4.53	5.29	4.79	$142	$118	$131

[a] Assuming 75% compliance with the regulations. Number of individuals protected reflects occupants of housing with LBP where LSWP are used as a result of the rule, and not just individuals for whom benefits are monetized (i.e., children under the age of 6, and adults over the age of 40).

[b] At-risk individuals are individuals living in housing units where RRP takes place, there is lead-based paint and the contractor does not already use the work practices prescribed in the regulation. The number protected may be higher under Scenario 1.

One measure of the impact of each option of the rule is the number of individuals protected by the regulation above and beyond those protected in the baseline conditions without the rule. Protected individuals (children, teenagers and adults) are those living in housing units where the following three conditions are met: Renovation, Repair and Painting (RRP) events take place, lead-based paint is both present and disturbed, and the occupant would not otherwise be protected to the level of the rule under the baseline work practices. The measures of costs and benefits estimated in this analysis address the incremental improvement in protection above these baseline conditions.

In the right-most set of columns in Table 6-2, the options are compared in terms of cost-per-individual protected. Option C is the most cost-effective in Year 1, but Option A is the most cost-effective in Year 2 because of the investment in training and certification that occurred in Year 1 under Option A. Using the 50-year annualized costs, the three flexible options (A, B and C) have approximately the same cost per at-risk individual protected and they all are more cost-effective than Option D, in which work practices are prescribed.[1]

[1] Because annualized annual costs are slightly higher when calculated using a 7 percent discount rate than with a 3 percent discount rate, annualized costs per individual protected are also slightly higher with a 7 percent discount rate. See Section 4.7.3 for more discussion of annualized costs under alternative discount rates.

Another way to compare the efficiency of the options is to examine their net benefits. Based on the subset of benefits that have been monetized, Table 6-3 and Table 6- 4 display net benefit calculations for the first year of the rule and the annualized value of the rule, respectively. Benefits are shown separately for Scenarios 1 and 2 (Tables a and b). As described in detail in Section 5.5.3, the two scenarios differ as to how much contractor and household cleaning already occurs in the baseline; in addition, adult benefits are not estimated under Scenario 2. There are additional uncertainties in the quantification of adult effects, which are addressed in Section 5.5.5. Scenario 2 produces a lower estimate of benefits because it assumes a higher level of baseline cleaning than Scenario 1 and quantifies only children's IQ benefits. Benefits in the form of IQ points gained are presented for each scenario and regulatory option. Adult health benefits for each regulatory option are also included in Scenario 1. There is a range of estimates for each option because each of the six alternative sets of blood-lead modeling assumptions for children's IQ produces a separate estimate. The range is composed of the lowest and the highest IQ point estimate for the option.

Under Scenario 1 (Table 6-3a), all of the net benefit estimates are positive. Under Scenario 2 (Table 6-3b) the first year costs are the same as under Scenario 1; however, the benefits and net benefit estimates are smaller. All of the net benefit estimates remain positive, except for the lowest estimate for Option A.[2]

There is no clearly preferred option based on first year net benefits because, under either scenario, the ranges of net benefit estimates overlap substantially. Under Scenario 1, Option A presents both the highest minimum and the highest maximum value. Under Scenario 2, Option B presents the highest minimum value for net benefits, while Option A presents the highest value overall for net benefits.

[2] As discussed in Chapter 5, the lowest value in the range of Children's IQ benefits is likely to underestimate the IQ benefits. For each option, this estimate assumes that the only children who benefit from the reduced exposure are children ages 1-2 years; other children under the age of 6 years are not included in this low estimate.

Table 6-3a: Comparison of Options – Scenario 1 -- First Year Net Benefits					
	First Year Cost[a] (millions 2005$)	**Children's IQ Benefits – First Year[b] (millions 2005$)**	**Adult Health Benefits – First Year[b] (millions 2005$)**	**Sum of Children's IQ and Adult Benefits (millions 2005$)**	**Net Benefits[c] -- Children's IQ and Adult Health (millions 2005$)**
Option A	$924	$990 -$5,583	$2,367	$3,357 -$7,950	$2,433 - $7,026
Option B	$531	$849 - $4,945	$2,057	$2,906 - $7,002	$2,375 - $6,471
Option C	$393	$668 - $3,810	$1,676	$2,344 - $5,486	$1,951 - $5,093
Option D	$645	$849 - $4,945	$2,057	$2,906 -$7,002	$2,261 - $6,357

[a] Developed in Chapter 4.
[b] Developed in Chapter 5 – range for children's IQ benefits reflects alternative models for blood lead, exposure estimates and population of children.
[c] Difference between sum of benefits and costs.

Table 6-3b: Comparison of Options – Scenario 2[a] -- First Year Net Benefits			
	First Year Cost[b] (millions 2005$)	**Children's IQ Benefits – First Year[c] (millions 2005$)**	**Net Benefits[d] – Children's IQ Only (millions 2005$)**
Option A	$924	$810 - $4,555	($114) - $3,631
Option B	$531	$695 - $3,901	$164 - $3,370
Option C	$393	$545 - $3,105	$152 - $2,712
Option D	$645	$695 - $3,901	$50 - $3,256

[a] While recognizing that adults will benefit from the rule, Scenario 2 does not try to quantify adult benefits.
[b] Developed in Chapter 4.
[c] Developed in Chapter 5 – range reflects alternative models for blood lead, exposure estimates and population of children.
[d] Difference between sum of benefits and costs.

When comparing options on the basis of annualized net benefits (Table 6- 4a and Table 6- 4b), very little difference appears among Options A, B and C. This is not surprising, since the primary differences in the options occur in the first year the rule takes effect. After that year, all options address the same universe of pre-1978 housing. And after the second year, the population of firms and renovators being trained and re-trained levels off to approximately the same number each year. Thus, over a 50-year period, there is little difference among the three flexible options. Scenario 2 produces a lower estimate of benefits from the rule because it assumes a higher level of baseline cleaning than Scenario 1; in addition, adult benefits are not estimated under Scenario 2. There are additional uncertainties in the quantification of adult effects, which are addressed in Section 5.5.5. Both benefits and costs have slightly higher annualized estimates when a 7 percent discount rate is used, as compared to a 3 percent discount rate. Under both scenarios, net benefits are also slightly higher under the 7 percent discount rate. Regardless of which scenario or discount rate is used, however, there is little difference among Options B, C and D. The only substantial difference among the options is between the flexible options (A, B and C) and the prescribed

option (D). The lack of flexibility appears as a roughly $100 million reduction in net benefits as compared to the other options.

Table 6- 4a: Comparison of Options – Scenario 1 -- Annualized Costs and Net Benefits

	Annualized Cost (millions 2005$)[a]	Children's IQ Benefits – Annualized (millions 2005$)[b]	Adult Health Benefits – Annualized (millions 2005$) [b]	Sum of Children's IQ and Adult Benefits -- Annualized (millions 2005$)	Net Benefits – Children's IQ and Adult Health -- Annualized [c] (millions 2005$)
	Annualized using 3 Percent Discount Rate				
Option A	$505	$947 - $5,336	$2,262	$3,209 - $7,599	$2,704 - $7,093
Option B	$492	$941 - $5,311	$2,250	$3,191 - $7,562	$2,699 - $7,069
Option C	$488	$934 - $5,267	$2,235	$3,170 - $7,503	$2,682 - $7,015
Option D	$588	$941 - $5,311	$2,250	$3,191 - $7,562	$2,603 - $6,973
	Annualized using 7 Percent Discount Rate				
Option A	$551	$1,008 - $5,680	$2,408	$3,415 - $8,087	$2,865 - $7,537
Option B	$526	$997 - $5,633	$2,385	$3,383 - $8,019	$2,857 - $7,493
Option C	$518	$984 - $5,551	$2,358	$3,342 - $7,909	$2,824 - $7,391
Option D	$629	$997 - $5,633	$2,385	$3,383 - $8,019	$2,754 - $7,390

[a] Developed in Chapter 4

[b] Developed in Chapter 5 – range for children's IQ benefits reflects alternative models for blood lead, exposure estimates and population of children

[c] Difference between sum of benefits and costs

Table 6-4b: Comparison of Options – Scenario 2[a] – Annualized Costs and Net Benefits

	Annualized Cost[b] (millions 2005$)	Children's IQ Benefits – Annualized[c] (millions 2005$)	Net Benefits[d] – Children's IQ Only (millions 2005$)
Annualized using 3 Percent Discount Rate			
Option A	$505	$774 - $4,354	$269 - $3,849
Option B	$492	$770 - $4,329	$277 - $3,837
Option C	$488	$764 - $4,298	$276 - $3,810
Option D	$588	$770 - $4,329	$181 - $3,741
Annualized using 7 Percent Discount Rate			
Option A	$551	$824 - $4,635	$273 - $4,084
Option B	$526	$816 - $4,587	$290 - $4,061
Option C	$518	$805 - $4,530	$287 - $4,012
Option D	$629	$816 - $4,587	$187 - $3,958

[a] While recognizing that adults will benefit from the rule, Scenario 2 does not try to quantify adult benefits.

[b] Developed in Chapter 4

[c] Developed in Chapter 5 – range reflects alternative models for blood lead, exposure estimates and population of children

[d] Difference between sum of benefits and costs

7. Sensitivity Analysis

To address some of the uncertainties in this analysis, this section considers the impacts of several alternative assumptions on the cost estimates presented in Chapter 4. Where the changes in assumptions also affect benefits, these benefit impacts are described. Fourteen alternative estimates are presented in this sensitivity analysis. They include:

Alternative Estimate 1: An estimate with an alternative assumption about the baseline level of required work practices; it is assumed that Renovation, Repair, and Painting (RRP) events in states and cities with similar RRP regulations do not incur work practice costs.
Alternative Estimate 2: An estimate with the alternative assumption that 100 percent of regulated RRP events are in compliance with the rule instead of 75 percent.
Alternative Estimate 3: An estimate with the alternative assumption that 60 percent of regulated RRP events are in compliance with the rule instead of 75 percent.
Alternative Estimate 4: An estimate with the alternative assumption that 30 percent of regulated RRP events are in compliance with the rule instead of 75 percent.
Alternative Estimate 5: An estimate with the alternative assumption that the false positive rate for the test kit is 47 percent, instead of 63 percent, in the first year.
Alternative Estimate 6: An estimate with the alternative assumption that the false positive rate for the test kit is 78 percent, instead of 63 percent, in the first year.
Alternative Estimate 7: An estimate with the alternative assumption that the false negative rate for the test kit is five percent, instead of zero.
Alternative Estimate 8: An estimate with the alternative assumption that using the test kit to check for the presence of lead-based paint (LBP) costs $20 per-event instead of $10.
Alternative Estimate 9: An estimate with the alternative assumption that the test kit is not available until the third year the rule is in effect, instead of the second year.
Alternative Estimate 10: An estimate with the alternative assumption that the improved test kit is not available until the sixth year the regulation is effective.
Alternative Estimate 11: An estimate with the alternative assumption that the expansion of the regulatory universe and the availability of the improved test kit is delayed until the sixth year the regulation is effective.
Alternative Estimate 12:An estimate with the alternative assumption that the improved test kit has a false positive rate of 15 percent rather than 10 percent.
Alternative Estimate 13: An estimate with an alternative assumption about the number of firms and individuals seeking training and certification.
Alternative Estimate 14: An estimate that considers the costs and benefits of an alternative regulatory option where cleaning verification is not required.

7.1 Alternative Estimate 1: Adjusted for State and Local RRP Regulations

In this section of the sensitivity analysis, EPA assumes that the baseline work practices utilized in certain states and cities are approximately the same as those that will be required under the RRP rule because of existing state and local RRP regulations. Thus, the compliance costs incurred in these states will include cleaning verification, training, and certification costs but not work practice compliance costs. Since only two states and one city currently require renovation contractors to seek lead-safe work practice training, the baseline level of training is minimal and therefore not considered in this analysis. Thus, there is no training cost adjustment in this section of the sensitivity analysis.

7.1.1 Overlap between State and Local Regulations and the Renovation, Repair and Painting Rule

Section 3.2.3 of Chapter 3 identified eight states and six cities that have promulgated rules that address Renovation, Repair, and Painting projects in older housing. These regulations vary from prohibitions against the use of certain work practices when disturbing LBP to specific site preparation and clean-up requirements.

The regulations promulgated in five of the identified states and four of the identified cities are similar (although not identical) to the work practice standards established by the RRP Rule, making it likely that regulated events in these states will not incur most of the work practice compliance costs associated with the new rule.[1] In Massachusetts, for example, workers performing RRP jobs in any pre-1978 housing unit are already required to remove all movable objects from the work area, to cover non-movable objects with plastic sheeting, and to shut down and seal off all HVAC ducts exposed to the work area. All surfaces contaminated with lead debris or dust must be cleaned using a HEPA vacuum, wet wiping, or another acceptable method. If Massachusetts contractors already comply with these regulations, they will not incur additional costs from corresponding work practice requirements in the RRP Rule. They will, however, still incur the costs of cleaning verification, which is not required by Massachusetts regulations.

Other states where regulated projects are likely to be in compliance with the RRP rule work practice standards (not including cleaning verification) are New Jersey, Vermont, Rhode Island and California.[2] Cities with similar regulations include Chicago (Illinois), New York City (New York), Kansas City (Missouri), and Cleveland (Ohio). In New Jersey, Vermont, Rhode Island, New York City, and Cleveland, local rules dictate the use of specific work practices when performing regulated projects. In California, as well as in Chicago and Kansas City, regulations prohibit the creation of uncontained lead dust and debris, implicitly requiring the use of containment during renovation work.

State and city regulations differ in terms of the regulated housing stock. Some apply to all pre-1978 housing, while others apply only to pre-1978 or pre-1960 rental units. Table 7-1 describes the housing stock covered by each state and city rule.

[1] The three remaining states promulgated regulations that prohibit certain work practices but do not require any site preparation or containment. These regulations do not overlap with the proposed RRP Rule and are thus not accounted for in this analysis. Projects conducted in these states are likely to incur the full work practice costs associated with the rule. In addition, voluntary programs are not accounted for in this analysis because of lack of data on the level of participation.

[2] San Francisco exterior events are exempted under the California regulations.

Table 7-1: Description of Housing Stock Subject to State and City Renovation Regulations		
State/City	**Interior Projects[a]**	**Exterior Projects**
California	All pre-1978 housing	All pre-1978 housing
Massachusetts	All pre-1978 housing	All pre-1978 housing
New Jersey	All pre-1978 multi-family housing, except owner-occupied units	All pre-1978 multi-family housing, except owner-occupied units
Vermont	All pre-1978 rental housing	All pre-1978 rental housing
Rhode Island[b]	**None**	All buildings and structures
New York City, NY	All pre-1978 multi-family rental housing with 3 or more units. Owner-occupied units exempt.	**None**
Chicago, IL	Pre-1978 buildings frequented by children six years old and younger	Pre-1978 buildings frequented by children six years old and younger
Kansas City, MO	Pre-1978 buildings	Pre-1978 buildings
Cleveland, OH	Pre-1978 target housing	Pre-1978 target housing

[a] Each state/city may provide for slightly different small construction job exceptions. This analysis assumes that the definition of a small job under each regulation is the same as the definition used in Section 4.5.5 of Chapter 4.

[b] The Rhode Island Department of Health regulations, which cover interior events, are not included in this analysis because they apply to a very small number of renovation projects (some EBL cases only). See Chapter 3 for further discussion.

7.1.2 Adjustment of the Work Practice Compliance Costs

For this sensitivity analysis, EPA assumes that events subject to city and state regulations incur the cost of the cleaning verification but will not incur any other work practice costs since they are assumed to already be using lead-safe renovation techniques.[3] EPA also assumes that the number of renovation events subject to state and city regulations is proportional to the regulated housing stock located in these states/cities. Thus, to account for the increased level of baseline work practices assumed under this sensitivity analysis alternative, the work practice compliance costs are reduced by the percentage of the U.S. housing stock (by age and occupancy) that is subject to more comprehensive state and local renovation rules.[4] Because some regulations apply only to exterior or only to interior events and others apply only to rental units, EPA calculates separate percentages for interior, exterior, owner-occupied, and renter-occupied RRP. These percentages are presented in Table 7-2.

[3] Because the majority of city and state regulatory requirements are not identical to the work practices established by the Renovation, Repair and Painting Rule, this assumption may underestimate the total cost of the RRP Rule under Alternative Estimate 1. At the same time, the assumption that cleaning verification costs will be incurred for all events may slightly overestimate the cost of the rule since New Jersey and New York City regulations require post-renovation dust testing. Furthermore, it is possible that the presence of local regulations encourages contractors to take additional precautions, even though these are not explicitly required by the law.

4 This is in addition to the percentage of events assumed to employ baseline work practices. The data collected on baseline work practices were collected in 1999, before most of these state and local regulations were in place.

Table 7-2: Percent of Nation-wide Housing Stock Subject to State and City Renovation Regulations			
Type of Event and Unit Affected	**Pre-1978[b]**	**Pre-1960**	**Pre-1950**
Interior Events, All Units[a]	19.12%	21.35%	21.79%
Interior Events, Owner-Occupied Units Only	13.58%	14.20%	13.51%
Interior Events, Renter-Occupied Units Only[a]	28.77%	34.61%	35.74%
Exterior Events, All Units[a]	17.63%	18.31%	18.05%
Exterior Events, Owner-Occupied Units Only	14.01%	14.72%	14.09%
Exterior Events, Renter-Occupied Units Only[a]	23.94%	24.95%	24.73%

[a] New York City data includes all pre-1960 renter-occupied multi-family structures with two units or more.

[b] The pre-1978 housing stock is approximated using pre-1980 housing stock data.

Source: U.S. Census Bureau 2000c.

7.1.3 Comparison of the Costs

Table 7-3 presents the 50-year annualized cost estimates for Alternative Estimate 1. The percentages reported in Table 7-2 are used to reduce the work practice costs to reflect the baseline utilization of required work practices in certain states and cities. Note that cleaning verification, training, and certification costs are the same as the Primary Estimates. Thus, under this alternative, 50-year annualized costs are about 14 to 16 percent lower than the Primary Estimates presented in Chapter 4 of this analysis.

Table 7-3: Alternative Estimate 1: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)								
Discount Rate	**3 Percent**				**7 Percent**			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 1: Adjusted for State and Local RRP Regulations	$432	$421	$417	$494	$471	$449	$442	$528
Percent Change	-14.5%	-14.5%	-14.5%	-16.0%	-14.5%	-14.6%	-14.5%	-16.1%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations

7.1.4 Comparison of the Benefits

In this analysis, the benefits of the RRP Rule are correlated with the numbers of children and adults protected from lead exposure, which in turn are a function of the number of events involving LSWP as a result of the regulation. Since it is assumed that a larger share of the population is protected in the baseline under Alternative Estimate 1, the increment of benefits associated with the new rule is smaller. If state and local regulations were as protective of human health as the proposed RRP Rule, estimated benefits would decline by the percentages presented in Table 7-2. In other words, since state and city rules already protect the health of people living in locally regulated housing, the benefits of this protection could not be attributed to the RRP Rule.

However, work practice standards alone are unlikely to be as protective of human health as a combination of containment, cleaning verification, training, and certification requirements. Contractors required to use

containment, for example, may not do so effectively unless they have been trained in how to properly lay down, affix, and dispose of plastic sheeting.

7.2 Alternative Estimate 2: 100% Compliance Assumption

Alternative Estimate 2 employs the alternative assumption that 100 percent of regulated RRP events are in compliance with the rule rather than 75 percent as in the Primary Estimate.

7.2.1 Comparison of the Costs

For the Primary Estimate it is assumed that 75 percent of events are in compliance based on compliance rates observed for the Occupational Safety and Health Administration's (OSHA) regulations (Gilkeya et al 2003 and Weil 1999). The alternative assumption that 100 percent of events will be in compliance is considered here. Although going from 75 percent to 100 percent compliance is a 33 percent increase in the compliance rate, the costs increase by over 50 percent (see Table 7-4). The percentage increase in costs is greater than the increase in the compliance rate because some compliance costs are incurred in the baseline under both alternatives.[5] That is, it is assumed that renovators who are using a work practice activity in the baseline that will be required by the rule will continue to use that practice and will comply with the rule under either estimate. The training and certification costs are 33 percent higher under Alternative Estimate 2 compared to the Primary Estimate; this reflects the 33 percent increase in the compliance rate.

Table 7-4: Alternative Estimate 2: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	A	B	C	D	A	B	C	D
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 2: 100% Compliance Assumption	$795	$774	$766	$940	$866	$827	$813	$1,004
Percent change	57.2%	57.2%	57.1%	59.7%	57.3%	57.1%	57.1%	59.7%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.2.2 Comparison of the Benefits

Scenario 1 and Scenario 2 have different assumptions about the level of protection provided by baseline work practices; more protection is assumed in the baseline under Scenario 2. See Section 5.5.3 for a more detailed discussion of the two scenarios.

[5] Specifically, in the baseline it is assumed that renovators are spending about 35 cents of every dollar of work practice costs needed to attain 100 percent compliance under the flexible options (A, B, and C). For the post-regulation Primary Estimate it is assumed that renovators spend 75 cents of every dollar of work practice costs that would be needed to attain 100 percent compliance. Therefore, there is a 63 percent increase in costs [(100-35)/(75-35) – 1 = 63%] under Alternative Estimate 2. Since training and certification costs increase 33 percent under this alternative, total costs rise by about 57 percent overall under the flexible options.

Scenario 1

Under Scenario 1 the level of protection provided by baseline work practices is assumed to be computationally equivalent to assuming that 20 out of every 100 individuals who reside where RRP is performed and LBP is present have adequate protection from baseline work practices to avoid harmful lead exposures (See Section 5.5.3 for further explanation). Under Alternative 2, all 100 of these individuals have adequate protection (compared to 75 of the 100 under the Primary Estimate). Thus, under Alternative Estimate 2 benefits are higher than for the Primary Estimate.

The assumptions underlying Alternative Estimate 2 imply that benefits are higher than for the Primary Estimate. If it is assumed that non-compliance is independent of household LBP likelihoods, the type of RRP activities performed, and occupant composition (e.g., number, age and sex of occupants), then estimated benefits would be 45 percent higher under this alternative.[6,7] That is, if the independence assumption holds, the monetized benefits presented in Chapter 5 would be precisely 45 percent higher for all options and all years under this alternative.

Scenario 2

Under Scenario 2 it is assumed that 20 out of every 100 individuals who reside where RRP is performed and LBP is present have adequate protection from baseline work practices to avoid harmful lead exposures (See Section 5.5.3 for further explanation). In addition, it is assumed that some households: (1) receive additional contractor cleaning (15 out of every 100 individuals who reside where RRP is performed and LBP is present), (2) receive additional household cleaning (15 out of every 100 individuals who reside where RRP is performed and LBP is present), and (3) additional contractor cleaning of the room adjacent to the work area (10 out of every 100 individuals who reside where RRP is performed and LBP is present). It is assumed that this additional contractor cleaning occurs in the subset of housing units that are in compliance with the rule.

Under Alternative Estimate 2 and Scenario 2, the benefits are 48 percent higher compared with the Primary Estimate. For Alternative Estimate 2, the benefits increase more under Scenario 2 compared to Scenario 1 because the baseline level of protection is greater under Scenario 2. This is because the benefits for the Primary Estimate are smaller under Scenario 2 compared to Scenario 1. In other words, if compliance increases to 100% the post-rule level of protection increases by the same amount under Scenarios 1 and 2, but this is a larger percentage of those incrementally benefiting under Scenario 2, because there are fewer of these individuals compared to Scenario 1.

[6] Similarly to the costs, the same level of protection from baseline work practices is assumed under both alternatives; therefore, the percentage increase in benefits is larger than the percentage increase in compliance. However, the assumed baseline level of protection (20 percent) is lower relative to the baseline work practice costs incurred (35 percent).

[7] The 45 percent is estimated as follows: Under Scenario 1 in the baseline, the level of protection provided by baseline work practices is assumed to be computationally equivalent to assuming that 20 out of every 100 individuals who reside where RRP is performed and LBP is present have adequate protection from baseline work practices to avoid harmful lead exposures. Under the Primary Estimate, 75 out of 100 individuals have adequate protection (an increase of 55). Under Alternative Estimate 2, all 100 individuals are assumed to avoid exposure; an increase of 80 from the baseline level. This represents a 45 percent increase in individuals avoiding exposure (80/55 – 1) = 45%.

These estimates are calculated under the assumption that non-compliance is independent of household LBP likelihoods, the type of RRP performed, and occupant composition (e.g., number, age and sex of occupants).

7.3 Alternative Estimate 3: 60% Compliance Assumption

Alternative Estimate 3 employs the alternative assumption that 60 percent of regulated RRP events are in compliance with the rule rather than 75 percent as in the Primary Estimate.

7.3.1 Comparison of the Costs

For the Primary Estimate it is assumed that 75 percent of events are in compliance based on compliance rates observed for the Occupational Safety and Health Administration's (OSHA) regulations (Gilkeya et al 2003 and Weil 1999). The alternative assumption that only 60 percent of events will be in compliance is considered here. Although going from 75 percent to 60 percent compliance is a 20 percent decline in the compliance rate, the costs decrease by over 30 percent (see Table 7-5). The percentage decrease in costs is larger than the decrease in the compliance rate because some compliance costs are incurred in the baseline under both alternatives.[8] That is, it is assumed that renovators who are using a work practice activity in the baseline that will be required by the rule will continue that practice and will comply with the rule under either estimate. The training and certification costs are 20 percent lower under Alternative Estimate 3 compared to the Primary Estimate; this reflects a 20 percent decrease in the compliance rate.

Table 7-5: Alternative Estimate 3: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	A	B	C	D	A	B	C	D
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 3: 60% Compliance Assumption	$342	$334	$331	$382	$373	$357	$351	$408
Percent Change	-32.3%	-32.2%	-32.2%	-35.1%	-32.3%	-32.2%	-32.2%	-35.1%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.3.2 Comparison of the Benefits

Scenario 1 and Scenario 2 have different assumptions about the level of protection provided by baseline work practices; more protection is assumed in the baseline under Scenario 2. See Section 5.5.3 for a more detailed discussion of the two scenarios.

[8] Specifically, in the baseline it is assumed that renovators are spending about 35 cents of every dollar of work practice costs needed to attain 100 percent compliance under the flexible options (A, B, and C). For the post-regulation Primary Estimate it is assumed that renovators spend 75 cents of every dollar of work practice costs that would be needed to attain 100 percent compliance. For Alternative Estimate 3 it is assumed that renovators spend 60 cents for every dollar of work practice costs that would be needed to attain 100 percent compliance. Therefore, there is a 38 percent decrease in costs [(60-35)/(75-35) – 1 = -38%] under Alternative Estimate 3. Since training and certification costs remain unchanged under this alternative, total costs decline by 30 percent overall.

Scenario 1

Under Scenario 1 the level of protection provided by baseline work practices is assumed to be computationally equivalent to assuming that 20 out of every 100 individuals who reside where RRP is performed and LBP is present have adequate protection from baseline work practices to avoid harmful lead exposures (See Section 5.5.3 for further explanation). Under Alternative 3, 60 of these 100 individuals have adequate protection (compared to 75 of the 100 under the Primary Estimate). Thus, under Alternative Estimate 3 benefits are lower than for the Primary Estimate.

If it is assumed that non-compliance is independent of household LBP likelihoods, the type of RRP activities performed, and occupant composition (e.g., number, age and sex of occupants), then estimated benefits would be 27 percent lower under this alternative.[9,10] That is, if the independence assumption holds, the monetized benefits presented in Chapter 5 would be precisely 27 percent lower for all options and all years under this alternative.

Scenario 2

Under Scenario 2 it is assumed that 20 out of every 100 individuals who reside where RRP is performed and LBP is present have adequate protection from baseline work practices to avoid harmful lead exposures (See Section 5.5.3 for further explanation). In addition, it is assumed that some households: (1) receive additional contractor cleaning (15 out of every 100 individuals who reside where RRP is performed and LBP is present), (2) receive additional household cleaning (15 out of every 100 individuals who reside where RRP is performed and LBP is present), and (3) additional contractor cleaning of the room adjacent to the work area (10 out of every 100 individuals who reside where RRP is performed and LBP is present). It is assumed that this additional contractor cleaning occurs in the subset of housing units that are in compliance with the rule.

Under Alternative Estimate 3 and Scenario 2, the benefits are 29 percent lower compared with the Primary Estimate. For Alternative Estimate 3, the benefits decline more under Scenario 2 compared to Scenario 1 because the baseline level of protection is greater under Scenario 2. In other words, the post-rule level of protection declines by the same amount under Scenarios 1 and 2, but this is a larger percentage of those incrementally benefiting under Scenario 2, because there are fewer of these individuals under Scenario 2.

These estimates are calculated under the assumption that non-compliance is independent of household LBP likelihoods, the type of RRP performed, and occupant composition (e.g., number, age and sex of occupants).

7.4 Alternative Estimate 4: 30% Compliance Assumption

Alternative Estimate 4 employs the alternative assumption that 30 percent of regulated RRP events are in compliance with the rule rather than 75 percent as in the Primary Estimate.

[9] Similarly to the costs, the same level of protection from baseline work practices is assumed under both alternatives; therefore, the percentage decrease in benefits is larger than the percentage decrease in compliance. However, the assumed baseline level of protection is lower relative to the baseline work practice costs incurred.
[10] The 27 percent is calculated using the same steps described in footnote 7.

7.4.1 Comparison of the Costs

For the Primary Estimate it is assumed that 75 percent of events are in compliance based on compliance rates observed for the Occupational Safety and Health Administration's (OSHA) regulations (Gilkeya et al 2003 and Weil 1999). The alternative assumption that only 30 percent of events will be in compliance is considered here. Although going from 75 percent to 30 percent compliance is a 60 percent decline in the compliance rate, the costs decrease by about 80 percent (see Table 7-5); this decline is driven by an 85% reduction in work practice costs. The percentage decrease in costs is larger than the decrease in the compliance rate because some compliance costs are incurred in the baseline under both alternatives. The training and certification costs are 60 percent lower under Alternative Estimate 4 compared to the Primary Estimate; this reflects a 60 percent decrease in the compliance rate.

Table 7-6: Alternative Estimate 4: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	A	B	C	D	A	B	C	D
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 4: 30% Compliance Assumption	$99	$97	$96	$101	$108	$104	$102	$108
Percent Change	-80.4%	-80.3%	-80.3%	-82.9%	-80.5%	-80.3%	-80.2%	-82.9%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.4.2 Comparison of the Benefits

Scenario 1

Under Scenario 1 the level of protection provided by baseline work practices is assumed to be computationally equivalent to assuming that 20 out of every 100 individuals who reside where RRP is performed and LBP is present have adequate protection from baseline work practices to avoid harmful lead exposures (See Section 5.5.3 for further explanation). Under Alternative 4, 30 of these 100 individuals have adequate protection (compared to 75 of the 100 under the Primary Estimate). Thus, under Alternative Estimate 4 benefits are lower than for the Primary Estimate.

If it is assumed that non-compliance is independent of household LBP likelihoods, the type of RRP performed, and occupant composition (e.g., number, age and sex of occupants), then estimated benefits would be 82 percent lower under this alternative.[11,12] That is, if the independence assumption holds, the monetized benefits presented in Chapter 5 would be precisely 82 percent lower for all options and all years under this alternative.

[11] Similarly to the costs, the same level of protection from baseline work practices is assumed under both alternatives; therefore, the percentage decrease in benefits is larger than the percentage decrease in compliance. However, the assumed baseline level of protection is lower relative to the baseline work practice costs incurred.
[12] The 82 percent is calculated using the same steps described in footnote 7.

Scenario 2

Under Scenario 2 it is assumed that 20 out of every 100 individuals who reside where RRP is performed and LBP is present have adequate protection from baseline work practices to avoid harmful lead exposures (See Section 5.5.3 for further explanation). In addition, it is assumed that some households: (1) receive additional contractor cleaning (15 out of every 100 individuals who reside where RRP is performed and LBP is present), (2) receive additional household cleaning (15 out of every 100 individuals who reside where RRP is performed and LBP is present), and (3) additional contractor cleaning of the room adjacent to the work area (10 out of every 100 individuals who reside where RRP is performed and LBP is present). It is assumed that this additional contractor cleaning occurs in the subset of housing units that are in compliance with the rule.

Under Alternative Estimate 4 and Scenario 2, the benefits are 85 percent lower compared with the Primary Estimate. For Alternative Estimate 4, the benefits decline more under Scenario 2 compared to Scenario 1 because the baseline level of protection is greater under Scenario 2. In other words, the post-rule level of protection declines by the same amount under Scenarios 1 and 2, but this is a larger percentage of those incrementally benefiting under Scenario 2, because there are fewer are these individuals under Scenario 2.

These estimates are calculated under the assumption that non-compliance is independent of household LBP likelihoods, the type of RRP performed, and occupant composition (e.g., number, age and sex of occupants).

7.5 Alternative Estimate 5: Test Kits with 47% Rate of False Positives

Test Kits that are currently available have false positive rates that range from 47 percent to 78 percent. The Primary Estimate assumes a false positive rate of 63 percent, the midpoint of the range, for the first year that the rule's requirements are effective. Alternative Estimate 5 employs an alternative assumption that the false positive rate for the Test Kit is 47 percent, instead of 63 percent, in the first year.

7.5.1 Comparison of the Costs

Since this alternative estimate only impacts the work practice standard costs during the first year of regulation, the impact on the 50-year annualized costs is less than 1 percent. In the first year, however, the costs are about 5 to 9 percent lower, since a more accurate Test Kit results in fewer cases where a false positive test results in the use of unnecessary and more expensive LSWP.

Table 7-7: Alternative Estimate 5: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 5: Test Kit with 47% Rate of False Positives	$502	$491	$487	$587	$544	$524	$516	$626
Percent Change	-0.7%	-0.3%	-0.2%	-0.3%	-1.1%	-0.5%	-0.3%	-0.5%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.5.2 Comparison of the Benefits

There is no impact on the benefits estimate under this alternative, because it is assumed that the test kit always identifies LBP when present. That is, the false negative rate is assumed to be zero for both estimates.

7.6 Alternative Estimate 6: Test Kits with 78% Rate of False Positives

Test kits that are currently available have false positive rates that range from 47 percent to 78 percent. The Primary Estimate assumes a false positive rate of 63 percent, the midpoint of the range, for the first year that the rule's requirements are effective. Alternative Estimate 6 employs an alternative assumption that the false positive rate for the test kit is 78 percent, instead of 63 percent, in the first year.

7.6.1 Comparison of the Costs

Since this alternative estimate only impacts the work practice standard costs during the first year of regulation, the impact on the 50-year annualized costs is one percent or less. In the first year, however, the costs are about 5 to 9 percent higher, since a less accurate test kit results in more cases where a false positive test results in the use of unnecessary and more expensive LSWP.

Table 7-8: Alternative Estimate 6: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 6: Test Kit with 78% Rate of False Positives	$508	$493	$488	$590	$556	$528	$519	$632
Percent Change	0.6%	0.2%	0.2%	0.3%	1.1%	0.4%	0.3%	0.5%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.6.2 Comparison of the Benefits

There is no impact on the benefits estimate under this alternative, because it is assumed that the test kit always identifies LBP when present. That is, the false negative rate is assumed to be zero for both estimates.

7.7 Alternative Estimate 7: Test Kits with 5% Rate of False Negatives

For the Primary Estimate in this analysis, it is assumed that there are never false negative test kit results; i.e., the test is always positive for LBP if it is present. Alternative Estimate 7 assumes that the new test kits will have a false negative rate of 5 percent.

7.7.1 Comparison of the Costs

The higher false negative rate assumed under Alternative Estimate 7 will lower costs because LSWP will not be used during some events where there is LBP. Table 7-9 shows the Alternative Estimate 7 50-year annualized costs; they decline by about 2.5 percent.

Table 7-9: Alternative Estimate 7: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	A	B	C	D	A	B	C	D
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 7: Test Kit with 5% Rate of False Negatives	$493	$480	$475	$572	$537	$513	$504	$611
Percent Change	-2.5%	-2.6%	-2.6%	-2.8%	-2.5%	-2.5%	-2.6%	-2.8%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.7.2 Comparison of the Benefits

Benefits are lower under this alternative, since some individuals will perform RRP activities where there is LBP, but will not use LSWP because a test kit found no LBP. If false negative results are independent of other factors that might affect the relative benefits of using LSWP, then benefits would be five percent lower for this alternative compared to the Primary Estimate (reflecting the five percent decline in LSWP use when LBP is present—the decline is 5 percent under both Scenario 1 and Scenario 2).

7.8 Alternative Estimate 8: Test Kits Cost $20 per Event

For the Primary Estimate, using a test kit is estimated to cost $10 per event. Lead test kits currently can be purchased in bulk at a cost of approximately $0.50 per test; it is assumed that about four tests will require about 15 minutes of a Certified Renovator's time, yielding a total cost for materials and time of $10 per event. There are several reasons why a test kit might be more expensive, for example (1) if they are not purchased in bulk, (2) if certified renovators decide to conduct more extensive testing than assumed, or (3) if the improved test kits are more expensive than those currently on the market. Thus, Alternative Estimate 8 assumes a testing cost of $20 per event, or an increase of $10 per-event over the Primary Estimate.

7.8.1 Comparison of the Costs

The 50-year annualized cost estimates are presented in Table 7-10. Under Alternative Estimate 8 costs increase by approximately 20 percent.

Table 7-10: Alternative Estimate 8: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)								
Discount Rate	**3 Percent**				**7 Percent**			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 8: $20 Test Kit	$608	$593	$588	$689	$660	$632	$622	$735
Percent Change	20.3%	20.4%	20.5%	17.1%	19.8%	20.1%	20.2%	16.8%
See Table 7-18 for Option Descriptions. *Source: EPA Calculations.*								

7.8.2 Comparison of the Benefits

There is no impact on the benefits estimate under this alternative, because it is assumed that the test kit always identifies LBP when present. That is, the false negative rate is assumed to be zero for both estimates.

7.9 Alternative Estimate 9: One Year Delay in Development of Improved Test Kits

In the Primary Estimate it is assumed that the more accurate test kit is available in the second year after the rule is in effect. Alternative Estimate 9 considers the alternative assumption that the improved test kit is not available until the third year the rule is in effect.

7.9.1 Comparison of the Costs

The 50-year annualized costs are two to almost four percent higher under the assumptions of Alternative Estimate 9 compared to the Primary Estimate (see Table 7-11). Since Alternative Estimate 9 considers a one-year delay in the availability of the new test kit, the only cost component that differs between this alternative and the Primary Estimate is the work practice costs in the second year the rule is in effect; they are about 70 percent higher under this alternative.

Table 7-11: Alternative Estimate 9: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)								
Discount Rate	**3 Percent**				**7 Percent**			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 9: 1-Year Delay in Development of Improved Test Kit	$516	$503	$498	$603	$570	$545	$537	$654
Percent Change	2.1%	2.2%	2.2%	2.4%	3.5%	3.7%	3.7%	4.1%
See Table 7-18 for Option Descriptions. *Source: EPA Calculations.*								

7.9.2 Comparison of the Benefits

There is no impact on the benefits estimate under this alternative, because both the current and improved test kits always identify LBP when present. That is, the false negative rates are zero for both test kits.

7.10 Alternative Estimate 10: Improved Test Kit Delayed Four Years

In the Primary Estimate it is assumed that the more accurate test kit is available in the second year after the rule is in effect. Alternative Estimate 10 considers the alternative where the improved test kit is not available until the sixth year the regulation is effective. Under the Primary Estimate it is assumed that the improved test kit is available in the second year.

7.10.1 Comparison of the Costs

For all options, the 50-year annualized costs are higher under Alternative 10 compared to the Primary Estimate because the delay in the availability of the improved test kit results in higher work practice costs in years two through five (see Table 7-12). Delaying the availability of the improved test kit is costly, because a test with a higher false positive rate will result in more instances where LSWP will be used even though no LBP is disturbed. In other words, the improved test kit will result in fewer cases where costly LSWP are used needlessly. Note that the rank of the options, in terms of the costs, does not change under these alternatives.

Table 7-12: Alternative Estimate 10: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 10: Improved Test Kit Delayed 4 Years.	$546	$533	$529	$643	$620	$596	$587	$721
Percent Change	8.1%	8.3%	8.4%	9.2%	12.6%	13.2%	13.4%	14.6%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.10.2 Comparison of the Benefits

There is no impact on the benefits estimate under this alternative, because the delay in the availability of the improved test kit does not impact any events with potential benefits.

7.11 Alternative Estimate 11: Improved Test Kit and Regulatory Universe Expansion Delayed Four Years

In the Primary Estimate it is assumed that the more accurate test kit is available in the second year after the rule is in effect. Alternative Estimate 11 considers the alternative where the expansion of the regulatory universe and the availability of the improved test kit are both delayed until the sixth year the regulation is effective. Under the Primary Estimate it is assumed that both the improved test kit and the regulatory expansion occurs in the second year.

7.11.1 Comparison of the Costs

Table 7-13 shows that the 50-year annualized costs are lower under Alternative 11 compared to the

Primary Estimate for Options B, C, and D; this implies that the cost savings from delaying the regulation of units built between 1960 and 1978 (Options B and D) and 1950 and 1978 (Option C), are greater than the increase in costs associated with the delayed availability of the improved test kit. Since Option A does not phase-in the regulation of any units, costs are higher under Alternative 11 compared to the Primary Estimate. Delaying the availability of the improved test kit is costly, because a test with a higher false positive rate will result in more instances where LSWP will be used even though no LBP is disturbed. In other words, the improved test kit will result in fewer cases where costly LSWP are used needlessly.

Table 7-13: Alternative Estimate 11: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years.	$546	$485	$464	$583	$620	$514	$476	$620
Percent Change	8.1%	-1.4%	-4.9%	-0.9%	12.6%	-2.4%	-8.0%	-1.5%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.11.2 Comparison of the Benefits

Chapter 5 presents the estimated monetized benefits of the RRP rule. The differences in benefits under each option stems solely from their different regulated universes. In the first year, benefits are highest under Option A (the largest regulated universe) and lowest under Option D (the smallest regulated universe); benefits under Options B and D are the same. In the second year, the options all have the same Primary Estimate benefits (they have the same regulated universe). Since the Primary Estimate and Alternative 11 assume the same regulated universe under Option A, the benefits are the same for the Primary Estimate and Alternative 11. However, the benefits of Alternative 11 are lower for Options B, C, and D: they are approximately equal to the first-year benefits of the Primary Estimates in years one through five, and approximately equal to the second year benefits of the Primary Estimate beginning in year six.[13] In other words, the jump in benefits from the expansion of the regulated universe is realized in year six rather than year two.

7.12 Alternative Estimate 12: Improved Test Kits Have 15% Rate of False Positives

Alternative Estimate 12 considers the alternative assumption that the improved test kit has a false positive rate of 15 percent rather than the 10 percent rate that is assumed for the Primary Estimate.

7.12.1 Comparison of the Costs

The 50-year annualized costs are 4.6 to 5.6 percent higher under the assumptions of Alternative Estimate 12 compared to the Primary Estimate (see Table 7-14). If the improved test kit has a higher false positive

[13] The pre-78 housing stock (and therefore the number of individuals affected and the benefits), declines by 0.41% each year.

rate, then LSWP will be used more frequently when LBP is not present. Therefore, under this alternative assumption the work practice costs are higher than under the Primary Estimate each year after the first year—when the improved test kits are assumed to become available.

Table 7-14: Alternative Estimate 12: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	A	B	C	D	A	B	C	D
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 12: Improved Test Kit with 15% Rate of False Positives	$530	$517	$512	$621	$576	$552	$543	$663
Percent Change	4.9%	5.0%	5.1%	5.6%	4.6%	4.9%	4.9%	5.4%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.12.2 Comparison of the Benefits

There is no impact on the benefits estimate under this alternative, because it is assumed that the test kits always identify LBP when present. That is, the false negative rates are zero under both alternatives.

7.13 Alternative Estimate 13: More Firms and Individuals Seek Certification

Alternative Estimate 13 assumes a different number of firms and individuals seek training and certification. Under the Primary Estimate, it is assumed that the number of firms and individuals seeking training and certification will be a function of the housing stock that is regulated. That is, it is assumed that some firms will specialize in RRP in regulated housing and other firms will not work in those units.

For Alternative Estimate 13 it is assumed that specialization in regulated units does not occur, so all firms and individuals that perform Residential Remodeling will seek training and certification. For the Primary Estimate of the number of firms and individuals that will seek training and certification, the number of firms and individuals that specialize in Residential Remodeling is adjusted downward to reflect the fact that only a fraction of Residential Remodeling occurs in regulated housing; this adjustment is omitted under Alternative Estimate 13.

It is worth clarifying that both estimates adjust the number of firms and individuals in the industries affected by the RRP rule to account for their relative revenues from Residential Remodeling; e.g., if only 25 percent of an industry's revenue is from Residential Remodeling, it is assumed only 25 percent of the firms and individuals in that industry seek training and certification. In addition, for both estimates there is no adjustment for the relative amount of RRP work that disturbs more than two square feet of a painted surface. For example, a substantial number of Residential Remodelers specialize in roofing, where they would be unlikely to be subject to any of the RRP rule's requirements.[14] Thus, for the Primary Estimate, a substantial amount of specialization is assumed, but not total specialization.

[14] Due to data limitations, the percentage of all Residential Remodeling that is regulated was not estimated.

7.13.1 Comparison of the Costs

Table 7-15 presents the estimated costs for an alternative with no specialization in regulated RRP. That is, the estimated number of firms are not adjusted by the proportion of housing units that are regulated. The number of Certified Renovators is assumed to increase proportionally to the increase in the number of firms. For Alternative Estimate 13, the training and certification costs are nearly two and a half times the Primary Estimate's costs. This results in a 19 to 26 percent increase in the 50-year annualized cost of the rule.

Table 7-15: Alternative Estimate 13: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	3 Percent				7 Percent			
Option	A	B	C	D	A	B	C	D
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 13: Alternative Assuming more Firms and Individuals Seek Certification	$602	$603	$599	$700	$660	$661	$654	$764
Percent Change	19.2%	22.6%	22.9%	18.9%	19.9%	25.7%	26.4%	21.5%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.13.2 Comparison of the Benefits

It is assumed that the regulated RRP work would be spread across more firms and individuals under this alternative, but this is not expected to impact benefits.

7.14 Alternative Estimate 14: No Cleaning Verification Required

Alternate Estimate 14 considers the potential costs and benefits if cleaning verification were not required by the proposed rule. Under this Alternative Estimate, a certified renovator would only need to perform a standard visual inspection after a renovation to determine whether visible dust, debris, or residue was still present in the work area, and would not have to use a disposable cleaning cloth as required under the proposed rule.

The Primary Estimate assumes that compliance with the work practice requirements in the rule (containment, cleaning, and cleaning verification) reduces lead levels in floor dust to 40 μg/ft^2. If this level is not reached upon the first verification, it is assumed that additional rounds of cleaning and verification will reduce lead levels to 40 μg/ft^2. The Primary Estimate uses a value of 40 μg/ft^2 to represent the distribution of lead levels from 0 to 40 μg/ft^2 that is assumed to result from compliance with the rule. Little information is available about the number of events that would fail to achieve the 40 μg/ft^2 or the distribution of lead levels for RRP events that fail to achieve the 40 μg/ft^2 level in the absence of cleaning verification. In the absence of data describing the distribution of dust lead levels following the initial cleanup, Alternate Estimate 14 assumes that, without cleaning verification, 30% of events would exceed the lead dust level of 40 ug/ft^2, and increases the average dust lead levels for those events in increments of 40 μg/ft^2 (80, 120, 160 ug/ft^2).

7.14.1 Comparison of the Costs

The 50-year annual costs are 7.6 to 8.6 percent lower under the assumptions of Alternative Estimate 14 compared to the Primary Estimate (see Table 7-16). In other words, the costs of cleaning verification account for about 8 percent of the total incremental increase in work practice costs due to the rule. It is worth noting that they represent a smaller percentage of the costs of using all required LSWP (i.e., when baseline work practice costs are not accounted for). This is because it is assumed that the baseline level of cleaning verification is zero.

Table 7-16: Alternative Estimate 14: 50-Year Annualized Cost Estimates and Percent Change: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)

Discount Rate	**3 Percent**				**7 Percent**			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	$505	$492	$488	$588	$551	$526	$518	$629
Alternative 14: Alternative regulatory option with no cleaning verification	$467	$455	$451	$538	$508	$486	$478	$575
Change	$38	$37	$37	$50	$43	$40	$40	$54
Percent Change	-7.7%	-7.6%	-7.6%	-8.6%	-7.7%	-7.6%	-7.6%	-8.6%

See Table 7-18 for Option Descriptions.

Source: EPA Calculations.

7.14.2 Comparison of the Benefits

Under Alternative Estimate 14, for both Scenarios 1 and 2, the annualized benefits do not decline as much as the annualized costs. While costs decline between $54 million and $37 million dollars (See Table 7-16), the benefits decline by as much as $20 million and as little as $0.1 million, depending on the option, scenario, assumed discount rate, and the blood-lead model specification for children's IQ (See Table 7-17).

It should be noted that Alternative Estimate 14 is based on assumptions and therefore must not be interpreted as conclusive evidence that the benefits of cleaning verification are not worth the additional cost. Although Alternative Estimate 14 considered scenarios where 30 percent of renovations had average dust lead levels of 80, 120, and 160 µg/ft2, there is considerable uncertainty about the number of renovations that have dust lead levels above or below 40 µg/ft2, as well as the concentration of lead dust in the absence of clearance verification.

Table 7-17: Range of Estimated Differences in Benefits Between Alternative Estimate 14 and the Primary Estimate (50-Year Annualized Benefits, millions $2005)				
Estimated Benefit Change	**A**	**B**	**C**	**D**
	3 Percent Discount Rate			
Scenario 1				
80 µg/ft2	-$0.1 to -$8	-$0.1 to -$8	-$0.1 to -$8	-$0.1 to -$8
120 µg/ft2	-$0.1 to -$8	-$0.1 to -$8	-$0.1 to -$8	-$0.1 to -$8
160 µg/ft2	-$0.6 to -$12	-$0.5 to -$11	-$0.5 to -$11	-$0.5 to -$11
Scenario 2				
80 µg/ft2	-$0.1 to -$7	-$0.1 to -$6	-$0.1 to -$6	-$0.1 to -$6
120 µg/ft2	-$0.3 to -$12	-$0.3 to -$12	-$0.3 to -$12	-$0.3 to -$12
160 µg/ft2	-$1.7 to -$19	-$1.7 to -$19	-$1.6 to -$19	-$1.7 to -$19
	7 Percent Discount Rate			
Scenario 1				
80 µg/ft2	-$0.1 to -$8	-$0.1 to -$8	-$0.1 to -$8	-$0.1 to -$8
120 µg/ft2	-$0.3 to -$8	-$0.2 to -$8	-$0.2 to -$8	-$0.2 to -$8
160 µg/ft2	-$1.0 to -$12	-$0.9 to -$12	-$0.9 to -$12	-$0.9 to -$12
Scenario 2				
80 µg/ft2	-$0.1 to -$7	-$0.1 to -$7	-$0.1 to -$7	-$0.1 to -$7
120 µg/ft2	-$0.3 to -$13	-$0.3 to -$13	-$0.3 to -$13	-$0.3 to -$13
160 µg/ft2	-$1.8 to -$20	-$1.7 to -$20	-$1.7 to -$20	-$1.7 to -$20
See Table 7-18 for Option Descriptions. The range of estimates reflects the different blood-lead model specifications. 80, 120, and 160 µg/ft2 refer to the average post-renovation dust lead levels assumed to occur in 30 percent of renovations in the absence of clearance verification. *Source: EPA Calculations.*				

7.15 Summary of Alternatives

Table 7-18 presents a summary of the 50-year annualized alternative cost estimates. The cost estimates are lower under Alternative Estimate 1 because work practice costs are assumed to be incurred in the baseline in states with existing RRP regulations. For Alternatives 2, 3, and 4, the table shows that costs are increasing with increases in the assumed compliance rate. Costs increase with the higher test kit cost (Alternative 8). Costs decrease with decreases in the false positive rate for the existing test kits (Alternative 5) and increase with increases in the false positive rate (Alternative 6), although costs are not very sensitive to changes in this rate. Costs move in the opposite direction of the rate of false negatives, decreasing as the false negative rate increases (Alternative 7). In Alternative 12, the cost increases with the increase in false positive rate for the improved test kit. The estimates for Alternatives 9, and 10 show that costs will be higher if the improved test kit development is delayed, but will be lower overall (for Options B, C and D) if a four-year delay in development of an improved test kit is accompanied by a four-year delay in regulatory expansion (Alternative 11). Alternative Estimate 13 shows that costs are higher if there is less specialization in RRP by firms choosing to work in regulated units such that more firms are seeking certification. Alternative 14 shows that removing cleaning verification reduces costs by about 8 percent, and the benefits are reduced by about 1.8 percent or less.

Table 7-19 and Table 7-20 present the 50-year annualized benefits of the alternative estimates compared to the primary estimates and Table 7-21 and Table 7-22 present the same kind of information for net benefits. The range of estimates in all these tables reflects the different blood-lead model specifications.

Not all alternatives are presented in these tables. Only those where the benefits estimate differs from the primary benefits estimate are presented.[15]

Alternative Estimates 2, 3, 4 consider alternative rates of compliance and indicate that net benefits are increasing with the assumed compliance rate. For Alternative Estimate 7, the net benefits are lower compared to the Primary Estimate because under this alternative more individuals will perform RRP activities where there is LBP, but will not use LSWP because a test kit did not indicate the presence of LBP. Under Alternative Estimate 11, the net benefits are slightly lower compared to the Primary Estimate. Under Alternative Estimate 14 the net benefits are slightly higher compared to the Primary Estimate.

[15] For Alternative Estimate 1, an alternative benefits estimate was not estimated because of data limitations. Benefits were not affected under all the other alternatives.

Table 7-18: Alternative 50-Year Annualized Cost Estimates for Sensitivity Analysis: Estimated with Discount Rates of 3 and 7 Percent (millions $2005)								
Discount Rate	**3 Percent**				**7 Percent**			
Option	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Primary Estimate	**$505**	**$492**	**$488**	**$588**	**$551**	**$526**	**$518**	**$629**
Alternative 1: Adjusted for State and Local RRP Regulations	$432	$421	$417	$494	$471	$449	$442	$528
Alternative 2: 100% Compliance Assumption	$795	$774	$766	$940	$866	$827	$813	$1,004
Alternative 3: 60% Compliance Assumption	$342	$334	$331	$382	$373	$357	$351	$408
Alternative 4: 30% Compliance Assumption	$99	$97	$96	$101	$108	$104	$102	$108
Alternative 5: Test Kit with 47% Rate of False Positives	$502	$491	$487	$587	$544	$524	$516	$626
Alternative 6: Test Kit with 78% Rate of False Positives	$508	$493	$488	$590	$556	$528	$519	$632
Alternative 7: Test Kit with 5% Rate of False Negatives	$493	$480	$475	$572	$537	$513	$504	$611
Alternative 8: $20 Test Kit	$608	$593	$588	$689	$660	$632	$622	$735
Alternative 9: One-Year Delay in Development of Improved Test Kit	$516	$503	$498	$603	$570	$545	$537	$654
Alternative 10: Improved Test Kit Delayed 4 Years	$546	$533	$529	$643	$620	$596	$587	$721
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	$546	$485	$464	$583	$620	$514	$476	$620
Alternative 12: Improved Test Kit with 15% Rate of False Positives	$530	$517	$512	$621	$576	$552	$543	$663
Alternative 13: Alternative Assuming More Firms and Individuals Seek Certification	$602	$603	$599	$700	$660	$661	$654	$764
Alternative 14: No Cleaning Verification Required	$467	$455	$451	$538	$508	$486	$478	$575

Option Descriptions: Option A: All pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option B: All pre-1960 renter-occupied target housing units and all pre-1960 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option C: All pre-1950 renter-occupied target housing units and all pre-1950 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option D: All pre-1960 renter-occupied target housing units and all pre-1960 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are prescriptive.

Source: EPA Calculations.

Table 7-19: 50-Year Annualized Benefits of Alternatives and the Primary Estimate[a, b] (3 Percent Discount Rate, millions 2005$)				
	Scenario 1			
Option	**A**	**B**	**C**	**D**
Primary Estimate	**3,209 to 7,599**	**3,191 to 7,562**	**3,170 to 7,503**	**3,191 to 7,562**
Alternative 2: 100% Compliance Assumption	4,653 to 11,018	4,628 to 10,964	4,596 to 10,879	4,628 to 10,964
Alternative 3: 60% Compliance Assumption	2,343 to 5,547	2,330 to 5,520	2,314 to 5,477	2,330 to 5,520
Alternative 4: 30% Compliance Assumption	578 to 1,368	574 to 1,361	571 to 1,350	574 to 1,361
Alternative 7: Test Kit with 5% Rate of False Negatives	3,049 to 7,219	3,032 to 7,184	3,011 to 7,128	3,032 to 7,184
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	3,209 to 7,599	3,096 to 7,108	2,979 to 6,752	3,096 to 7,108
Alternative 14: Alternative regulatory option with no cleaning verification	3,209 to 7,587	3,191 to 7,550	3,170 to 7491	3,191 to 7,550
	Scenario 2			
Primary Estimate	**774 to 4,354**	**770 to 4,329**	**764 to 4,298**	**770 to 4,329**
Alternative 2: 100% Compliance Assumption	1,146 to 6445	1,139 to 6407	1,131 to 6361	1,139 to 6407
Alternative 3: 60% Compliance Assumption	550 to 3,092	547 to 3,074	542 to 3,052	547 to 3,074
Alternative 4: 30% Compliance Assumption	116 to 653	115 to 649	115 to 645	115 to 649
Alternative 7: Test Kit with 5% Rate of False Negatives	736 to 4,137	731 to 4,113	726 to 4,083	731 to 4,113
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	774 to 4,354	747 to 4,069	718 to 3,868	747 to 4,069
Alternative 14: Alternative regulatory option with no cleaning verification	774 to 4,336	770 to 4,310	764 to 4,279	770 to 4,310

[a]Presents only the alternatives where the alternative estimate differs from the primary benefits estimate. For Alternative Estimate 1, an alternative benefits estimate was not estimated because of data limitations. Benefits were not affected under all the other alternatives.

[b]The range of estimates reflects the different blood-lead model specifications.

Source: EPA Calculations

Table 7-20: 50-Year Annualized Benefits of Alternatives and the Primary Estimate[a, b] (7 Percent Discount Rate, millions 2005$)				
	Scenario 1			
Option	**A**	**B**	**C**	**D**
Primary Estimate	**3,415 to 8,087**	**3,383 to 8,019**	**3,342 to 7,909**	**3,383 to 8,019**
Alternative 2: 100% Compliance Assumption	4,952 to 11727	4,905 to 11,627	4,846 to 11,468	4,905 to 11,627
Alternative 3: 60% Compliance Assumption	2,493 to 5904	2,469 to 5,854	2,440 to 5,774	2,469 to 5,854
Alternative 4: 30% Compliance Assumption	615 to 1,456	609 to 1,443	602 to 1,424	609 to 1,443
Alternative 7: Test Kit with 5% Rate of False Negatives	3,245 to 7,683	3,214 to 7,618	3,175 to 7,513	3,214 to 7,618
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	3,415 to 8,087	3,281 to 7,538	3,142 to 7,118	3,281 to 7,538
Alternative 14: Alternative regulatory option with no cleaning verification	3,415 to 8,075	3,383 to 8,007	3,342 to 7,897	3,383 to 8,007
	Scenario 2			
Primary Estimate	**824 to 4,635**	**816 to 4,587**	**805 to 4,530**	**816 to 4,587**
Alternative 2: 100% Compliance Assumption	1,220 to 6,859	1,207 to 6,789	1,191 to 6,704	1,207 to 6,789
Alternative 3: 60% Compliance Assumption	585 to 3,291	579 to 3,257	571 to 3,216	579 to 3,257
Alternative 4: 30% Compliance Assumption	124 to 695	122 to 688	121 to 679	122 to 688
Alternative 7: Test Kit with 5% Rate of False Negatives	783 to 4,403	775 to 4,358	765 to 4,303	775 to 4,358
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	824 to 4,635	791 to 4,312	757 to 4,077	791 to 4,312
Alternative 14: Alternative regulatory option with no cleaning verification	824 to 4,614	816 to 4,567	805 to 4,510	816 to 4,567

[a] Presents only the alternatives where the alternative estimate differs from the primary benefits estimate. For Alternative Estimate 1, an alternative benefits estimate was not estimated because of data limitations. Benefits were not affected under all the other alternatives.

[b] The range of estimates reflects the different blood-lead model specifications.

Source: EPA Calculations

Table 7-21: 50-Year Annualized Net Benefits of Alternatives and the Primary Estimate[a, b] (3 Percent Discount Rate, millions 2005$)				
	Scenario 1			
Option	**A**	**B**	**C**	**D**
Primary Estimate	**2,704 to 7,093**	**2,699 to 7,069**	**2,682 to 7,015**	**2,603 to 6,973**
Alternative 2: 100% Compliance Assumption	3,858 to 10,223	3,854 to 10,191	3,830 to 10,113	3,688 to 10,025
Alternative 3: 60% Compliance Assumption	2,000 to 5,205	1,996 to 5,186	1,983 to 5,146	1,948 to 5,138
Alternative 4: 30% Compliance Assumption	479 to 1,269	478 to 1,264	474 to 1,254	474 to 1,260
Alternative 7: Test Kit with 5% Rate of False Negatives	2,556 to 6,726	2,552 to 6,704	2,536 to 6,653	2,460 to 6,612
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	2,663 to 7,052	2,611 to 6,623	2,516 to 6,289	2,512 to 6,525
Alternative 14: Alternative regulatory option with no cleaning verification	2,742 to 7,121	2,737 to 7,096	2,719 to 7,041	2,653 to 7,012
	Scenario 2			
Primary Estimate	**269 to 3,849**	**277 to 3,837**	**276 to 3,810**	**181 to 3,741**
Alternative 2: 100% Compliance Assumption	351 to 5,650	366 to 5,633	364 to 5,595	199 to 5,467
Alternative 3: 60% Compliance Assumption	208 to 2,750	213 to 2,740	212 to 2,721	164 to 2,692
Alternative 4: 30% Compliance Assumption	17 to 554	19 to 552	18 to 548	15 to 549
Alternative 7: Test Kit with 5% Rate of False Negatives	243 to 3,644	252 to 3,633	251 to 3,608	159 to 3,541
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	228 to 3,808	261 to 3,584	254 to 3,405	163 to 3,486
Alternative 14: Alternative regulatory option with no cleaning verification	308 to 3,869	315 to 3,855	313 to 3,829	231 to 3,772

[a]Presents only the alternatives where the alternative estimate differs from the primary benefits estimate. For Alternative Estimate 1, an alternative benefits estimate was not estimated because of data limitations. Benefits were not affected under all the other alternatives.

[b]The range of estimates reflects the different blood-lead model specifications.

Source: EPA Calculations

Table 7-22: 50-Year Annualized Net Benefits of Alternatives and the Primary Estimate[a, b] (7 Percent Discount Rate, millions 2005$)				
	Scenario 1			
Option	**A**	**B**	**C**	**D**
Primary Estimate	**2,865 to 7,537**	**2,857 to 7,493**	**2,824 to 7,391**	**2,754 to 7,390**
Alternative 2: 100% Compliance Assumption	4,086 to 10,861	4,078 to 10,800	4,033 to 10,655	3,901 to 10,623
Alternative 3: 60% Compliance Assumption	2,121 to 5,531	2,113 to 5,497	2,089 to 5,423	2,061 to 5,445
Alternative 4: 30% Compliance Assumption	507 to 1,348	505 to 1,340	499 to 1,321	501 to 1,336
Alternative 7: Test Kit with 5% Rate of False Negatives	2,708 to 7,146	2,701 to 7,105	2,671 to 7,009	2,602 to 7,006
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	2,795 to 7,467	2,768 to 7,024	2,665 to 6,642	2,661 to 6,918
Alternative 14: Alternative regulatory option with no cleaning verification	2,907 to 7,567	2,897 to 7,521	2,864 to 7,419	2,807 to 7,432
	Scenario 2			
Primary Estimate	**273 to 4,084**	**290 to 4,061**	**287 to 4,012**	**187 to 3,958**
Alternative 2: 100% Compliance Assumption	354 to 5,993	380 to 5,962	378 to 5,891	203 to 5,785
Alternative 3: 60% Compliance Assumption	212 to 2,918	223 to 2,900	221 to 2,865	171 to 2,849
Alternative 4: 30% Compliance Assumption	16 to 588	19 to 584	18 to 577	15 to 580
Alternative 7: Test Kit with 5% Rate of False Negatives	246 to 3,866	262 to 3,845	260 to 3,799	163 to 3,746
Alternative 11: Improved Test Kit and Regulatory Universe Expansion Delayed 4 Years	204 to 4,014	278 to 3,798	280 to 3,600	171 to 3,692
Alternative 14: Alternative regulatory option with no cleaning verification	316 to 4,106	330 to 4,081	327 to 4,032	240 to 3,992

[a] Presents only the alternatives where the alternative estimate differs from the primary benefits estimate. For Alternative Estimate 1, an alternative benefits estimate was not estimated because of data limitations. Benefits were not affected under all the other alternatives.

[b] The range of estimates reflects the different blood-lead model specifications.

Source: EPA Calculations

References

Gilkeya, David; Jacob Hautaluomaa, Taslim Ahmeda, Thomas Keefea, Robert Herrona, Philip Bigelowb. 2003. Construction Work Practices and Conditions Improved After 2-Years' Participation in the HomeSafe Pilot Program. American Industrial Hygiene Association Journal, May/June 2003.

Weil, David. 1999. Assessing OSHA Performance: Evidence from the Construction Industry. Boston University, October 1999.

U.S. Census Bureau. 2000c. "H34. Year Structure Built [10] - Universe: Housing Units." American Fact Finder. Available at: http://factfinder.census.gov/ (Downloaded 10/26/2005)

8. Estimated Impacts of §402(c)

In addition to the cost and benefit analyses presented in Chapters 4 to 6, several other types of impacts are important to consider in evaluating a regulation. This chapter presents analyses that report the impact of the Renovation, Repair and Painting (RRP) Rule on the paperwork burden, the financial condition of small entities, whether the regulation has a disproportionate effect on low-income and or minority persons, and the environmental health risk or safety risk to children due to the regulation. It also responds to the Unfunded Mandates Reform Act (UMRA) and the National Technology Transfer and Advancement Act (NTAA), as well as to Executive Orders 13132 (Federalism), 13175 (Tribal Implications), 13211 (Energy Effects), and 12898 (Environmental Justice).

8.1 Paperwork Reduction Act

The Paperwork Reduction Act of 1995 (PRA) (superseding the PRA of 1980) is implemented by the Office of Management and Budget (OMB) and requires that agencies submit a supporting statement to OMB for any information collection that solicits the same data from more than nine parties. The PRA seeks to ensure that Federal agencies balance their need to collect information with the paperwork burden imposed on the public by the collection.

The definition of "information collection" includes activities required by regulations, such as permit development, monitoring, recordkeeping, and reporting. The term "burden" refers to the "time, effort, or financial resources" the public expends to provide information to or for a Federal agency, or to otherwise fulfill statutory or regulatory requirements. PRA paperwork burden is measured in terms of annual time and financial resources the public devotes to meet one-time and recurring information requests (44 U.S.C. 3502(2); 5 C.F.R. 1320.3(b)).

Information collection activities may include:

- reviewing rule requirements;
- using technology to collect, process, and disclose information;
- adjusting existing practices to comply with requirements;
- searching data sources;
- completing and reviewing the response; and
- transmitting or disclosing information.

Agencies must provide information to OMB on the parties affected, the annual reporting burden, and the annualized cost of responding to the information collection.

8.1.1 RRP Firm Paperwork Burden

RRP Firms are estimated to spend approximately half an hour to fill out and mail the Application for Renovator Certification when they are applying for initial certification or re-certification (which occurs every three years). It is estimated that firms will spend an average of three hours to familiarize themselves with the RRP rule's requirements when becoming certified. In addition, firms will spend an average of 5 minutes per RRP event keeping records that demonstrate compliance with the Renovation, Repair and Painting Rule training and work practice requirements. As there are a little over 60 events per firm annually, this translates to approximately 5 burden hours per firm on average. This adds up to an average burden in the first year of 8.7 hours per firm. At a loaded wage rate of $31.64, the paperwork

cost in the first year will average $276 per firm (See Table 8-1). Additional costs are minor; these costs include an application printout, one photocopy for personal records, an envelope, and a stamp. The total first year information collection cost is estimated to average $276 per firm. Every three years firms must complete the certification form to apply for re-certification, as well as keep records that demonstrate compliance with the RRP Rule. The total time required during a re-certification year is 5.7 hours, at a cost of $181 per firm. In years where firms do not need to apply for certification or re-certification, firms will only incur the five-hour recordkeeping burden at a cost of $165.

Table 8-1: Costs to RRP Firms Associated with Information Collection

	First Year/Initial Certification Year		Re- Certification Year		Other Years	
Activity	**Burden Hours**	**Cost**	**Burden Hours**	**Cost**	**Burden Hours**	**Cost**
Certification form[a]	0.5	$15.82	0.5	$15.82		$0
Rule familiarization [a]	3	$94.93		$0		$0
Recordkeeping [a]	5.2	$164.85	5.2	$164.85	5.2	$164.85
2 photocopies[b]		$0.16		$0.16		$0
1 envelope[c]		$0.02		$0.02		$0
1 stamp		$0.37		$0.37		$0
Total*	**8.7**	**$276**	**5.7**	**$181**	**5.2**	**$165**

*Rounded to nearest dollar.

Sources: [a]Wages: Bureau of Labor Statistics (SOC 47-1011). Wages were inflated from 2004$ to 2005$ using the BLS Employment Cost Index for the Construction Industry.; [b] The average price of a photo copy is eight cents; [c]The average cost of a business envelope is two cents.

8.1.2 Training Provider Paperwork Burden

EPA has also estimated the information collection burden imposed on Training Providers. Similarly to certified firms, accredited Training Providers incur an accreditation and re-accreditation paperwork burden. To comply with the RRP rule, Training Providers must gain accreditation and keep records on both the courses they provide and the students they train. In addition, they must notify EPA before offering each course (to facilitate EPA's enforcement activities) and after each course (so EPA has a record of the individuals who have completed the course).

Burden Associated with Obtaining and Maintaining Accreditation

It is assumed that Training Providers will spend an average of four hours of professional time and two hours of clerical time completing the accreditation statement.[1] It is assumed that accredited Training Providers will spend an average of eight hours familiarizing themselves with the rule. An average of one additional hour of clerical time will be spent on annual recordkeeping. This results in an average burden of 15 hours in the first year. Using a loaded wage rate of $38.76 for professional time and $23.54 for clerical time, the average accreditation cost to Training Providers is $536. Additional costs considered include one printout of the accreditation statement, one copy of course records, an envelope, and a stamp. Training Providers applying for re-accreditation will incur an average of four hours of professional time and two hours of clerical time, as well as one hour of recordkeeping time. This is an average of seven hours of burden at a cost of $226. In other years, the Training Providers will only incur the average of one hour of recordkeeping time at a cost of $24.

[1] Time assumptions are based on information provided in the EPA's (2005) *Supporting Statement for OMB Review under The Paperwork Reduction Act: TSCA Sections 402/404 Training, Certification, Accreditation and Standards for Lead-Based Paint Activities. (EPA ICR No. 1715.06, OMB Control No:2070-0155).*

Burden Associated with Notification Requirements

It is assumed that the pre-notification for each class requires an average of 0.15 hours and that each post-notification requires an average of 1.54 hours. The post notifications are more time consuming because the Training Provider must send records pertaining to each student who attended the course. Approximately 12 percent of courses will also require a re-notification, which is also estimated to take 0.15 hours. This adds up to an average of 1.7 clerical hours per course. The number of courses offered per year depends on the number of individuals who need to be trained. It is assumed that Training Providers offer 40 courses in the first year, or a total of 70 hours. It is assumed that each notification requires one photocopy, one envelope, and one stamp; thus approximately two of each are required per-course. The average cost of notifications in the first year is approximately $1,700 per Training Provider. There will be approximately 30 courses offered per Training Provider in the second year of the rule at an average cost of a little under $1,300. In year three of the rule there will be 15 courses offered per training provider with a total cost of about $630 on average.

Total Training Provider Burden

As shown in Table 8-2, training providers who are accredited in the first year the rule is in effect will incur an average cost of $2,224 for paperwork costs in year one ($536 in accreditation costs and $1,688 in notification costs). Total costs for subsequent years of the rule depend on whether or not the Training Provider undergoes accreditation or re-accreditation in that year.

Table 8-2: Costs to Training Providers Associated with Information Collection

Accreditation Costs						
	First Year/Initial Accreditation Year		**Re- Accreditation Year**		**Other Years**	
Accreditation/Re-Accreditation Activities	**Burden Hours**	**Cost**	**Burden Hours**	**Cost**	**Burden Hours**	**Cost**
Accreditation statement [a]	4	$155.04	4	$155.04		$0
Rule familiarization [a]	8	$310.08		$0		$0
Clerical time statement [a]	2	$47.08	2	$47.08		$0
Recordkeeping [a]	1	$23.54	1	$23.54	1	$23.54
2 photocopies[b]		$0.16		$0.16		$0
1 envelope[c]		$0.02		$0.02		$0
1 stamp[d]		$0.37		$0.37		$0
Total*	15	$536	7	$226	1	$24
Notification Costs						
	Year 1 of the RRP Rule (40 Courses)		**Year 2 of the RRP Rule (30 Courses)**		**Year 3 of the RRP Rule (15 Courses)**	
Notification Activities	**Burden Hours**	**Cost**	**Burden Hours**	**Cost**	**Burden Hours**	**Cost**
Clerical time burden [a]	70	$1,647.80	53	$1,247.62	26	$612.04
Photocopies[b]		$6.80		$5.10		$2.55
Envelopes[c]		$1.70		$1.28		$0.64
Stamps[d]		$31.45		$23.59		$11.80
Total*	70	$1,688	53	$1,278	35	$627

*Rounded to nearest dollar.

Sources: [a]Wages: Bureau of Labor Statistics (SOC 47-1011); [b] The average price of a photo copy at Copy Cop, Kinkos, Staples, and Office Max is eight cents; [c]The average cost of a business envelope at Staples, Office Max, and Office Depot [d]U.S. Postal Service

8.2 Unfunded Mandates Reform Act (UMRA)

Title II of the Unfunded Mandates Reform Act of 1995, Pub. L. 104-4, establishes requirements for Federal agencies to assess the effects of their regulatory actions on State, local, and Tribal governments, and the private sector. Under section 202 of the UMRA, EPA generally must prepare a written statement, including a cost-benefit analysis, for proposed and final rules with "Federal mandates" that might result in expenditures by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100 million or more in any one year.

Before promulgating a regulation for which a written statement is needed, section 205 of the UMRA generally requires EPA to identify and consider a reasonable number of regulatory alternatives and adopt the least costly, most cost-effective, or least burdensome alternative that achieves the objectives of the rule. The provisions of section 205 do not apply when they are inconsistent with applicable law. Moreover, section 205 allows EPA to adopt an alternative other than the least costly, most cost-effective, or least burdensome alternative if the Administrator publishes with the rule an explanation of why that alternative was not adopted. Before EPA establishes any regulatory requirements that might significantly or uniquely affect small governments, including Tribal governments, it must have developed under section 203 of the UMRA a small government agency plan. The plan must provide for notifying potentially affected small governments, enabling officials of affected small governments to have meaningful and timely input in the development of EPA regulatory proposals with significant

intergovernmental mandates, and informing, educating, and advising small governments on compliance with regulatory requirements.

This section identifies the government entities that may be affected by the proposed rules. It also assesses the impact on the various regulatory options under consideration.

8.2.1 Affected Government Entities

The Renovation, Repair, and Painting (RRP) Rule will affect activities in publicly owned housing. While most of what is commonly referred to as public housing is owned by state or local governments and provided for the benefit of low-income and/or elderly households, other public entities (such as public colleges and universities) may provide regulated housing. As with the private sector, the RRP regulations will increase the cost of operating this housing by requiring that staff be trained and appropriate work practices be undertaken, including cleaning verification.

Public housing that receives funding from the U.S. Department of Housing and Urban Development already must comply with HUD regulations regarding lead paint and so are unlikely to incur additional costs due to this rule. These housing units and their RRP events have been excluded from the cost and benefit estimates presented in Chapters 4, 5 and 6 of this report. Four states (Massachusetts, New York, Hawaii, and Connecticut) and one local government (New York City) have been identified as operating public housing that does not receive HUD funds. RRP activities in these units are likely to be covered by this rule.

Massachusetts has approximately 50,000 state-funded public housing units operated through 235 local housing authorities (Stainton 2001).

New York is home to the country's first state-subsidized public housing program. New York has constructed 143 housing developments that are owned by 42 municipal housing authorities since the program began in 1939. Due to the increased burden on the State's Public Housing Modernization Program (PHMP), New York has federalized some of their units. Units that have been federalized must adhere to federal rules and regulations, including existing lead standards (DHCRb 2005). Housing that has been updated through PHM has undergone lead testing.

The New York City Housing Authority (NYCHA) is the largest public housing authority in North America, housing 175,116 families in 345 developments. Of these, 12,158 units are state-funded and 7,971 of these units are city-funded.

The Housing and Community Development Corporation of Hawaii (HCDCH) manages 6,200 units in 81 developments of federal and state public housing, which support 14,000 residents. State-funded public housing makes up 14 percent (868 units) of HCDCH's housing stock. Both private and public employees manage these units and operating costs are completely funded by rental income (HCDCH 2002).

The state of Connecticut does not officially sponsor public housing. Local housing authorities run Connecticut public housing. These housing authorities receive municipal tax-breaks and municipalities receive Payments in Lieu of Taxes (PILOT) from the state.

While these state and local programs make up only a relatively small percentage of all public housing, they are locally important. At the same time, it is important to note that in Massachusetts state regulations already require the use of certain work practices when performing renovations in pre-1978

housing. New York City also has an extensive regulatory program that applies to multi-unit dwellings where children under the age of seven reside. In both cases, these requirements may partially reduce the incremental burden of complying with the RRP Rule. See Chapter 3 of this Economic Analysis for more information on these programs.

In 2000, there were over 14 million students enrolled in colleges and universities in the United States and over 3 million students enrolled in graduate or professional schools. Of these students, over 11 million attend public colleges and nearly 2 million attend public graduate schools (U.S. Census Bureau 2000d). According to the US Census, over 2 million students reside in dormitories—group quarters that are not affected by the RRP rule (U.S. Census Bureau 2000e). The remaining students must either reside off-campus in private housing, or in college-owned apartments and individual units. Individual, college-owned housing units include but are not limited to, undergraduate suites and apartments, married student housing, graduate student apartments, and faculty housing. These types of units are not differentiated from the general housing stock in the Census; therefore it is difficult to determine how many of these units exist or the age of these units.

8.2.2 Expenditures by State, Local, and Tribal Governments

Information is not available on the number of renovation events in target housing with lead-based paint owned by State, local, and Tribal governments not already covered by HUD regulations. However, it is possible to calculate how many events would be needed to exceed the $100 million UMRA threshold. Under the preferred option there will be 5.8 million regulated RRP events as a result of the rule in the first year (Phase 1), at a cost of $531 million. In the second year (Phase 2), there will be 10.7 million regulated events at a cost of $552 million (discounted at 3 percent)[2]. This is equivalent to an average cost of about $92 per event in the first year and $52 per event in the second year.[3] In order to generate $100 million in costs, there would have to be over 1.0 million events in the first year, and over 1.9 million such events in the second year. It seems unlikely that there would be this many events in the public housing that does not receive HUD grants, or in other government owned housing that is covered by the rule. Therefore, the rule is not expected to result in the expenditure by State, local, and Tribal governments, in the aggregate, of $100 million or more. However, given the cost results presented in Chapter 4, the rule is expected to result in an expenditure by the private sector of $100 million or more in any one year.

8.3 Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) of 1980, amended by the Small Business Regulatory Enforcement Fairness Act (SBREFA) of 1996, requires regulators to assess the effects of regulations on small entities including businesses, nonprofit agencies, and governments. In some instances, agencies are also required to examine regulatory alternatives that may reduce adverse economic effects on significantly impacted small entities. The RFA requires agencies to prepare an initial and final regulatory flexibility analysis for each rule unless the Agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. The RFA, however, does not specifically define "a significant economic impact on a substantial number" of small entities. Sections 603 and 604 of the RFA require

[2] Using a 7 percent discount rate, the total cost of the 5.8 million events in the second year is estimated to be $532 million, or about $50 per event. At a per-event cost of $50, there would have to be over 2 million regulated events in the second year to yield $100 million in costs.

[3] Note that these average costs include some events where the only costs incurred are those of a lead-based paint test kit. Note also that these costs differ from the costs used in the Regulatory Flexibility Analysis because they represent first and second year, rather than annualized, costs of the rule.

that regulatory flexibility analyses identify the types, and estimate the numbers, of small entities to which the proposed rule will apply; and describe the rule requirements to which small entities will be subject and any regulatory alternatives, including exemptions and deferral, which would lessen the rule's burden on small entities.

This analysis looks at the impacts of the Renovation, Repair and Painting Rule on small businesses in the affected construction and residential real estate industry sectors, as well as on small governments and non-profit organizations. The rule requires that all establishments that perform renovation work in regulated housing get certified by EPA, ensure that their employees are trained as either renovators or workers, and use lead-safe work practices whenever disturbing more than the exempt amount of lead-based paint. As such, construction and real estate establishments, as well as government agencies and non-profits that renovate or repair properties subject to the rule, will incur the costs of training, certification, and lead-safe work practice use.

The impacts on Training Providers are not analyzed because the rule will result in an increased demand for their services and thus the impacts are positive. Although the rule may also result in additional costs for Training Providers (i.e. costs of developing and becoming accredited for a new course, keeping records, and submitting notifications), Training Providers are expected to recoup these costs via tuition fees. These tuition fees are accounted for in the training costs of renovation and real estate firms.

8.3.1 Definitions of Small Entity

The Regulatory Flexibility Act defines a small government as a government of a city, county, town, school district or special district with a population of less than 50,000. A small non-profit organization is defined as any not-for-profit enterprise which is independently owned and operated and is not dominant in its field. The RFA relies on the definition of a "small business" found in the Small Business Act, which authorizes the Small Business Administration (SBA) to develop definitions for "small business." For this analysis, EPA uses SBA's definition of a small business for each industry.

For many industry sectors, the SBA definition of a small business is based on revenues, with the revenue standards varying by industry. In establishing revenue standards, SBA considers a number of economic and market characteristics that may allow a firm to exercise dominance in an industry. These standards represent the maximum revenue that a for-profit enterprise may have, and still qualify as a small business.

The following eleven NAICS codes are the general and specialty contractors this rule will impact, and their respective SBA threshold. These are followed with the two NAICS codes for residential real estate industries that are also likely to be affected by the rule.

Table 8-3: SBA Revenue Thresholds for Small Business by NAICS Code		
NAICS	**Industry Description**	**SBA Revenue Threshold (Millions $)**
General and Specialty Contractor Industries		
236118	Residential remodelers	$28.5
238170	Siding contractors	$12
238350	Finish carpentry contractors	$12
238290	Other building equipment contractors	$12
238390	Other building finishing contractors	$12
238340	Tile and terrazzo contractors	$12
238220	Plumbing and HVAC contractors	$12
238150	Glass and glazing contractors	$12
238320	Painting and wall covering contractors	$12
238210	Electrical contractors	$12
238310	Drywall and insulation contractors	$12
Residential Property Owners and Managers		
531311	Residential Property Managers	$1.5
531110	Lessors of Residential Buildings and Dwellings	$6.0
Source: U.S. Small Business Administration 2004.		

In this analysis, impacts of the RRP rule on small businesses are considered first, followed by impacts on small governments and non-profit organizations.

8.3.2 Impacts on Small Businesses - General Methodology Overview

This analysis measures the potential impacts of the Renovation, Repair and Painting (RRP) Rule on small businesses in terms of annual compliance costs as a percentage of annual revenues, or the cost impact ratio. This approach is based on the premise that the cost impact percentage is an appropriate measure of an entity's ability to afford the costs attributable to a regulatory change. For purposes of determining small entity impacts, comparing annual compliance costs to annual revenues provides a reasonable indication of the magnitude of the regulatory burden relative to a commonly available and objective measure of a company's business volume. Where regulatory costs represent a very small fraction of a typical establishment's revenue, the impacts of a regulation are likely to be minimal.

General Assumptions and Approach

Two groups of regulated businesses are considered in this analysis: small construction establishments and small residential real estate businesses. The goal of this analysis is to evaluate the impacts of the RRP Rule on small businesses in a typical year. Several assumptions are made throughout this analysis so as to develop a more realistic portrayal of the long-term effects of the rule on small businesses. First, annualized costs of the rule are used to measure the impacts of the regulation. Second, the analysis recognizes that both construction and residential real estate establishments will pass some of their compliance costs to their customers, either through higher prices charged for renovation, or through increases in rent. A cost pass-through scenario is developed based on data on the elasticities of supply and demand for housing and incorporated into the analysis.

Establishment, rather than firm-level data is used throughout the analysis. Census information was available primarily at the establishment level, making a firm-level analysis unfeasible. Because

establishments, and not firms, are analyzed, an assumption is made that none of the small establishments are subsidiaries of larger firms. This assumption leads to an overestimate of the number of small independent establishments affected by the rule. Furthermore, since firm-level revenues of multi-establishment businesses are higher than establishment revenues, the use of establishment data may result in a higher cost-impact ratio than is actually the case.

The cost-impact ratios estimated for the residential real estate industries (NAICS 531110 and NAICS 531311) in this small business analysis are based on employment and revenue data for employer establishments only. As discussed in Chapter 4, there are no Census data on the amount of renovation and repair work performed by residential property managers and lessors on their own properties. EPA thus assumed that all establishments with employees that manage or lease housing units subject to the regulation would seek certification and train their employees as renovators or workers, as appropriate. Since it is likely that only some of these establishments will get certified and those that do obtain certification will train only some of their employees, this approach leads to an overestimate of the number of establishments certified and the number of people trained.

While it is likely that both employer establishments and self-employed managers/lessors perform some regulated RRP work, self-employed managers/lessors (who have no staff and thus lower manpower) are much more likely to hire an outside firm to perform renovation work on their properties than employer establishments. Because the approach used to estimate the number of certified employers in these industries already results in an overestimate of the number of establishments and people certified and trained, and because self-employed managers/lessors are less likely to perform regulated renovation work themselves, EPA did not include non-employer establishments in these sectors in its estimates of training and certification costs. In reality, residential property manager and lessor establishments with employees will train only some of their staff and some non-employers in these industries will seek training and certification.

Costs Incurred by Small Establishments

Establishments that perform RRP work in regulated housing will incur the costs of training, certification and using lead-safe work practices during projects that involve lead-based paint. In order to distribute the total costs of the rule between small and large establishments, EPA assumed that the compliance cost incurred by each establishment is a function of the number of regulated renovation events that the establishment performs in a typical year. EPA thus calculated an average compliance cost per event by dividing the total annualized cost of the rule by the estimated annual number of renovation events taking place in regulated housing (See Section 8.3.5 for further discussion). This per-event cost includes the costs of complying with work practice, training and certification requirements. The use of annualized costs provides a more accurate representation of the long-term (typical year) impacts of the rule.

Cost-Impact Ratio Estimation for the Construction and Residential Real Estate Industries

The following seven steps describe the general approach used to calculate the cost-impact ratios for the construction and residential real estate industry sectors. To estimate the impacts of the costs of the rule on small entities in the affected industries, the following calculations were performed for each sector:

1. Certified establishments were classified as either small or large businesses, depending on their revenues. Self-employed contractors were combined with small employer establishments to form one small business category.
2. Census data were used to characterize a "typical" small establishment (including revenues and number of employees) in each of the affected industry sectors.

3. The average number of regulated events performed by an establishment each year was estimated by multiplying the ratio of regulated events to trained personnel by the establishment employment size.
4. An average per-event compliance cost was calculated using the annualized 50-year cost of the rule under each option and the average number of renovation events performed in regulated housing in a typical year.
5. The change in per-event price and quantity of regulated events, as well as the resulting change in contractor revenues were estimated using available data on the elasticities of supply and demand for housing.
6. Establishment compliance costs were calculated by multiplying the post-rule number of events performed by the establishment by the average annualized compliance cost per event under each option.
7. Cost-impact ratios were calculated for a typical small establishment in each industry sector by dividing the compliance costs incurred by the establishment (Step 6) by the establishment's post-rule RRP revenues (Step 5).

The following sections present a detailed discussion of the steps taken to estimate the various parameters (number of establishments and employees, events per establishment, establishment revenues, etc.) used to obtain the cost-impact ratios for small construction and residential real estate establishments.

8.3.3 Number of Small Establishments and Individuals Affected Under Each Option

Number of Small Businesses Affected – First Year

The data used in this analysis were drawn primarily from the 2002 U.S. Economic Census. As discussed in Chapter 2, Census data were used to estimate the number of non-employer establishments (self-employed contractors) in the affected construction industries (see Table 2-5 in Chapter 2). The 2002 Census also provides data on the number, revenue and employment of establishments with payroll by revenue bracket for each of the eleven construction industry sectors affected by the rule. In Chapter 2, these data were used to classify construction establishments into two main size classes – establishments with annual revenues of less than $10 million, and establishments with annual revenues of $10 million or more. The percent of establishments, employees, net value of construction and total value of business contributed by establishments in each revenue bracket can be found in Table 2-8 of Chapter 2.

Because 2002 revenue bracket data for Lessors of Residential Buildings and Dwellings and Residential Property Managers are not yet available, 1997-year data were used to estimate the percent of establishments in these sectors that were small businesses. These percentages, as well as the percent of industry revenues and employment contributed by small and large establishments, are presented in Table 2-12 (Chapter 2).

The Small Business Administration revenue thresholds for establishments in the construction sectors are currently set at $28.5 million for Residential Remodelers and at $12 million for the ten specialty contractor industries. However, in applying the U.S. Economic Census data to the SBA definition of small business, it is not possible to estimate the exact number of construction establishments that have revenues below the SBA threshold because the U.S. Economic Census groups all establishments with revenues of $10 million or more into one revenue bracket. Applying the U.S. Economic Census data therefore requires either under or overestimating the number of small businesses affected by the rule. On the one hand, using data for the entire industry would overestimate the number of small businesses affected by the rule. It would also underestimate the rule's impact on small businesses because the impacts would be calculated using the revenues of large businesses in addition to small businesses. On

the other hand, applying the closest, albeit lower, revenue bracket would underestimate the number of small businesses affected by the rule while at the same time overestimating the impacts. For example, because the $10 million cut-off is below the SBA threshold for the Residential Remodeler industry, using the U.S. Economic Census data may lead to an underestimate of the number of small businesses in this sector, although likely a small underestimate.[4] At the same time, using these data may lead to a slight overestimate of the impacts of the rule, as the average revenues of small businesses will appear smaller when larger establishments (those with revenues of $10 to $28.5 million) are left out. Section 8.3.2 already discussed assumptions that may result in an overestimation of the number of affected small businesses. Moreover, using data on all small businesses regardless of size would defeat the purpose of estimating impacts on small business. EPA has concluded that a substantial number of small businesses will be affected by the rule. Consequently, EPA has chosen to be more conservative in estimating the cost impacts of the rule on small businesses by using the $10 million threshold for construction industry sectors.

As with the Residential Remodelers and the ten specialty contractor industries discussed above, it is not possible to estimate the exact number of small Residential Property Manager establishments or Lessor of Residential Buildings and Dwellings establishments, because Census-defined revenue brackets group establishments with revenues of $1 million to $5 million and $5 million to $10 million, respectively. For the same reasons set forth above (i.e., EPA has already concluded that a substantial number of small businesses in these industries will be affected by the rule and the Agency had the choice to either overestimate or underestimate the impacts), it has chosen to overestimate the impacts. Thus, EPA has applied the U.S. Economic Census data for establishments with revenues of less than $1 million to Residential Property Managers , and the U.S. Census Economic data for establishments with revenues of less than $5 million to Lessor of Residential Buildings.[5]

In order to estimate the number of certified small establishments with paid employees, EPA assumed that the number of certified small employers is proportional to the total number of small employer establishments in the industry. The total number of certified establishments in each industry (calculated in Chapter 4) was multiplied by the percentage of establishments in that industry that have revenues below the revenue thresholds described above. For the 11 construction industry sectors, the resulting number of small employer establishments was added to the total number of certified self-employed contractors to obtain the total number of small certified establishments. The resulting first-year estimates (by industry and option) are presented in Table 8-4.

[4] Because 99.7 percent of Residential Remodeler establishments earn less than $10 million per year, any underestimate of the number of establishments is likely to be minimal.

[5] Approximately 85 percent of Residential Property Manager establishments earn less than $1 million per year, and about 99 percent of Lessor of Residential Buildings and Dwellings establishments earn less than $5 million per year.

Table 8-4: Number of Certified Small Establishments by Option (First Year)				
NAICS	**Description**	**Option A[a,b]**	**Options B &D[a,b]**	**Option C[a,b]**
236118	Residential remodelers	44,165	23,307	16,044
238170	Siding contractors	3,213	1,696	1,167
238350	Finish carpentry contractors	31,361	16,551	11,394
238290	Other building equipment contractors	1,457	769	530
238390	Other building finishing contractors	1,995	1,053	725
238340	Tile and terrazzo contractors	4,480	2,364	1,628
238220	Plumbing and HVAC contractors	15,072	7,955	5,476
238150	Glass and glazing contractors	1,329	701	484
238320	Painting and wall covering contractors	17,407	9,188	6,323
238210	Electrical contractors	10,716	5,655	3,893
238310	Drywall and insulation contractors	7,329	3,868	2,663
Total, Small Construction Establishments		**138,524**	**73,105**	**50,327**
531311	Residential Property Managers	6,335	3,343	2,301
531110	Lessors of Residential Real Estate	17,372	9,169	6,312
Total, All Industries		**162,232**	**85,617**	**58,939**

a. EPA applied U.S. Economic Census data regarding: entities with less than $10 million in revenues to establishments in the 11 construction sectors; entities with less than $1 million in revenues to Residential Property Manager establishments; and entities with less than $5 million in revenues to Lessors of Residential Real Estate.

b. Option Descriptions: Option A: All pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option B: All pre-1960 renter-occupied target housing units and all pre-1960 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option C: All pre-1950 renter-occupied target housing units and all pre-1950 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are flexible. Option D: All pre-1960 renter-occupied target housing units and all pre-1960 owner-occupied target housing units where children under the age of six reside are subject to the rule in the first year it is in effect (Phase 1); in the second year (Phase 2), all pre-1978 renter-occupied target housing units and all pre-1978 owner-occupied target housing units where children under the age of six reside are subject to the rule; WPS requirements are prescriptive. Note that in the first year, Options B, C and D also apply to any pre-1978 housing where a child with an increased blood-lead level resides.

Source: U.S. Census Bureau 2000a; U.S. Census Bureau 2004b; U.S. Census Bureau 2005 b-f,i; U.S. Small Business Administration 2005.

Number of Small Establishments Affected - Long Term

Table 8-5 shows the total first, second, third and 50-year average numbers of small businesses affected by the regulations under each option. Under all four options, all firms performing RRP projects in pre-1978 renter-occupied target housing units and pre-1978 owner-occupied target housing units where a child under the age of six resides will be subject to the regulations from the second year onward. As such, starting with the second year, the total number of small businesses affected by the rule will be the same under all options. The number of affected businesses is expected to decrease proportionally to the number of regulated events, which in turn decline at an annual rate of 0.41 percent (see Section 4.2.6 of Chapter 4 for discussion).

Table 8-5: Total Number of Small Establishments Affected, by Option			
	Option A[a]	**Options B &D[a]**	**Option C[a]**
Year 1	162,232	85,617	58,939
Year 2	161,567	161,567	161,567
Year 3	160,904	160,904	160,904
50-year Average	**146,955**	**145,423**	**144,889**

a. See Table 8-4, Footnote 2 for option definitions.

Source: EPA calculations

8.3.4 Average Small Establishment Revenues, Employment Size and Number of Renovation Events Performed

As discussed in Chapter 4, the total number of people trained and the number of establishments certified are assumed to change from option to option and over time in proportion to the regulated housing stock and the number of regulated events. Since both the number of establishments and the number of people trained are changing proportionally, however, the average establishment employment size, revenues, and number of events performed each year are, for the purposes of this analysis, assumed to stay constant across options and over time.

Revenues

Cost-impact ratio analysis compares the cost of a regulation to a firm's (in this case, establishment's) total revenues, not just to its revenues from the regulated activity. As such, for construction establishments, the costs of the rule were compared to the total value of business done, rather than just to the total value of construction work. For real estate establishments, total revenues were used. Because no data are available specifically for establishments expected to seek certification under the regulations, EPA assumed that average revenues of these businesses do not differ significantly from industry averages.

EPA calculated the revenues of a small certified construction business as a weighted average of small employer and non-employer revenues. The 2002 U.S. Economic Census presents data on the number of and total value of business done by construction establishments with total annual revenues of $0 to $10 million and $10 million or more. To estimate the average revenues of small employers in each of the affected construction sectors, the total value of business done by establishments in the $0 to $10 million bracket was divided by the total number of establishments in that bracket. Since Census presents revenue figures in year 2002 dollars, the resulting average revenues were inflated to 2005 dollars using the Consumer Price Index.[6] In Chapter 2, EPA estimated the number of non-employers in each of the affected construction sectors as well as the revenues of these establishments (Table 2-5, Chapter 2). Per-establishment revenues were estimated for the cost impact ratio analysis by dividing non-employer revenues (inflated to 2005 dollars) by the number of non-employer establishments in each industry. Average revenues of certified small establishments are presented in Table 8-6.[7] Because the 2002 U.S. Economic Census does not yet provide data by revenue bracket for Residential Property Manager and the Lessor of Residential Buildings and Dwellings sectors, EPA used data from the 1997 Economic Census to estimate the percent of establishments in each industry that qualify for small business status. EPA used 1997 Census data to calculate the percent of industry revenues contributed by these establishments (See Table 2-12, Chapter 2). These percentages were then applied to the 2002 numbers of establishments and

[6] All items, US city average, Series Id: CUUR0000SA0. Used annual data for 2002 and half-year data for 2005.

[7] There may be some slight variation in average small establishment revenues from option to option due to rounding. From the second year onward, however, the number of regulated events and trained personnel will be the same as under Option A. Thus, Option A data was used in this analysis.

industry revenue figures to estimate the number and revenues of small and large employers in each industry. Average small and large employer revenues (calculated by dividing the revenues of establishments in each industry and revenue bracket by the corresponding number of establishments) were inflated to 2005 dollars using the Consumer Price Index.[8] The resulting estimates are presented in Table 8-6.

Table 8-6: Average Revenues of Small Businesses Affected by the RRP Rule

NAICS	Industry Description	Small Business Revenues (2005$)
236118	Residential remodelers	$182,932
238170	Siding contractors	$201,569
238350	Finish carpentry contractors	$100,713
238290	Other building equipment contractors	$585,771
238390	Other building finishing contractors	$231,442
238340	Tile and terrazzo contractors	$130,097
238220	Plumbing and HVAC contractors	$432,677
238150	Glass and glazing contractors	$336,896
238320	Painting and wall covering contractors	$86,839
238210	Electrical contractors	$351,694
238310	Drywall and insulation contractors	$240,488
Total	**Average, Construction Establishments**	**$217,546**
531311	Residential Property Managers	$342,477
531110	Lessors of Residential Real Estate	$821,350
Total2	**Average, All Industries**	**$289,530**

Weighted average of employer and non-employer revenues.
Source: EPA Calculations; U.S. Census Bureau 2005c,f,i; U.S. Small Business Administration 2005; U.S. Census Bureau 2004b; U.S. Census Bureau 2000a.

Employment Size of Small Construction Establishments

In order to estimate the employment size of an average small establishment in each affected industry, EPA used U.S. Economic Census data to determine the portion of each industry's employees that work for small businesses. This percentage was applied to the estimated number of trained employees in each sector to calculate the number of trained renovators and workers employed by small certified establishments and, for the eleven construction industry sectors, combined with the number of certified self-employed contractors to calculate an average small business employment size.

Table 8-7 presents the percent of the workforce employed by small establishments,[9] the total number of trained personnel in each industry (under Option A), and the estimated average numbers of trained professionals working for small certified establishments. While numbers in this table are based on the Option A scenario, as discussed at the beginning of this section, the average employment size of establishments in each industry is the same under each option.

[8] All items, US city average. Series Id: CUUR0000SA0.
[9] See Sections 2.2.4 and 2.5.2 of Chapter 2 for discussion of these percentages.

Table 8-7: Number of Trained Employees per Small Certified Establishment (Option A)				
NAICS	**Description**	**% Workforce employed by Small Employers[a,b]**	**Trained Employees, Small Estab.[c]**	**Average Small Estab. Employment Size[d]**
236118	Residential remodelers	95	62,479	1.4
238170	Siding contractors	90	6,169	1.9
238350	Finish carpentry contractors	86	42,284	1.3
238290	Other building equipment contractors	60	6,060	4.2
238390	Other building finishing contractors	81	4,268	2.1
238340	Tile and terrazzo contractors	91	7,005	1.6
238220	Plumbing and HVAC contractors	70	46,962	3.1
238150	Glass and glazing contractors	82	3,025	2.3
238320	Painting and wall covering contractors	92	26,687	1.5
238210	Electrical contractors	68	33,737	3.1
238310	Drywall and insulation contractors	64	16,202	2.2
Average, Small Construction Establishments			**254,880**	1.8
531311	Residential Property Managers	40	33,192	5.2
531110	Lessors of Residential Real Estate	86	71,285	4.1
Average, All Industries			**359,357**	2.2

a. EPA applied U.S. Economic Census data regarding: entities with less than $10 million in revenues to establishments in the 11 construction sectors; entities with less than $1 million in revenues to Residential Property Manager establishments; and entities with less than $5 million in revenues to Lessors of Residential Real Estate.
b. Percentages shown for presentation purposes only. Calculations used unrounded ratio of small establishment data to industry data.
c. Total number of trained employees working for small construction establishments is the sum of trained personnel working for small employers and the total number of certified self-employed contractors.
d. For construction industry sectors calculated by dividing the total number of trained employees of small establishments by the sum of certified small employer establishments and certified self-employed contractors.

Source: U.S. Census Bureau 2000a; U.S. Census Bureau 2004b; U.S. Census Bureau 2005 b-f,i; U.S. Small Business Administration 2005.

Average Number of Events Performed by Small Construction Establishments

As discussed in Section 8.3.2, in this analysis the costs of the rule are attributed to establishments on a per-event basis. In order to estimate the total number of events performed by establishments in each of the affected industries, and in order to distribute these events between small and large establishments, EPA assumed that the number of events performed by each establishment is proportional to the number of people the establishment employs. Furthermore, EPA assumed that the number of events performed by each trained employee will be the same across all industries, including Residential Property Managers and Lessors of Residential Buildings and Dwellings. If property managers and lessors perform fewer events than estimated here, the impacts on these establishments will be slightly smaller, and the impacts on construction firms will be larger.

The number of events per small establishment in a particular industry was calculated as follows:

$$\text{Number of Events} = (\text{Events/Employee}) \times (\text{Establishment Employment Size})$$

EPA estimated the average number of events per certified renovator or worker by calculating the ratio of the total number of regulated RRP events to the total number of trained personnel. Because the number

of people trained, as estimated in Chapter 4, was assumed to be proportional to the regulated housing stock and the number of regulated events, the number of RRP events per employee does not change over time and is approximately the same across options.[10]

To estimate the average number of events performed by a small establishment in a given industry, the establishment's average employment size (Table 8-7) was multiplied by the average number of events per person (23). Table 8-8 presents the average estimated number of events per small establishment.

Table 8-8: Number of Events performed by Small Establishments

NAICS	Description	Annual Number of Events per Employee	Average Small Establishment Employment Size	Annual Number of Events per Small Establishment [a]
236118	Residential remodelers	23.0	1.4	33
238170	Siding contractors	23.0	1.9	44
238350	Finish carpentry contractors	23.0	1.3	31
238290	Other building equipment contractors	23.0	4.2	96
238390	Other building finishing contractors	23.0	2.1	49
238340	Tile and terrazzo contractors	23.0	1.6	36
238220	Plumbing and HVAC contractors	23.0	3.1	72
238150	Glass and glazing contractors	23.0	2.3	52
238320	Painting and wall covering contractors	23.0	1.5	35
238210	Electrical contractors	23.0	3.1	72
238310	Drywall and insulation contractors	23.0	2.2	51
Average, Small Construction Establishments		23.0	1.8	**42**
531311	Residential Property Managers	23.0	5.2	121
531110	Lessors of Residential Real Estate	23.0	4.1	94
Average, All Industries		23.0	2.2	**51**

a. Number of events per establishment rounded to the nearest event.
Source: EPA Calculations.

[10] While there are slight differences in the estimates of the number of events per person under each of the four options in the first year, from the second year onward the number of regulated events and trained personnel under each option will be the same as under Option A. Option A data is used in this analysis.

8.3.5 Estimating the Costs of the RRP Rule Incurred by Small Establishments

Average Per-Event Cost of Compliance

In Section 4.7.3 of Chapter 4, EPA estimated the 50-year annualized costs of the RRP Rule under each of the four regulatory options considered. Using costs discounted at a 3 percent rate, the total per-event cost was estimated as the total annualized cost of the rule under each option divided by the average annual number of regulated events.[11] The number of events taking place in a "typical" year over the 50-year period covered by the annualized costs was calculated assuming that the number of events will decrease annually in proportion to the demolition of the pre-1980 housing stock, or at a rate of 0.41 percent per year. Table 8-9 presents the total number of events taking place in the first year and the second year the rule is in effect, as well as the average number of regulated events taking place in a "typical" year. The table also presents the total annualized cost of the rule under each of the options and the estimated average annualized compliance cost per event. Note that total annualized and per-event costs are significantly higher under Option D, which includes prescriptive work practice requirements. Because the per-event cost is derived from the total annualized cost of compliance, it includes the cost of training, certification and lead-safe work practices. This average cost includes some RRP events where the only cost incurred is that of the lead-based paint (LBP) test kit, where the test showed no lead.

Table 8-9: Total Number of Regulated Events, Total Annualized Costs and Average Compliance Cost per Event

	Option A[a]	Options B [a]	Option C[a]	Option D[a]
Year 1 Events	10,727,895	5,818,980	4,298,336	5,818,980
Year 2 Events	10,683,911	10,683,911	10,683,911	10,683,911
50-year Average Events	9,717,689	9,619,510	9,589,097	9,619,510
Annualized Cost (millions $)	$505	$492	$488	$588
Per-Event Cost ($)	$52.00	$51.17	$50.86	$61.17

a. See Table 8-4, Footnote b for option definitions.

Source: EPA Calculations

Firms' Ability to Pass Costs of Compliance on to their Customers

As demonstrated in Table 8-9, small establishments are estimated to incur an average annualized compliance cost of about $51 to $61 per regulated renovation event. The requirements of the RRP Rule thus effectively raise the cost of performing renovation work in housing subject to the rule by $51 to $61. Contractors faced with this cost increase have two options – they can either choose to absorb this cost, decreasing their per-event profits, or they can try to pass at least a portion of the cost on to their customers, increasing the price of renovation work.

[11] Costs annualized using a 3 percent discount rate are used because the analysis assumes that establishments will pass some of the costs of compliance onto their customers. As such, compliance costs are expected to offset consumption rather than investment.

A firm's ability to pass on costs depends largely on the elasticities of supply and demand for renovation services. The role of supply and demand elasticities in determining the impacts of a rule are discussed in detail in Appendixes 3A and 3B of this economic analysis. In general, given a fixed supply curve, the more inelastic the demand for renovation services, the greater the portion of the costs that suppliers can pass on to their customers. Given a fixed demand curve, higher supply elasticity allows for greater cost pass-through.

In order to estimate the impacts of the regulations on small businesses assuming that these establishments will be able to pass some of the costs on to their customers, EPA reviewed a variety of literature on the supply and demand elasticities of housing, construction and renovation. Based on this literature, EPA selected values for the elasticities of supply and demand to be used in this small business impact analysis.

The vast majority of available literature focused on the supply/demand elasticities for new housing construction, rather than renovation and repair work. In addition, more information was available on the demand for housing than on supply.

The elasticity of demand for housing services is generally considered to be in the range of –0.5 to –1.0 (Mayo 1981; Malpezzi and Maclennan 2001) or –0.75 to –1.2 (Ellwood and Polinski 1979), with a preferred estimate of slightly less than 1.0 in absolute value. While intuitively the demand for housing might appear less elastic than the demand for renovation[12], one paper estimated a renovation demand elasticity of –0.28 and stated that renovation demand is "very inelastic" (Gyourko and Saiz, 2003). Because the elasticity of demand estimates are fairly consistent across the literature surveyed, EPA used the median of the –0.28 to –1.2 range, or –0.74, as an estimate of the elasticity of demand for lead-safe renovation services. As such, the demand is considered slightly inelastic in this analysis. Since at least some of the renovation jobs covered by the rule are necessary maintenance and repair projects rather than discretionary alteration and remodeling jobs, assuming a somewhat inelastic demand for renovation is reasonable.

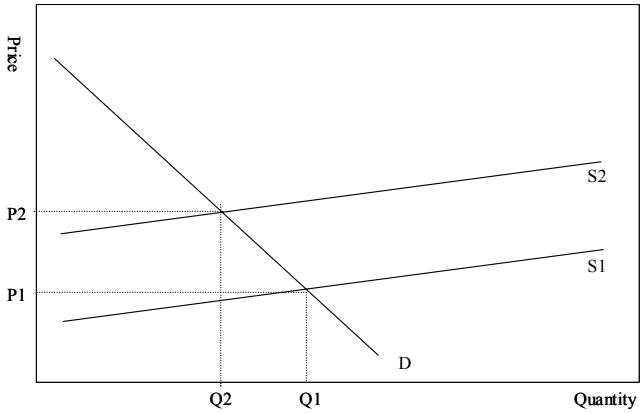
Based on the literature surveyed, the supply of housing services, unlike the demand for these services, is believed to be highly elastic, especially in the long run. Estimates of housing supply elasticities generally range from 1.0 to 13 (DiPasquale and Wheaton 1994, Topel and Rosen 1988; Blackley 1999; Malpezzi and Maclennan 2001), with one study identifying a much higher elasticity of supply for physical structures (ES = 38, Gyourko and Saiz 2004). No elasticity numbers specific to the supply of renovation services could be found. Given the range of data presented in the literature, EPA estimated a supply elasticity of 6 for renovation services. This estimate is likely to be conservative, and as such, to lead to an overestimate of the impacts of the regulation on small construction establishments.

[12] While housing is a basic necessity, many renovation projects are discretionary. In addition to being able to choose whether to do a renovation project at all, consumers can choose between doing the work themselves or hiring an outside contractor. In the case of regulated renovation work, they can also choose between hiring a firm that is in compliance and a firm that is not.

Changes in Price and Quantity; Post-Rule Revenues

The costs of training, certification and lead-safe work practices required by the RRP Rule increase the cost of performing renovation work by about $51 to $61 per event. As demonstrated in Figure 8.1, an increase in the cost of supplying a service causes the supply curve, S1 to shift upward to S2. As a result of this shift, the equilibrium price of the service increases from P1 to P2, and the equilibrium quantity of services demanded decreases from Q1 to Q2. These changes in price and quantity, in turn, result in a change in supplier revenues. Whereas prior to the cost increase, the supplier earned the equivalent of Q1*P1 from his services, after the cost increase, he earns the equivalent of Q2*P2.

Figure 8.1: Shifts in supply and market equilibrium resulting from increases in supply costs



The resulting changes in the price and quantity of services (in this case, regulated renovation projects), as well as in the revenues of suppliers providing these services (in this case, contractors and residential real estate establishments) can be calculated as follows:

$\Delta P = (ES*C)/(ES-ED)$
$\Delta Q = [ES*ED*(C/P1)*Q1]/[ES-ED]$
$\Delta R = (P1+\Delta P)*(Q1+\Delta Q) - (P1*Q1)$

Where:

- ΔP= Change in price
- ΔQ= Change in quantity
- ΔR = Change in revenues from regulated renovation events
- ES = Price elasticity of supply (ES = 6)
- ED = Price elasticity of demand (ED = -0.74)
- C = Per unit cost increase (Cost of compliance, varies from option to option)
- P1 = Initial equilibrium price ($1,900)
- Q1 = Initial equilibrium quantity

Note: This model assumes that the changes in quantity and price will be small enough that the elasticities will remain unchanged (Model based on HUD 1994).

These calculations were performed for small establishments in each of the construction sectors, under each of the regulatory options considered. In each case, Q1 was equal to the average number of events per small establishment (Table 8-9) and P1 was equal to $1,900, the median cost per task subject to the

regulation.[13] The resulting estimates of the changes in price and quantity of regulated renovation services demanded (and supplied), and the resulting changes in contractor revenues are presented in Table 8-10 to Table 8-13 (for Options A through D). Note that with relatively inelastic demand and elastic supply, the average revenues of small construction establishments increase slightly under the rule.

As demonstrated in these tables, the number of events performed by each establishment decreases slightly with the increase in price. This reduction in the quantity of events performed represents a decrease in the number of events that are in compliance with the regulations, rather than a decrease in the cumulative number of renovations performed. Throughout this analysis, EPA has assumed that about 75 percent of all regulated renovation events will be performed in compliance with the RRP Rule requirements. The decrease in the number of events performed by certified establishments contributes to the 25 percent of regulated events that are likely to be conducted by untrained personnel using non-compliant work practices.

Table 8-10: Estimated changes in the price and number of renovation events, and resulting changes in small establishment revenues: Option A (Per-Event Cost Increase = $52.00)

NAICS	Industry Description	Q1 (Initial Number of Events per Estab.)	Per-Event Price Increase (Cost passed on to consumers)	Decrease in Quantity	New Number of Regulated Events per Estab.	Change in Revenues	New Small Establishment Revenues
236118	Residential remodelers	33	$46.29	-0.59	32.41	+$370	$183,302
238170	Siding contractors	44	$46.29	-0.79	43.21	+$493	$202,062
238350	Finish carpentry contractors	31	$46.29	-0.56	30.44	+$347	$101,060
238290	Other building equipment contractors	96	$46.29	-1.73	94.27	+$1,075	$586,846
238390	Other building finishing contractors	49	$46.29	-0.88	48.12	+$549	$231,991
238340	Tile and terrazzo contractors	36	$46.29	-0.65	35.35	+$403	$130,500
238220	Plumbing and HVAC contractors	72	$46.29	-1.30	70.70	+$806	$433,483
238150	Glass and glazing contractors	52	$46.29	-0.94	51.06	+$582	$337,478
238320	Painting and wall covering contractors	35	$46.29	-0.63	34.37	+$392	$87,231
238210	Electrical contractors	72	$46.29	-1.30	70.70	+$806	$352,500
238310	Drywall and insulation contractors	51	$46.29	-0.92	50.08	+$571	$241,059
Average, Small Construction Establishments		**42**	**$46.29**	**-0.76**	**41.24**	**+$470**	**$218,016**
531311	Residential Property Managers	121	$46.29	-2.18	118.82	+$1,355	$343,832
531110	Lessors of Residential Real Estate	94	$46.29	-1.69	92.31	+$1,053	$822,403
Average, All Industries		**51**	**$46.29**	**-0.92**	**50.08**	**+$571**	**$290,101**

Source: EPA Calculations

[13] The $1,900 median cost per task is estimated using the 2003 American Housing Survey. Only spending reported for the tasks that are assumed to potentially disturb surfaces with LBP are included in the estimates (see Chapter 4). However, some spending on out-of-scope tasks may be included and some spending on in-scope tasks may be excluded, because the costs of multiple RRP tasks are sometimes reported under a single task of the respondents choosing.

Table 8-11: Estimated changes in the price and number of renovation events, and resulting changes in small establishment revenues: Option B (Per-Event Cost Increase = $51.17)

NAICS	Industry Description	Q1 (Initial Number of Events per Estab.)	Per-Event Price Increase (Cost passed on to consumers)	Decrease in Quantity	New Number of Regulated Events per Estab.	Change in Revenues	New Small Establishment Revenues
236118	Residential remodelers	33	$45.55	-0.59	32.41	+$364	$183,296
238170	Siding contractors	44	$45.55	-0.78	43.22	+$486	$202,055
238350	Finish carpentry contractors	31	$45.55	-0.55	30.45	+$342	$101,055
238290	Other building equipment contractors	96	$45.55	-1.70	94.30	+$1,059	$586,830
238390	Other building finishing contractors	49	$45.55	-0.87	48.13	+$541	$231,983
238340	Tile and terrazzo contractors	36	$45.55	-0.64	35.36	+$397	$130,494
238220	Plumbing and HVAC contractors	72	$45.55	-1.28	70.72	+$795	$433,472
238150	Glass and glazing contractors	52	$45.55	-0.92	51.08	+$574	$337,470
238320	Painting and wall covering contractors	35	$45.55	-0.62	34.38	+$386	$87,225
238210	Electrical contractors	72	$45.55	-1.28	70.72	+$795	$352,489
238310	Drywall and insulation contractors	51	$45.55	-0.90	50.10	+$563	$241,051
Average, Small Construction Establishments		**42**	**$45.55**	**-0.75**	**41.25**	**+$464**	**$218,010**
531311	Residential Property Managers	121	$45.55	-2.15	118.85	+$1,335	$343,812
531110	Lessors of Residential Real Estate	94	$45.55	-1.67	92.33	+$1,037	$822,387
Average, All Industries		**51**	**$45.55**	**-0.90**	**50.10**	**+$563**	**$290,093**

Source: EPA Calculations

Table 8-12: Estimated changes in the price and number of renovation events, and resulting changes in small establishment revenues: Option C (Per-Event Cost Increase = $50.86)

NAICS	Industry Description	Q1 (Initial Number of Events per Estab.)	Per-Event Price Increase (Cost passed on to consumers)	Decrease in Quantity	New Number of Regulated Events per Estab.	Change in Revenues	New Small Establishment Revenues
236118	Residential remodelers	33	$45.27	-0.58	32.42	+$362	$183,294
238170	Siding contractors	44	$45.27	-0.78	43.22	+$483	$202,052
238350	Finish carpentry contractors	31	$45.27	-0.55	30.45	+$340	$101,053
238290	Other building equipment contractors	96	$45.27	-1.69	94.31	+$1,053	$586,824
238390	Other building finishing contractors	49	$45.27	-0.86	48.14	+$538	$231,980
238340	Tile and terrazzo contractors	36	$45.27	-0.63	35.37	+$395	$130,492
238220	Plumbing and HVAC contractors	72	$45.27	-1.27	70.73	+$790	$433,467
238150	Glass and glazing contractors	52	$45.27	-0.92	51.08	+$571	$337,467
238320	Painting and wall covering contractors	35	$45.27	-0.62	34.38	+$384	$87,223
238210	Electrical contractors	72	$45.27	-1.27	70.73	+$790	$352,484
238310	Drywall and insulation contractors	51	$45.27	-0.90	50.10	+$560	$241,048
Average, Small Construction Establishments		**42**	**$45.27**	**-0.74**	**41.26**	**+$461**	**$218,007**
531311	Residential Property Managers	121	$45.27	-2.13	118.87	+$1,328	$343,805
531110	Lessors of Residential Real Estate	94	$45.27	-1.66	92.34	+$1,031	$822,381
Average, All Industries		**51**	**$45.27**	**-0.90**	**50.10**	**+$560**	**$290,090**

Source: EPA Calculations

Table 8-13: Estimated changes in the price and number of renovation events, and resulting changes in small establishment revenues: Option D (Per-Event Cost Increase = $61.17)

NAICS	Industry Description	Q1 (Initial Number of Events per Estab.)	Per-Event Price Increase (Cost passed on to consumers)	Decrease in Quantity	New Number of Regulated Events per Estab.	Change in Revenues	New Small Establishment Revenues
236118	Residential remodelers	33	$54.46	-0.70	32.30	+$429	$183,361
238170	Siding contractors	44	$54.46	-0.93	43.07	+$572	$202,141
238350	Finish carpentry contractors	31	$54.46	-0.66	30.34	+$403	$101,116
238290	Other building equipment contractors	96	$54.46	-2.04	93.96	+$1,248	$587,019
238390	Other building finishing contractors	49	$54.46	-1.04	47.96	+$637	$232,079
238340	Tile and terrazzo contractors	36	$54.46	-0.76	35.24	+$468	$130,565
238220	Plumbing and HVAC contractors	72	$54.46	-1.53	70.47	+$936	$433,613
238150	Glass and glazing contractors	52	$54.46	-1.10	50.90	+$676	$337,572
238320	Painting and wall covering contractors	35	$54.46	-0.74	34.26	+$455	$87,294
238210	Electrical contractors	72	$54.46	-1.53	70.47	+$936	$352,630
238310	Drywall and insulation contractors	51	$54.46	-1.08	49.92	+$663	$241,151
Average, Small Construction Establishments		**42**	**$54.46**	**-0.89**	**41.11**	**+$546**	**$218,092**
531311	Residential Property Managers	121	$54.46	-2.57	118.43	+$1,573	$344,050
531110	Lessors of Residential Real Estate	94	$54.46	-1.99	92.01	+$1,222	$822,572
Average, All Industries		**51**	**$54.46**	**-1.08**	**49.92**	**+$663**	**$290,193**

Source: EPA Calculations

Small Establishment Compliance Costs and Calculations of Cost-Impact Ratios

As discussed earlier in this analysis, contractors are expected to pass some of the costs of the rule onto their customers, increasing their revenues. The impacts of the rule are measured by a cost-impact ratio that compares the total annualized compliance costs per establishment (calculated as the per-event cost of compliance multiplied by the new, lower number of events per establishment) to the new revenues that account for the higher price charged to consumers and the decrease in the number of renovation events. The results are presented in Table 8-14 through Table 8-17. As demonstrated in these tables, under these elasticity assumptions, the cost of the rule incurred by small businesses is expected to amount to between 0.6 and 2.0 percent of their revenues under Options A through C (0.9 percent on average) and between 0.7 and 2.4 percent of their revenues under the prescriptive Option D (1.1 percent on average).

Table 8-14: Estimated Direct Costs Incurred by Contractors under the RRP Rule and Resulting Cost-Impact Ratios by Industry (Option A)

NAICS	Industry Description	Per-Event Compliance Cost	Post-Rule Number of Regulated Events	Direct Cost of Rule Incurred by Contractor	Post-Rule Contractor Revenues	Cost-Impact Ratio
236118	Residential remodelers	$52.00	32.41	$1,685	$183,302	0.9%
238170	Siding contractors	$52.00	43.21	$2,247	$202,062	1.1%
238350	Finish carpentry contractors	$52.00	30.44	$1,583	$101,060	1.6%
238290	Other building equipment contractors	$52.00	94.27	$4,902	$586,846	0.8%
238390	Other building finishing contractors	$52.00	48.12	$2,502	$231,991	1.1%
238340	Tile and terrazzo contractors	$52.00	35.35	$1,838	$130,500	1.4%
238220	Plumbing and HVAC contractors	$52.00	70.70	$3,676	$433,483	0.8%
238150	Glass and glazing contractors	$52.00	51.06	$2,655	$337,478	0.8%
238320	Painting and wall covering contractors	$52.00	34.37	$1,787	$87,231	2.0%
238210	Electrical contractors	$52.00	70.70	$3,676	$352,500	1.0%
238310	Drywall and insulation contractors	$52.00	50.08	$2,604	$241,059	1.1%
Average, Small Construction Establishments		**$52.00**	**41.24**	**$2,145**	**$218,016**	**1.0%**
531311	Residential Property Managers	$52.00	118.82	$6,178	$343,832	1.8%
531110	Lessors of Residential Real Estate	$52.00	92.31	$4,800	$822,403	0.6%
Average, All Industries		**$52.00**	**50.08**	**$2,604**	**$290,101**	**0.9%**

Source: EPA Calculations

Table 8-15: Estimated Direct Costs Incurred by Contractors under the RRP Rule and Resulting Cost-Impact Ratios by Industry (Option B)

NAICS	Industry Description	Per-Event Compliance Cost	Post-Rule Number of Regulated Events	Direct Cost of Rule Incurred by Contractor	Post-Rule Contractor Revenues	Cost-Impact Ratio
236118	Residential remodelers	$51.17	32.41	$1,659	$183,296	0.9%
238170	Siding contractors	$51.17	43.22	$2,212	$202,055	1.1%
238350	Finish carpentry contractors	$51.17	30.45	$1,558	$101,055	1.5%
238290	Other building equipment contractors	$51.17	94.30	$4,825	$586,830	0.8%
238390	Other building finishing contractors	$51.17	48.13	$2,463	$231,983	1.1%
238340	Tile and terrazzo contractors	$51.17	35.36	$1,810	$130,494	1.4%
238220	Plumbing and HVAC contractors	$51.17	70.72	$3,619	$433,472	0.8%
238150	Glass and glazing contractors	$51.17	51.08	$2,614	$337,470	0.8%
238320	Painting and wall covering contractors	$51.17	34.38	$1,759	$87,225	2.0%
238210	Electrical contractors	$51.17	70.72	$3,619	$352,489	1.0%
238310	Drywall and insulation contractors	$51.17	50.10	$2,563	$241,051	1.1%
Average, Small Construction Establishments		**$51.17**	**41.25**	**$2,111**	**$218,010**	**1.0%**
531311	Residential Property Managers	$51.17	118.85	$6,082	$343,812	1.8%
531110	Lessors of Residential Real Estate	$51.17	92.33	$4,725	$822,387	0.6%
Average, All Industries		**$51.17**	**50.10**	**$2,563**	**$290,093**	**0.9%**

Source: EPA Calculations

Table 8-16: Estimated Direct Costs Incurred by Contractors under the RRP Rule and Resulting Cost-Impact Ratios by Industry (Option C)						
NAICS	**Industry Description**	**Per-Event Compliance Cost**	**Post-Rule Number of Regulated Events**	**Direct Cost of Rule Incurred by Contractor**	**Post-Rule Contractor Revenues**	**Cost-Impact Ratio**
236118	Residential remodelers	$50.86	32.42	$1,649	$183,294	0.9%
238170	Siding contractors	$50.86	43.22	$2,198	$202,052	1.1%
238350	Finish carpentry contractors	$50.86	30.45	$1,549	$101,053	1.5%
238290	Other building equipment contractors	$50.86	94.31	$4,796	$586,824	0.8%
238390	Other building finishing contractors	$50.86	48.14	$2,448	$231,980	1.1%
238340	Tile and terrazzo contractors	$50.86	35.37	$1,799	$130,492	1.4%
238220	Plumbing and HVAC contractors	$50.86	70.73	$3,597	$433,467	0.8%
238150	Glass and glazing contractors	$50.86	51.08	$2,598	$337,467	0.8%
238320	Painting and wall covering contractors	$50.86	34.38	$1,749	$87,223	2.0%
238210	Electrical contractors	$50.86	70.73	$3,597	$352,484	1.0%
238310	Drywall and insulation contractors	$50.86	50.10	$2,548	$241,048	1.1%
Average, Small Construction Establishments		**$50.86**	**41.26**	**$2,098**	**$218,007**	**1.0%**
531311	Residential Property Managers	$50.86	118.87	$6,045	$343,805	1.8%
531110	Lessors of Residential Real Estate	$50.86	92.34	$4,696	$822,381	0.6%
Average, All Industries		**$50.86**	**50.10**	**$2,548**	**$290,090**	**0.9%**
Source: EPA Calculations						

Table 8-17: Estimated Direct Costs Incurred by Contractors under the RRP Rule and Resulting Cost-Impact Ratios by Industry (Option D)						
NAICS	**Industry Description**	**Per-Event Compliance Cost**	**Post-Rule Number of Regulated Events**	**Direct Cost of Rule Incurred by Contractor**	**Post-Rule Contractor Revenues**	**Cost-Impact Ratio**
236118	Residential remodelers	$61.17	32.30	$1,976	$183,361	1.1%
238170	Siding contractors	$61.17	43.07	$2,635	$202,141	1.3%
238350	Finish carpentry contractors	$61.17	30.34	$1,856	$101,116	1.8%
238290	Other building equipment contractors	$61.17	93.96	$5,748	$587,019	1.0%
238390	Other building finishing contractors	$61.17	47.96	$2,934	$232,079	1.3%
238340	Tile and terrazzo contractors	$61.17	35.24	$2,156	$130,565	1.7%
238220	Plumbing and HVAC contractors	$61.17	70.47	$4,311	$433,613	1.0%
238150	Glass and glazing contractors	$61.17	50.90	$3,114	$337,572	0.9%
238320	Painting and wall covering contractors	$61.17	34.26	$2,096	$87,294	2.4%
238210	Electrical contractors	$61.17	70.47	$4,311	$352,630	1.2%
238310	Drywall and insulation contractors	$61.17	49.92	$3,054	$241,151	1.3%
Average, Small Construction Establishments		**$61.17**	**41.11**	**$2,515**	**$218,092**	**1.2%**
531311	Residential Property Managers	$61.17	118.43	$7,245	$344,050	2.1%
531110	Lessors of Residential Real Estate	$61.17	92.01	$5,628	$822,572	0.7%
Average, All Industries		**$61.17**	**49.92**	**$3,054**	**$290,193**	**1.1%**
Source: EPA Calculations						

8.3.6 Impacts on Small Governments

Similarly to privately-owned businesses, public agencies and authorities that conduct renovation work on regulated properties will incur the costs of certification, training and work practice compliance under the RRP Rule. Specifically, the rule could potentially affect housing authorities and other governmental bodies such as educational institutions operated by small governments that use an in-house crew to perform renovation work on their properties that qualify as target housing.

As noted earlier, public housing authorities that receive funding from the U.S. Department of Housing and Urban Development must comply with HUD regulations regarding lead paint, and so are unlikely to incur additional costs due to this rule. None of the housing authorities identified in section 8.2.1 as operating public housing that does not receive HUD funding qualifies as a small government under the Regulatory Flexibility Act. Nor were any colleges or universities operated by small governments identified. To the extent that there are any small governments that conduct renovation work on regulated properties, the cost of the rule to them is likely to be low. As shown in Table 8-9, under Option B, the cost of the rule is estimated to be $51 per event when averaged across all regulated events. The cost per event for small governments would be similar.

8.3.7 Impacts on Small Non-profit Organizations

The Renovation, Repair and Painting Rule also may affect several types of small non-profit organizations that offer housing. These organizations may serve a number of populations, including elderly, recovering alcoholics or drug addicts, low-income families, or political refugees. There are also private colleges and universities operated by non-profits that provide apartment-style housing for graduate students and married students. Non-profit organizations that provide housing and use an on-site crew for renovation work in buildings subject to the regulations will incur certification, training and work practice costs.

The number of non-profits that conduct renovation work on regulated housing units is not known, nor is the number of RRP events they conduct that would require lead safe work practices as a result of the rule. The cost for small non-profit organizations is likely to be low. As shown in Table 8-9, under Option B, the cost of the rule is estimated to be $51 per event when averaged across all regulated events. The cost per event for small non-profit organizations would be similar. Some small non-profit organizations (such as colleges and universities) may be able to pass some of the costs on to their customers.

8.3.8 Conclusions

The RRP Rule is expected to affect, on average, approximately 145,000 small contractors and real estate establishments per year under the preferred option. After accounting for the ability of firms to pass some of the costs through to their customers, impacts on small businesses are expected to range from 0.6 to 2.0 percent of revenues under the preferred option. The number of small governments and small non-profits affected was not calculated, but the cost per event is expected to be similar to that for businesses.

8.4 Executive Order 13132 - Federalism

Under Executive Order 13132, entitled *Federalism* (64 FR 43255, August 10, 1999), EPA must determine whether this proposed rule has "federalism implications," (i.e. whether it has substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132).

As discussed in Chapter 4, states would be able to apply for, and receive authorization to administer these proposed requirements, but would be under no obligation to do so. In the absence of a state authorization, EPA will administer these requirements. While the cost analysis assumes that EPA will administer and enforce the program in all places, it also assumes that states would incur similar costs if they administer and enforce the regulation.

As discussed in Section 8.2, much of the target housing owned by state governments receives funding from HUD, and must already comply with HUD regulations regarding lead paint. These state governments are unlikely to incur additional costs due to this rule. The small number of states with housing authorities that do not receive HUD funding may incur additional costs due to this rule, as are certain other types of entities such as state colleges and universities that operate apartment type housing for graduate students and married students. Given the low cost per event, this rule is not expected to have a significant impact on states.

8.5 Executive Order 13175 - Tribal Implications

Under Executive Order 13175, entitled *Consultation and Coordination with Indian Tribal Governments* (59 FR 22951, November 6, 2000), EPA must determine that this proposed rule does not have tribal implications (i.e. whether it has substantial direct effects on tribal governments, on the relationship between the Federal government and the Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes). Tribes would be able to apply for and receive authorization to administer these proposed requirements on Tribal lands, but Tribes would be under no obligation to do so. In the absence of a Tribal authorization, EPA will administer these requirements.

The number of Tribal authorities that conduct renovation work on regulated properties is not known. But given the low cost per event, this rule is not expected to have a significant impact on Tribes.

8.6 Protection of Children from Environmental Health Risk and Safety Risks

Under Executive Order 13045, a regulation must be reviewed if the regulatory action is economically significant and concerns an environmental health risk or safety risk that may disproportionately affect children. Since children are particularly susceptible to the IQ loss and adverse health effects caused by exposure to lead dust, a significant objective of the RRP regulation is the protection of children's health.

All four of the regulatory options cover all children living in regulated homes where RRP events occur; the options differ in terms of the definition of regulated homes. Option C (units built before 1950) covers the fewest housing units (and thus the fewest children) in year one, while Option A (units built before 1978) covers the largest number of housing units and thus children in year one. The options are identical in terms of number of children covered in year two and beyond. As shown in Table 8-18, Options B and D cover about 85% of potentially affected children in the first year, while Option C covers about 66%.

Thus substantially more children are protected in the first year of the rule under option A than under any other Option. This difference disappears in year two.

Table 8-18: Number of Children Under 6 Residing in Affected Housing by Option and Year of Rule – Units where RRP take place and LBP present [a]

Option	First Year of the Rule		Second Year and Each Subsequent Year of the Rule	
	Number	Percent of Option A	Number	Percent of Option A
Option A	786,562	100%	783,337	100%
Option B	668,010	85%	783,337	100%
Option C	519,941	66%	783,337	100%
Option D	668,010	85%	783,337	100%

a. These data have been adjusted downward to account for the baseline level of lead-safe work practice use.

Source: EPA Estimates – see chapter 5

8.7 Executive Order 13211 - Energy Effects

Under the Executive Order 13211, entitled *Actions concerning Regulations that Significantly Affect Energy Supply, Distribution, or Use* (66 FR 28355, May 22, 2001), EPA must identify actions that will have a significant adverse energy effect. Adverse effects are defined as:

1. Reductions in crude oil supply in excess of 10,000 barrels per day;
2. Reductions in fuel production in excess of 4,000 barrels per day;
3. Reductions in coal production in excess of 5 million tons per year;
4. Reductions in natural gas production in excess of 25 million mcf per year;
5. Reductions in electricity production in excess of 1 billion kilowatt-hours per year or in excess of 500 megawatts of installed capacity;
6. Increases in energy use required by the regulatory action that exceed any of the thresholds above;
7. Increases in the cost of energy production in excess of one percent;
8. Increases in the cost of energy distribution in excess of one percent; or
9. Other similarly adverse outcomes.

The regulations under consideration will not significantly reduce energy production nor significantly increase energy costs.

8.8 National Technology Transfer and Advancement Act

Section 12(d) of the National Technology Transfer and Advancement Act of 1995 ("NTTAA"), Public Law No. 104-113, 12(d) (15 U.S.C. 272 note) directs EPA to use voluntary consensus standards in its regulatory activities unless to do so would be inconsistent with applicable law or otherwise impractical. Voluntary consensus standards are technical standards (e.g., materials specifications, test methods, sampling procedures, and business practices) that are developed or adopted by voluntary consensus standards bodies. The NTTAA directs EPA to provide Congress, through OMB, explanations when the Agency decides not to use available and applicable voluntary consensus standards.

As detailed in Chapter 4, EPA is proposing to adopt a number of work practice requirements that could be considered technical standards for performing renovation projects in residences that contain lead-based paint. EPA is not proposing, however, to require traditional clearance examinations, including dust sampling, following renovation projects. Instead, it is proposing to require that a visual inspection for dust, debris, and residue be conducted after cleaning and before post-renovation cleaning verification is performed.

8.9 Executive Order 12898 – Environmental Justice

Under Executive Order 12898, when promulgating a regulation, EPA investigates whether there are disproportionately high and adverse human health or environmental effects on minority and low income populations. The proposed regulation requires that contractors, when undertaking renovation activities in regulated housing, reduce the risk of exposure to lead by employing the use of safe work practices. In addition, contractors are required to undertake cleaning verification at the end of each project.

This environmental justice analysis looks at the distribution of renovation events and individuals protected across three race and two income groups. Although it would be preferable to perform a joint environmental justice analysis for the race and income groups, relevant data was not available to make these population inferences. Therefore, the analysis was performed separately for the race and income groups.

Overall, the disadvantaged groups considered appear to have similar distributions of households and individuals affected under the various options. However, since these disadvantaged groups are more likely to reside in rental and older housing they are more likely to be affected under the options that emphasize regulating older and/or rental housing. In addition, individuals and children with food insecurity (i.e. those who do not have healthy diets or do not eat enough because of poverty) are more susceptible to ill health effects from lead dust. Thus, they stand to accrue greater benefits under all of the options considered.

Following the work practice, cleaning, and cleaning verification steps in the rule will increase costs for renovation, repair and painting activities in housing covered by the rule. These additional costs may lead some lower income homeowners or some landlords of properties in lower income neighborhoods to avoid using certified renovators or recommended practices. The incremental costs of the rule's work practices range from $23 to $528, depending on the size of the work area, not including the cost of the lead-based paint test kit. These costs are likely to be a small part of the total cost of the renovation, repair, and painting projects. EPA believes that these costs are unlikely to result in significant changes in consumer behavior. If however, the increased costs result in more projects being undertaken by uncertified firms or by do-it-yourselfers, the risks in these instances would be the same as in the baseline and would not constitute new risks resulting from the rule. EPA believes that the rule would result in new risks only if the increased costs caused individuals to delay work such as painting until lead-based paint began peeling and chipping, creating a lead hazard. This is expected to occur infrequently given the rule's low cost per event.

Low Income:
For the purposes of this analysis, EPA defines low income individuals as individuals who reside below the level set by the federal government's official poverty definition. Based on data from the *2000 Decennial Census*, 12.4% of individuals were living below the poverty level (U.S. Census Bureau 2000f).

It is therefore relevant to determine if the potential costs and benefits resulting from the proposed RRP regulations will have a disproportionately greater effect on low income individuals.

The data in Table 8-19 compares the relative numbers of householders below the poverty level who are owners and renters. As is evident from the data, low income individuals are much more likely to be renters than homeowners. For each definition of old housing listed (i.e. pre-1980[14], pre-1960, pre-1950), it is more than three times more likely that a renter of old housing will be a low income individual than it is for an owner. The number of low income householders living below poverty in rental housing is almost double the number who are living in owned housing. Further, out of all pre-2000 rental households, 17% of individuals reside below the poverty level and in pre-1980 rental housing units. Because of the disproportionately high number of low income individuals living in rental housing, it is reasonable to conclude that a rule affecting all pre-1978 rental housing will benefit a significant proportion of low income families in housing where lead-based paint is disturbed by RRP activities.

Table 8-19: Number and Percentage of Householders Below Poverty by Year Housing Built by Tenure

	Owner Occupied Housing		Renter Occupied Housing	
Year Housing Built	**Total Below Poverty**	**Percentage Below Poverty Out of All Pre-2000 Owner Housing**	**Total Below Poverty**	**Percentage Below Poverty Out of All Pre-2000 Rental Housing**
Pre-2000	4,371,712	6.26%	8,086,254	22.67%
Pre-1980	3,133,302	4.49%	6,059,817	16.99%
Pre-1960	1,765,185	2.53%	3,100,214	8.69%
Pre-1950	1,167,604	1.67%	2,093,142	5.87%

Source: U.S. Census Bureau 2000g.

Race:

The 2000 Census data shows that Black/African American individuals and Asian individuals tend to reside in rental housing more than White individuals. The data in Table 8-20 compares the percentages of owners and renters for three categories of race, "White Alone," "Black/African American Alone," and "Asian Alone." Compared with 28.73% of White individuals who resided in rental housing in 2000, 53.67% and 46.76% of Black/African American and Asian individuals, respectively, resided in rental housing. Also, in 2000, there were more Black/African American individuals who were renters than owners. Thus, an RRP regulation aimed at rental housing will serve to benefit these minority groups. Although no data were available for race by age of housing unit, this analysis uses pre-2000 housing to provide a general idea of these proportions.

[14] Note: For the purposes of this analysis, since Census data are not available for the category of all pre-1978 housing, pre-1980 housing data is used to approximate pre-1978 housing.

Table 8-20: Number and Percentage of Householders by Race by Tenure in 2000			
Race	**Total**	**Percentage Owner**	**Percentage Renter**
White Alone	83,715,168	71.27%	28.73%
Black/African American Alone	11,977,309	46.33%	53.67%
Asian Alone	3,117,356	53.24%	46.76%
Source: U.S. Census Bureau 2000h.			

Conclusions

The Renovation, Repair and Painting Rule seeks to protect both children and adults residing in rental target housing units or owner-occupied target housing units where a child under the age if six resides from exposure to lead during renovation work. As such, EPA concludes that the rule will not lead to disproportionately high and adverse human health or environmental effects on minority and low income populations. On the contrary, since a larger percentage of poor and minority households reside in rental housing, they may reap a greater share of the benefits.

REFERENCES

Blackley, D.M. 1999. "The Long-Run Elasticity of New Housing Supply in the United States: Empirical Evidence for 1950 to 1994." *Journal of Real Estate Finance and Economics*, 18: 25-42.

The Community Giving Resource (CGR). 2004. Public Housing. http://www.communitygivingresource.org/housing/housing_list.htm

DiPasquale, Denise and William C. Wheaton. 1994. "Housing Market Dynamics and the Future of Housing Prices." Journal of Urban Economics, 35: 1-27.

Division of Housing and Community Renewal (DHCRa). 2005. Modernization Program. http://www.dhcr.state.ny.us/ohm/progs/public/ohmprgpu.htm.

Division of Housing and Community Renewal (DHCRb). 2005. Public Housing. http://www.dhcr.state.ny.us/ohm/progs/modern/ohmmod.htm.

Gyourko, Joseph and Albert Saiz. 2003. *Urban Decline and Housing Reinvestment: The Role of Construction Costs and the Supply Side*. Federal Reserve Bank of Philadelphia. Working Paper 03-9.

Gyourko, Joseph and Albert Saiz. 2004 (Draft). *Is There a Supply Side to Urban Revival?* Federal Reserve Bank of Philadelphia. Working Paper #453. Available at: http://realestate.wharton.upenn.edu/pdf/news-apr04.pdf.

Housing and Community Development Corporation of Hawaii (HCDCH). 2002. Annual Report, 2002. http://www.hcdch.hawaii.gov/02annualrpt.pdf.

Malpezzi, Stephen and Duncan Maclennan. 2001. "The Long-Run Price Elasticity of Supply of New Residential Construction in the United States and the United Kingdom," Journal of Housing Economics, 10: 278-306.

New York City Housing Authority. 2005. Development Data Book 2005. http://www.ci.nyc.ny.us/html/nycha/pdf/dev_data_book.pdf.

New York City Housing Authority. 2005. Fact Sheet. http://www.ci.nyc.ny.us/html/nycha/pdf/factsheet.pdf

Stainton, John; Regan, Charleen. Protecting the Commonwealth's Investment: Securing the Future of State-Aided Public Housing. 2001. Citizens' Housing and Planning Association.

Topel, R. and S. Rosen. 1988. "Housing Investment in the United States." *Journal of Political Economy*, 96: 718-740.

U.S. Bureau of Labor Statistics. 2005. Occupational Employment Statistics Series.

U.S. Bureau of Labor Statistics. 2005. Consumer Price Index: All urban consumers; other goods and services. Bureau of Labor Statistics, Washington, DC.

U.S. Census Bureau. 1997 and 2003. *American Housing Survey (AHS)*.

U.S. Census Bureau. 1995. Property Owners and Managers Survey (POMS)

U.S. Census Bureau. 2000a. Establishment and Firm Size (Including Legal Form and Organization). *1997 Economic Census: Subject Series for Real Estate and Rental and Leasing.* Subject Series. EC97F53S-SZ. Available at: http://www.census.gov/prod/ec97/97f53-sz.pdf

U.S. Census Bureau. 2000h. "H11. Tenure by Race of Householder." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/DTSubjectShowTablesServlet?_lang=en&_ts=149707537374 (Downloaded 11/9/2005)

U.S. Census Bureau. 2000d. "QT-P19. School Enrollment." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/QTTable?_bm=y&-geo_id=01000US&-qr_name=DEC_2000_SF3_U_QTP19&-ds_name=DEC_2000_SF3_U&-_lang=en&-redoLog=false&-_sse=on (Downloaded 11/4/05)

U.S. Census Bureau. 2000e. "P37. Group Quarters Population by Group Quarters Type." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/DTTable?_bm=y&-geo_id=01000US&-ds_name=DE (Downloaded 10/20/2005).

U.S. Census Bureau. 2000f. "QT-P34. Poverty Status in 1999 of Individuals." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/QTTable?_bm=y&-geo_id=01000US&-qr_name=DEC_2000_SF3_U_QTP34&-ds_name=DEC_2000_SF3_U&-_lang=en&-_caller=geoselect&-state=qt&-format= (Downloaded 11/2/2005)

U.S. Census Bureau. 2000g. "HCT23. Tenure by Poverty Status in 1999 by Year Structure Built." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/DTSubjectShowTablesServlet?_lang=en&_ts=149707416170 (Downloaded 11/9/2005)

U.S. Census Bureau. 2004b. "Sector 53: Industry Series: Summary Statistics for the US: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=53&ds_name=EC0200A1&_lang=en&_ts=141736463723 (Downloaded 8/3/2005)

U.S. Census Bureau. 2004d. "R2514: Median Monthly Housing Costs for Renter-occupied Housing Units." 2004 American Community Survey. *American Fact Finder*. Available at: http://factfinder.census.gov/servlet/GRTTable?_bm=y&-_box_head_nbr=R2514&-ds_name=ACS_2004_EST_G00_&-format=US-30.

U.S. Census Bureau. 2005b. "Sector 23: Industry Series: Detailed Statistics for Establishments: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005c. "Sector 23: Industry Series: Selected Statistics for Establishments by Value of Business Done: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005d. "Sector 23: Industry Series: Value of Construction for Establishments by Type of Construction: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005e. "Sector 23: Construction: Industry Series: Selected Statistics for Establishments by Specialization in Types of Construction: 2002." *American Fact Finder.* Available at: http://factfinder.census.gov/servlet/EconSectorServlet?caller=dataset&sv_name=*&_SectorId=23&ds_name=EC0200A1&_lang=en&_ts=141735361508 (Downloaded 6/30/2005)

U.S. Census Bureau. 2005f. 2002 Economic Census: Industry Series: Residential Remodelers EC02-23I-236118 (RV). Available at: http://www.census.gov/prod/ec02/ec0223i236118.pdf (Accessed 8/3/2005).

U.S. Census Bureau. 2005i. 2002 Economic Census: Construction: By Industry. Available at: http://www.census.gov/econ/census02/data/us/US000_23.HTM (Accessed 8/3/2005).

U.S. Department of Housing and Urban Development (HUD). 1994. Regulatory Impact Analysis of Improved Wind Standards for Manufactured Housing. Washington, DC: U.S. Government Printing Office.

U.S. Department of Defense (DOD). 2005. Military Housing 101. http://www.acq.osd.mil/housing/housing101.htm.

U.S. EPA. 2005. *40 CFR Part 745.* RIN 2070-AC83. October.

U.S. EPA. 2005. *Supporting Statement for OMB Review under The Paperwork Reduction Act: TSCA Sections 402/404 Training, Certification, Accreditation and Standards for Lead-Based Paint Activities.* EPA ICR No. 1715.06; OMB 2070-0155.

U.S. Small Business Administration. 2004. "Small Business Size Standards matched to North American Industry Classification System." Available at: http://www.sba.gov/size/sizetable2002.html. (January 21, 2004).

U.S. Small Business Administration. 2005. "Non-Employer Statistics." *Firm Size Data*. Available at: http://www.sba.gov/advo/research/data.html. (Downloaded 8/3/2005).