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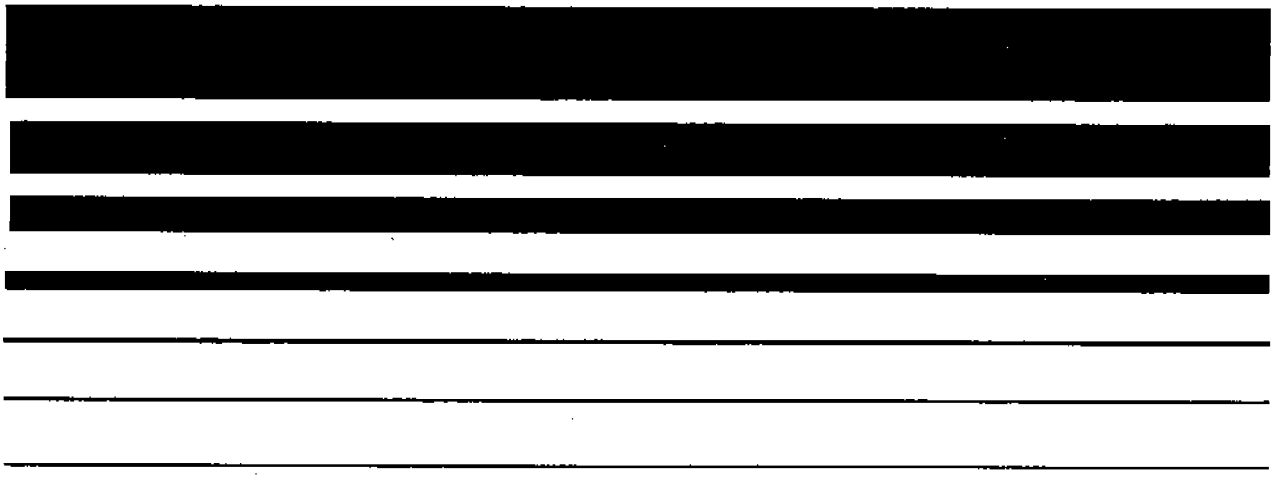
REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR LEAD:

ASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

OAQPS STAFF PAPER



Preface

Though this document was finalized in December 1990, it does not incorporate information from all the potentially relevant studies of lead health effects or exposures that were published after March 1989. However, this document does reflect the complete Lead Criteria Document, comprised of: 1) the Air Quality Criteria for Lead, 1986; 2) the Addendum to the Air Quality Criteria for Lead, 1986; and 3) the Supplement to the 1986 Addendum to the Air Quality Criteria for Lead, 1990.

This report has been reviewed by the Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products is not intended to constitute endorsement or recommendation for use.

REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR LEAD: ASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

OAQPS STAFF PAPER

Air Quality Management Division
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
Research Triangle Park, N.C. 27711

December 1990

Acknowledgments

This staff paper is the product of the Office of Air Quality Planning and Standards. The principal authors include Jeff Cohen, Gail Brion, and John Haines. Technical contributions were provided by David McLamb, Neil Berg, and Neil Frank. THe report incorporates comments from OAQPS, the Office of Research and Development, the Office of General Counsel, and the Office of Drinking Water within EPA, and was formally reviewed by the Clean Air Scientific Advisory Committee.

Helpful comments were also submitted by independent scientists, and by environmental and industry groups including the Environmental Defense Fund, the Lead Industries Association, and the International Lead and Zinc Research Organization.

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EXECUTIVE SUMMARY

This paper evaluates and interprets the available scientific and technical information that the EPA staff believes is most relevant to the review of primary (health) and secondary (welfare) National Ambient Air Quality Standards (NAAQS) for lead and presents staff recommendations on revising the standards. Review of the NAAQS is a periodic process instituted to ensure the scientific adequacy of air quality standards and is required by Section 109 of the 1977 Clean Air Act Amendments. The assessment in this staff paper is intended to help bridge the gap between the scientific review contained in the EPA criteria document "Air Quality Criteria for Lead", its 1986 Addendum and 1990 Supplement, the "Review of National Ambient Air Quality Standards for Lead: Exposure Methodology and Validation" and the judgments required of the Administrator in setting ambient standards for lead. The staff paper is, therefore, an important element in the standards review process and provides an opportunity for public comment on proposed staff recommendations before they are presented to the Administrator.

Human exposure to lead occurs through multiple pathways including: paint pigments, solder in food cans and plumbing, and airborne emissions from motor vehicles and a variety of stationary lead point sources. Over the past decade, there has been a marked decline in lead exposure. Significant dietary declines have resulted from the gradual phaseout of lead in solder and reductions in deposition of atmospheric lead. Additional exposure reductions are expected due to the impact of new drinking water regulations and the continued shrinking leaded gasoline market.

Total lead emissions to air have dropped 94% between 1978 and 1987 resulting in an air lead level of 0.1 to 0.3 $\mu g/m^3$ in most U.S. cities without a major lead point source. Most of

this is directly attributable to the lead-in-gasoline phasedown. Analysis indicated the largest single year drop in average air lead concentrations (42%) occurred between 1985 and 1986 when the lead content in gasoline shifted from 1.0 grams/gallon at the start of 1985, to 0.5 grams/gallon in July 1985, and finally to 0.1 grams/gallon in January 1986. The decline in air lead attributable to leaded gasoline is expected to continue as the leaded gasoline market shrinks.

While these downward trends are encouraging, several important sources of lead exposure persist. The focus of this review is on areas near stationary sources of lead emissions. Although such sources in the past have not made a significant contribution (as compared to lead-in-gasoline) to the overall lead pollution across large, urban or regional areas, lead emissions from such sources can have a significant impact on a local scale; air, and especially soil and dust lead concentrations have been associated with elevated levels of lead absorption in children and adults in numerous lead point source community studies. Exceedances of the current NAAQS (1.5 $\mu g/m^3$) are found only in the vicinity of nonferrous smelters or other point sources of lead.

Primary Standard

The staff has reviewed scientific and technical information on the known and potential health effects of lead cited in the Criteria Document, its 1986 Addendum and 1990 Supplement. This includes information on sensitive populations, mechanisms of lead toxicity, health effects of concern, and relationships between blood lead (PbB), the most commonly used index of exposure, and different health effects of concern. Based on this review, the staff derives the following conclusions and recommendations.

1) Everyone is susceptible to toxic effects from lead. The major subgroups of the population who appear to be especially sensitive are young children, middle-aged men, and pregnant women and their fetuses.

2) Although it remains uncertain whether a common underlying mechanism is involved in the diverse functional impairments produced by lead, it does appear that lead affects biological systems directly, rather than through metabolic transformation, and that there may be no biological threshold for effects of lead ions at subcellular or cellular sites of action.

3) The major low-level effects of concern include:

- Heme biosynthesis and related functions
- Neurological development and function
- Reproduction and physical development
- Kidney function
- Cardiovascular function

4) The critical dose-response findings at low PbB levels are as follows:

- Inhibition of the activity of enzymes involved in red blood cell metabolism, ALA-D and Py-5-N, at 10-15 µg/dl and possibly below, with no evident threshold.
- Interference in heme synthesis indicated by elevated EP (erythrocyte protoporphyrin) levels at 12-23 µg/dl in children, depending on their iron status.
- Interference with vitamin D hormone synthesis in children with no apparent threshold down to the lowest levels measured (12 µg/dl);
- Reduced auditory function in children with no apparent threshold down to the lowest measured levels (4-6 µg/dl);
- Altered electrical brain wave activity with no evident threshold down to 15 µg/dl, and possibly lower;

- Deficits in IQ and other measures of cognitive function (e.g., attention span) in children at PbB levels above 30 µg/dl, and small deficits as low as 15 µg/dl (or possibly lower) in socially disadvantaged children;

- Slowed peripheral nerve conduction at PbB as low as 20-30 µg/dl in children;

- Deficits in mental developmental indices in infants with maternal or umbilical cord PbB levels as low as 10-15 µg/dl.

- Low birth weight and decreased gestational age, which may also influence early neurological development, at maternal PbB levels above 12-14 µg/dl;

- Reduction in early childhood growth with no apparent threshold in one study across the range of 5-35 µg/dl; a threshold at 40 µg/dl was identified in another study;

- Small increases in blood pressure in adult men with no apparent threshold from cross-sectional data down possibly, to 7 µg/dl.

5) There is evidence that lead produces renal tumors in lab animals and lead has been classified a probable carcinogen. While this is of concern, the non-cancer effects at low lead exposure levels are the focus of this staff paper.

The lack of an apparent PbB threshold in several studies is supported by the fact that many of the biochemical changes, or mechanisms, that appear to underlie lead toxicity (e.g., altered enzyme activity, membrane receptors, calcium homeostasis) have been observed at the lowest experimental dosages administered, often with no discernible threshold. There is a great deal of uncertainty regarding the point at which subtle molecular changes individually or collectively, become significant enough that they should be regarded as constituting "adverse" effects for purposes of standard setting under the Clean Air Act. However, such effects clearly become more pronounced (and likely), and broaden

to cause more severe disruptions of the normal functioning of many organ systems, as PbB levels increase. This continuum of effects, from biochemical responses, cellular dysfunction and morphological changes, to organ system alterations and clinical toxicity, makes it difficult to identify clearly what PbB level constitutes an appropriate "threshold", if any, below which there are no significant risks of adverse effects.

The approach taken in this staff paper is to identify those effects that individually or collectively represent an adverse pattern that should be avoided. For children, the collective impact of the effects at PbB levels above 15 µg/dl can be seen as representing a clear pattern of adverse effects worthy of avoidance. At levels of 10-15 µg/dl, there appears to be a convergence of evidence of lead-induced interference with a diverse set of physiological functions and processes, particularly evident in several independent studies showing impaired neurobehavioral function and development. The available data do not indicate a clear threshold at 10-15 µg/dl, but rather suggest a continuum of health risks down to the lowest levels measured. The effects of lead below this range become increasingly difficult to detect and their significance more difficult to determine. For purposes of comparing the relative protectiveness of alternative lead NAAQS, the staff has estimated the percentages of children with PbB levels above 10 and above 15 µg/dl.

While the dose-response information on blood pressure changes in men is less clear than the information on children, the same approximate range of PbB levels can also be considered for assessing risks among adult men. In this staff paper, percentages of middle-aged men with PbB levels above 10 and 12 µg/dl are estimated to compare relative protection afforded by alternative NAAQS.

Quantitative analyses of differences in prenatal lead exposures under alternative lead NAAQS are not done in this review. Although it is likely that there is extensive mobilization of lead, like calcium, during pregnancy, there are no biokinetic data available to quantify this dynamic process. Given the sensitivity of the fetus and neonate, potential risks associated with fetal lead exposures must be considered in determining an appropriate margin of safety for the lead standard. There are approximately 140,000 women of child-bearing age living near major lead point sources whose offspring may be at risk.

Other factors that warrant consideration in evaluating the margin of safety are the significance and persistence of observed or potential health effects, the persistence of lead in the body and in accessible environmental reservoirs (i.e., soil), the sensitivity of exposure analyses to alternative assumptions, and the potential carcinogenicity of lead. It should be considered that for groups that have excessive background exposures, children with pica and/or children living in deteriorated lead-paint homes, any reduction in ambient air lead levels is beneficial. Also other groups, not quantified in this paper, (e.g., post-menopausal women) will also benefit from a reduction in ambient lead levels.

Based on scientific and technical reviews, as well as policy considerations, the staff makes the following recommendations with respect to the primary lead standard.

1) The range of standards for consideration for the primary lead NAAQS should be from .5 to 1.5 $\mu g/m^3$. The results of exposure analyses for children living near three lead smelter sites are summarized in Table 1.

TABLE 1. ESTIMATED CHILDREN'S (0-6 YRS.) PbB LEVELS UNDER ALTERNATIVE LEAD NAAQS IN 3 CASE STUDY ANALYSES: 1990-1996*

Case Study (# Children) / PbB Level[a]	Lead NAAQS Level ($\mu g/m^3$) Baseline[b]	1.5 Quarterly[c]	1.5 Monthly[d]	1.25 Monthly[d]	1.0 Monthly[d]	0.75 Monthly[d]	0.5 Monthly[d]
Dallas (241)							
Mean PbB ($\mu g/dl$)	6.9	4.9	4.8	4.8	4.7	4.6	4.5
% > 10 $\mu g/dl$	14.2	2.2	1.9	1.7	1.5	1.4	1.2
% > 15 $\mu g/dl$	1.3	0.08	0.06	0.05	0.04	0.04	0.03
East Helena (217)							
Mean PbB ($\mu g/dl$)	6.2	5.2	5.1	4.9	4.8	4.6	4.4
% > 10 $\mu g/dl$	8.3	2.9	2.6	2.1	1.7	1.4	1.0
% > 15 $\mu g/dl$	0.6	0.1	0.1	0.07	0.05	0.04	0.02
Tampa (10)							
Mean PbB ($\mu g/dl$)	10.1	8.3	7.8	7.4	7.0	6.6	6.3
% > 10 $\mu g/dl$	50.9	29.7	23.4	19.4	15.6	12.1	9.2
% > 15 $\mu g/dl$	12.9	4.6	3.0	2.2	1.5	1.0	0.6

* Assumes soil Pb remains at baseline levels
[a] PbB distributions calculated assuming GSD = 1.42
[b] Baseline scenario represents current conditions for air quality, as well as soil and dust Pb. Dietary intake assumed to be at 1990-1996 levels
[c] Current NAAQS level and averaging time (calendar quarter)
[d] Alternative NAAQS levels with monthly averaging time

2) A monthly averaging period would better capture short-term increases in lead exposure and would more fully protect children's health than the current quarterly average.

3) The most appropriate form of the standard appears to be the second highest monthly averages in a 3-year span. This form would be nearly as stringent as a form that does not permit any exceedances and allows for discounting of one "bad" month in 3 years which may be caused, for example, by unusual meteorology.

4) With a revision to a monthly averaging time more frequent sampling is needed, except in areas, like roadways remote from lead point sources, where the standard is not expected to be violated. In those situations, the current 1-in-6 day sampling schedule would sufficiently reflect air quality and trends.

5) Because exposure to atmospheric lead particles occurs not only via direct inhalation, but via ingestion of deposited particles as well, especially among young children, the hi-volume sampler provides a reasonable indicator for determining compliance with a monthly standard and should be retained as the instrument to monitor compliance with the lead NAAQS until more refined instruments can be developed.

The analyses summarized in Table 1 omit young children who cannot be substantially affected by any changes in atmospheric lead emissions under different standards. These children (e.g., those with excessive pica and/or living in overtly deteriorated lead-paint homes) total several million and require direct parental and public health intervention to reduce their high-level exposures. Nevertheless, any reduction in air lead levels can be expected to have at least a small beneficial effect on these children and should be considered in establishing the lead NAAQS. Similarly, adult women whose blood pressure is affected by ongoing lead exposure, and women experiencing bone

demineralization during osteoporosis (as well as during pregnancy) and increased lead mobilization, will also benefit from any reduction in ambient air lead levels.

The results from Tampa should not be extrapolated since the secondary smelter and battery plant modeled there were surrounded by mainly non-residential areas and thus only 10 children and 20 men live close enough to these point sources to be significantly effected by changes in emissions. Further analyses are necessary to determine whether these results are applicable to other point source areas with small populations nearby.

Because young children are exposed to, absorb, and retain proportionally more environmental lead than other populations, the staff believes they are most responsive to changes in atmospheric lead emissions and provide sensitive indications of relative protection afforded by alternative NAAQS. Any lead standard designed to protect them should also protect other sensitive groups evaluated quantitatively (adult men) or qualitatively (pregnant women/fetus). Case-study analyses of children populations living near Dallas and East Helena smelters indicate that substantial reductions in lead exposure could be achieved through attainment of the current lead NAAQS. Progressively smaller improvements are estimated for the alternative monthly lead NAAQS levels evaluated, ranging from 1.5 $\mu g/m^3$ to 0.5 $\mu g/m^3$.

According to the best estimate analyses, over 99.5% of children living in areas significantly affected by the smelters would have PbB levels below 15 $\mu g/dl$ if the current standard (1.5 $\mu g/m^3$) were achieved. However, the staff believes that evaluation of alternative standards based on children's PbB levels above 10 $\mu g/dl$ is more appropriate given the health risks associated with lead. Reducing the NAAQS levels would reduce the

estimated proportion of children with PbB levels above 10 μg/dl. For the Dallas and East Helena case studies, assuming a GSD value of 1.42, an estimated 8.3-14.2% of nearby children currently exceed 10 μg/dl, whereas a monthly lead NAAQS of 1.5 $\mu g/m^3$ would reduce this fraction to 1.9-2.6%, and a monthly NAAQS of 0.5 $\mu g/m^3$ would reduce it to 1.0-1.2%. Because of unavoidable background exposures to lead in the diet, historically-contaminated soils and dusts, and maternal bone lead stores in utero, no lead air emission standard can keep all children below a PbB of 10 μg/dl. It is estimated that even with zero air lead emissions, 0.7% of children would have PbB levels above 10 μg/dl and there would be a range of average PbBs from 4.2 to 5.2 μg/dl. Compared to a zero air lead scenario, a NAAQS of 0.5 $\mu g/m^3$ appears to minimize the number of children with PbB levels above 10 μg/dl, the range being from 1.0 to 1.2%. The 0.5 $\mu g/m^3$ NAAQS also appears to be a reasonable lower bound for consideration of a revised lead standard because it would keep more than 99.97% of the exposed children below a PbB of 15 μg/dl. Intermediate increments are indicated for lead NAAQS levels of 0.75, 1.0 and 1.25 $\mu g/m^3$.

While the basis for a decision on the lead standard should be the most sensitive population, i.e., young children, the case-study results on adult men indicated small PbB reductions with progressively lower monthly lead NAAQS levels evaluated, beginning with 1.5 $\mu g/m^3$ down to 0.5 $\mu g/m^3$. A PbB threshold for blood pressure effects in men has not been defined. Two PbB levels, 10 and 12 μg/dl, are selected to compare the relative protectiveness of alternative lead NAAQS. The results indicate that a monthly NAAQS between 0.5 and 1.5 $\mu g/m^3$ would result in between 1.4 - 3.5% of non-occupationally exposed men with PbB levels above 10 μg/dl, compared to 7.2-12.1% at current baseline exposures and 0.6% above 10 μg/dl simply because of non-air background exposure. The percentages above 12 μg/dl for this

range of standards are estimated to be 0.3-0.9%, compared to 0.1% due to background exposures.

SECONDARY STANDARD

The staff review of available laboratory and field data indicate that at high concentrations, lead can:

1) affect certain plants (inhibition of photosynthesis, reduced growth, changes in species composition);
2) affect fish (neurological changes);
3) alter the composition of soil microbial communities and inhibit invertebrate activity resulting in delayed decomposition, reduced nutrient supply, and altered soil properties (lower organic content).

Toxicological data suggests that domestic animals and wildlife are as susceptible to the effects of lead as laboratory animals used to investigate human lead toxicity risks.

The available data also raise concerns about the continued accumulation of lead in soil and sediment reservoirs. Due to the persistence of lead in the environment, such accumulations are expected to continue as long as inputs exceed outputs. Thus, even at relatively low deposition rates, lead could affect an ecosystem over time. This concern is primarily directed to urban and stationary source areas that may already be approaching or have exceeded their soil capacity to bind lead.

Until a stronger data base is developed that more accurately quantifies ecological effects of different lead concentrations, the staff recommends that consideration be given to retaining a secondary standard at or below the level of the current secondary standard of 1.5 $\mu g/m^3$. If the level, averaging time, or form is changed for the primary standard, consideration should be given to making a similar change for the secondary standard to facilitate implementation.

REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR LEAD: ASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

OAQPS DRAFT STAFF PAPER

I. INTRODUCTION

A. Purpose

This paper evaluates and interprets the most relevant scientific and technical information reviewed in the EPA document "Air Quality Criteria for Lead" (EPA, 1986a), the 1986 Addendum to the Air Quality Criteria Document for Lead (1986b), and the 1990 Supplement to the Addendum (EPA 1990), that EPA staff believes is most relevant to the review of the primary and secondary National Ambient Air Quality Standards (NAAQS) for lead. This assessment is intended to help bridge the gap between the scientific review contained in the air quality criteria document and the judgments required of the Administrator in setting ambient standards for lead. Particular emphasis is placed on identifying those conclusions and uncertainties in the available scientific literature that the staff believes should be considered in selecting the averaging times, forms, and levels for the primary and secondary standards. While the paper should be of use to all parties interested in the standards review, it is written for those decision makers, scientists, and staff who have some familiarity with the technical discussions contained in the criteria document, the 1986 Addendum, and the 1990 supplement (hereafter referenced as "CD", "CDA" and the "CDA Supplement", respectively).

A critical element to this review is the assessment of lead exposure from multiple sources, including air, and prediction of lead exposures among sensitive populations under alternative standards. A separate staff report (EPA, 1989a) summarizes

relevant information on lead exposure and presents the exposure modeling methodologies that the staff believes should be considered for the lead NAAQS exposure analysis. Using methodologies described and validated in that report, exposure analyses of populations living near stationary lead sources are presented here to better inform the Administrator of the potential impacts of alternative standards.

B. Background

Since 1970 the Clean Air Act, as amended, has provided authority and guidance for the listing of certain ambient air pollutants that may endanger public health or welfare and the setting and revising of NAAQS for those pollutants. Primary standards must be based on health effects criteria and provide an adequate margin of safety to ensure protection of public health. As several judicial decisions have made clear, the economic and technological feasibility of attaining primary standards are not to be considered in setting them, although such factors may be considered to a degree in the development of state plans to implement the standards (D.C. Cir., 1980, 1981). Further guidance provided in the legislative history of the Act indicates that the standards should be set at "the maximum permissible ambient air level . . . which will protect the health of any [sensitive] group of the population." Also, margins of safety are to be provided such that the standards will afford "a reasonable degree of protection . . . against hazards which research has not yet identified" (Committee on Public Works, 1974). In the final analysis, the EPA Administrator must make a policy decision in setting the primary standard, based on his judgment regarding the implications of all the health effects evidence and on the requirement that an adequate margin of safety be provided.

Secondary ambient air quality standards must be adequate to protect the public welfare from any known or anticipated adverse

effects associated with the presence of a listed ambient air pollutant. Welfare effects, which are defined in section 302(h) of the Act, include effects on vegetation, visibility, water, crops, man-made materials, animals, economic values and personal comfort and well-being. In specifying a level or levels for secondary standards the Administrator must determine at which point the effects become "adverse" and base his judgment on the welfare effects criteria.

The current primary standard for lead (to protect public health) is 1.5 micrograms per cubic meter ($\mu g/m^3$), maximum arithmetic mean averaged over a calendar quarter. The current secondary standard for lead (to protect public welfare) is identical to the primary standard. For both primary and secondary standards, lead and its compounds are measured as elemental lead and currently are collected using a high volume air sampler.

C. Approach

The approach used in this paper is to assess and integrate information derived from the criteria review and the OAQPS staff exposure report (EPA, 1989a) in the context of those critical elements that the staff believes should be considered in the review of the primary and secondary standards. Particular attention is drawn to those judgments that must be based on the careful interpretation of incomplete or uncertain evidence. In such instances, the paper states the staff's evaluation of the evidence as it relates to a specific judgment, sets forth appropriate alternatives that should be considered, and recommends a course of action.

Since the original lead NAAQS was established in 1978, the use of lead in gasoline has dropped dramatically. As a result, controlling and monitoring air lead emissions has shifted from an area-wide problem to one of specific, localized sources. Accordingly, the focus of this paper is on the effects of inorganic lead, either airborne or deposited from the air onto

dusts, soils, vegetation, food, and water, from point sources of lead. The multi-media aspects of lead exposure, related to both air and non-air sources, are addressed in the staff exposure report (EPA, 1989a). Hazardous concentrations of lead in and around lead-based painted housing and in soils with historical accumulations will remain persistent problems not significantly diminished by any change in ambient air emissions. Such hazards will require further coordinated public health intervention measures by parents and appropriate governmental activities.

Section II summarizes information on current air lead exposures; information on other routes of exposure is presented and incorporated into exposure modeling methodologies in EPA (1989a). Section III addresses the critical elements in the review of the primary standards including: 1) identification of the most sensitive population groups; 2) mechanisms of toxicity; 3) health effects of concern; and 4) dose-response information relating the health effects of concern to lead exposures. Drawing on information presented in Sections II and III and the OAQPS staff exposure report (EPA, 1989a), Section IV identifies and assesses the critical elements the staff believes should be considered in selecting an averaging time, form, and level of the primary standard. Results from exposure analyses described in the staff exposure report are presented in Section IV that include estimated blood lead distributions in sensitive populations under alternative lead NAAQS. Staff conclusions regarding alternative policy options in each of these areas are also presented.

Section V examines relevant information on the welfare effects of lead and presents the staff recommendation concerning the secondary standard.

II. AIR QUALITY AND LEAD EXPOSURE CONSIDERATIONS

Human exposure to lead occurs through multiple pathways, and can be traced primarily to lead in paint pigments, solder in canned foods and plumbing, and atmospheric emissions from motor vehicles and stationary lead sources. Although airborne lead is a principal starting point of environmental contamination, oral intake of deposited atmospheric lead is often the primary identifiable factor in predicting blood lead levels, particularly in young children. It is necessary, therefore, to assess not only human exposures through direct inhalation of lead containing particles, but also the ingestion of lead deposited onto soil, dusts, vegetation and other environmental surfaces. The principal pathways of human exposure can be seen in Figure 2-1.

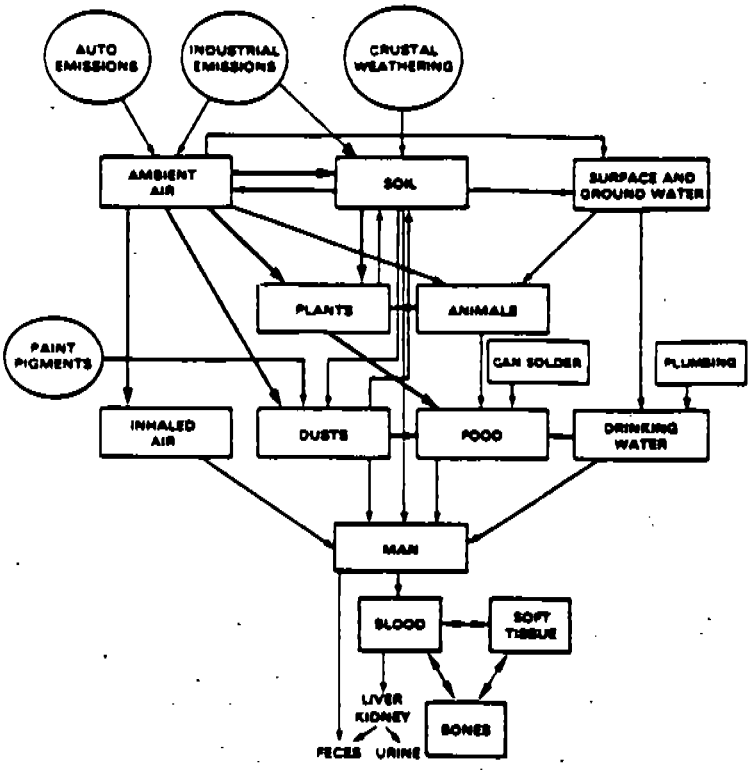

Figure 2-1. PRINCIPAL PATHWAYS OF HUMAN EXPOSURE TO LEAD AND SUBSEQUENT PHYSIOLOGICAL DISTRIBUTION. ADAPTED FROM CD, FIGURE 7-1.

The OAQPS staff exposure report (EPA, 1989a) discusses the relevant information on the principal pathways of lead exposure: airborne lead, and lead in soil, dust, diet, water and paint. As detailed in that report and the CD, there have been marked downward trends in lead exposure from several sources. For example, total lead emissions to air dropped 94% between 1978 and 1987 (see Table 2-1 and Figure 2-2). Most of this decline is attributable to reductions in gasoline lead consumption, which has dropped by about 90% since 1978. This trend will continue as compliance with the 1986 gasoline phasedown regulations progresses, and as the fleet of lead-burning cars shrinks. In addition, lead emissions from stationary sources have been substantially reduced by control programs oriented toward attainment of the particulate matter and lead NAAQS. In 1987, lead emissions from industrial sources (e.g., primary and secondary smelters) dropped by more than one-half from levels reported in the late 1970's (EPA, 1989c). Emissions of lead from solid waste disposal are down 35% since the late 1970's but now represent the second largest category of total air lead emissions behind transportation. If emissions from sewage sludge incineration were included, the two categories would be nearly equal. While aggregate solid waste emissions are relatively high because of the numerous sources, local air quality impacts from individual incinerators are generally low, particularly compared to major stationary industrial sources.

The overall effect of the different control programs has been paralleled by a major reduction in ambient air lead levels, which now average between 0.1 and 0.3 $\mu g/m^3$ in most U.S. cities without major point sources. Recent (1980-1986) air quality data for both point source-oriented sites (predominantly "SLAMS" sites), roadside sites ("NAMS", micro-scale) and other sites (middle-scale, neighborhood), are summarized in Table 2-2 (Battye, 1988a). By 1986, the only quarterly average concentrations over 1.5 $\mu g/m^3$ were recorded at monitors near stationary sources. Twelve counties in the U.S. reported

TABLE 2-1. NATIONAL AIR LEAD EMISSION ESTIMATES, 1978-1987

(thousand metric tons/year)

Source Category	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987
Transportation	112.4	94.6	59.4	46.4	46.9	40.7	34.7	15.5	3.5	3.0
Fuel Combustion	6.1	4.9	3.9	2.8	1.7	0.6	0.5	0.5	0.5	0.5
Industrial Processes	5.4	5.2	3.6	3.0	2.7	2.4	2.3	2.3	1.9	2.0
Solid Waste *	4.0	4.0	3.7	3.7	3.1	2.6	2.6	2.8	2.7	2.6
Total	127.9	108.7	70.6	55.9	54.4	46.3	40.1	21.1	8.6	8.1

NOTE: The sums of sub-categories may not equal total due to rounding.
SOURCE: EPA, 1989c
* Does not include lead emissions from sewage sludge incineration which currently amounts to 0.2 - 0.3 thousand metric tons per year.

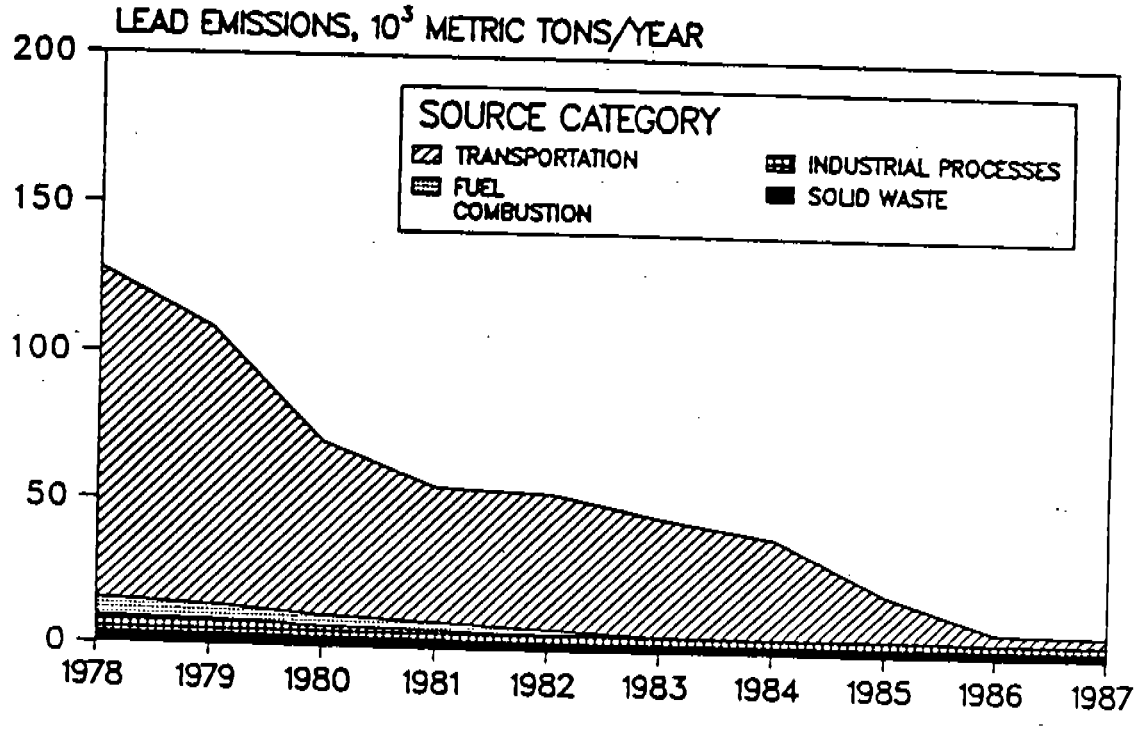

Figure 2-2. NATIONAL TREND IN AIR LEAD EMISSIONS, 1978 - 1987 (from EPA, 1989c)

quarterly averages above 1.5 $\mu g/m^3$ in the 1986-1987 period; 13 more were on the margin of exceeding the NAAQS but either had inadequate numbers of samples or were slightly below the standard level.

Trends in maximum quarterly averages for 97 urban- and 24-point source sites over 10 years (1978-1987) are illustrated in Figure 2-3. Data selected for this trends analysis had to satisfy data completeness criteria of at least 8 out of 10 "valid" years of data in the 1978-1987 period. A year was included as valid if at least 3 of the 4 quarterly averages were available (EPA, 1989d). Some of the dramatic improvement in air quality near point sources is attributable to plant shutdowns. Average air lead trends were also studied over the shorter period 1983-1987 to include more monitoring sites (1989c). This analysis indicated that the largest single year drop in average lead concentrations, 42 percent, occurred as expected between 1985 and 1986, because of the shift from 1.0 grams/gallon of lead in leaded gasoline for the first half of 1985 to 0.5 grams/gallon of lead in July 1985, and finally to 0.1 grams of lead/gallon on January 1, 1986. Average lead concentrations in 1987 declined by 19% from 1986 levels. This trend is expected to continue primarily because the leaded gasoline market will continue to shrink. Some major petroleum companies have discontinued refining leaded gasoline because of the dwindling market.

There have also been significant declines in dietary lead intake as a result of the gradual phaseout of lead solder in canned food manufacturing, and reductions in atmospheric deposition as ambient lead levels have declined (Section II.E; EPA, 1989a). Additional reductions are expected as the recent ban of lead solder in plumbing takes effect and compliance with a revised National Primary Drinking Water Regulation for lead occurs within the next few years. These recent and anticipated changes in nationwide exposures, and other expected future trends in contributions from non-air sources of lead (e.g., contaminated

TABLE 2-2. FREQUENCY DISTRIBUTION OF MAXIMUM QUARTERLY AIR LEAD CONCENTRATIONS ($\mu g/m^3$)[a]

Site type/time frame	Percentage of sites in concentration ranges (concentrations in $\mu g/m^3$) <0.5	0.5-1.0	1.0-1.5	1.5-2.0	>2.0	Mean	Number of site-years
1980 through 1986							
All monitors[b]	77.5	15.4	3.2	1.5	2.3	0.39	3,279
NAMS[c]	76.9	17.2	4.7	1.1	0.2	0.41	471
SLAMS	75.4	16.7	2.8	1.7	3.4	0.38	1,158
Microscale roadside[d]	24.1	37.9	25.9	10.3	1.7	0.74	58
Middle scale	45.7	47.1	7.1	0.0	0.0	0.46	70
Neighborhood scale	68.7	24.3	7.0	0.0	0.0	0.37	115
1986 only							
All monitors	93.0	2.5	1.2	1.6	1.8	0.17	514
NAMS	97.5	1.3	1.3	0.0	0.0	0.14	79
SLAMS	92.9	2.2	0.9	1.3	2.7	0.21	226
Microscale roadside	100.0	0.0	0.0	0.0	0.0	0.18	9
Middle scale	100.0	0.0	0.0	0.0	0.0	0.12	9
Neighborhood scale	94.4	0.0	0.0	5.6	0.0	0.14	18
1987 only							
All monitors	93.0	2.8	1.7	0.4	2.0	0.20	458
NAMS	97.4	0.0	1.3	0.0	1.3	0.20	78
SLAMS	93.1	2.3	1.7	0.0	2.9	0.20	175

[a]Data are from the SAROAD and AIRS systems and represent the number of site-years for which the maximum quarterly concentration fall within the designated ranges. To be included, a valid site-year must have at least three quarters of data with at least 6 observations per quarter.

[b]Includes sites previously classified into categories (e.g., "urban") that do not meet any of the current definitions.

[c]NAMS refers to the National Ambient Monitoring Station network, while SLAMS refers to the State and Local Ambient Monitoring Station network. Each of these two networks includes both roadside and point source monitors; however, in the case of lead, the NAMS network tends to focus on roadside sites, while the SLAMS network incorporates more point sources and other special purpose monitors.

[d]Microscale sites were within 5-15 meters from a major roadway. Middle scale sites had further setbacks and define concentrations up to several city blocks. Neighborhood scale sites define concentrations in more extended areas of uniform land use within cities (0.5-4 km^2). After 1986, data collection at these sites stopped.

Source: Battye (1988a)

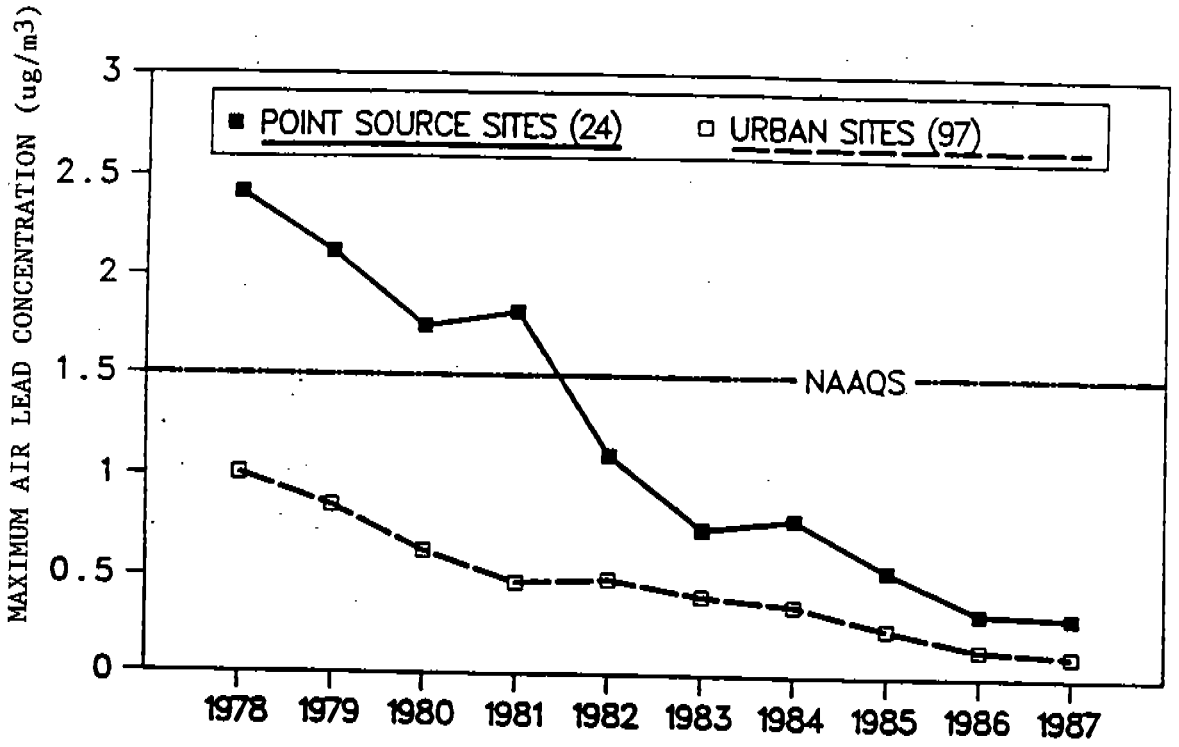

FIGURE 2-3. TRENDS IN MAXIMUM QUARTERLY AIR LEAD CONCENTRATIONS FOR URBAN AND POINT-SOURCE ORIENTED MONITOR SITES (EPA, 1989c)

soils and dusts), are important considerations in estimating lead exposures among sensitive populations under alternative lead NAAQS (see Section IV.C).

While these downward trends are encouraging, several important sources of lead exposure persist. Lead-based paint continues to be the major source of high-dose lead exposure and symptomatic lead poisoning for children in the U.S. As discussed in Section III.A, children excessively exposed to lead-based paint cannot be protected by a lead NAAQS and quantitative exposure analyses for them will not be presented in this paper. Similarly, soils contaminated by a long history of atmospheric lead deposition will remain a potential hazard around roadways and closed industrial facilities and will not be substantially affected by changes in the lead NAAQS.

The focus of this review is on areas near stationary sources of lead emissions. Although such sources in the past have not made a significant contribution (as compared to lead-in-gasoline) to the overall lead pollution across large, urban or regional areas, lead emissions from such sources can have a significant impact on a local scale; air, and especially soil and dust lead concentrations have been associated with elevated levels of lead absorption in children and adults in numerous lead point source community studies (CD, Chapter 11). Figure 2-4 displays the maximum quarterly average air lead concentrations in the nation. Exceedances of the current NAAQS (1.5 $\mu g/m^3$) are found only in the vicinity of nonferrous smelters or other point sources of lead. When assessing the available air quality data, it is important to recognize that up to this time, the focus of the monitoring networks has been on mobile rather than stationary sources of lead. Thus the available data may under-represent or understate stationary source problems.

High lead concentration levels which are found around lead smelters in particular, result mainly from fugitive emissions

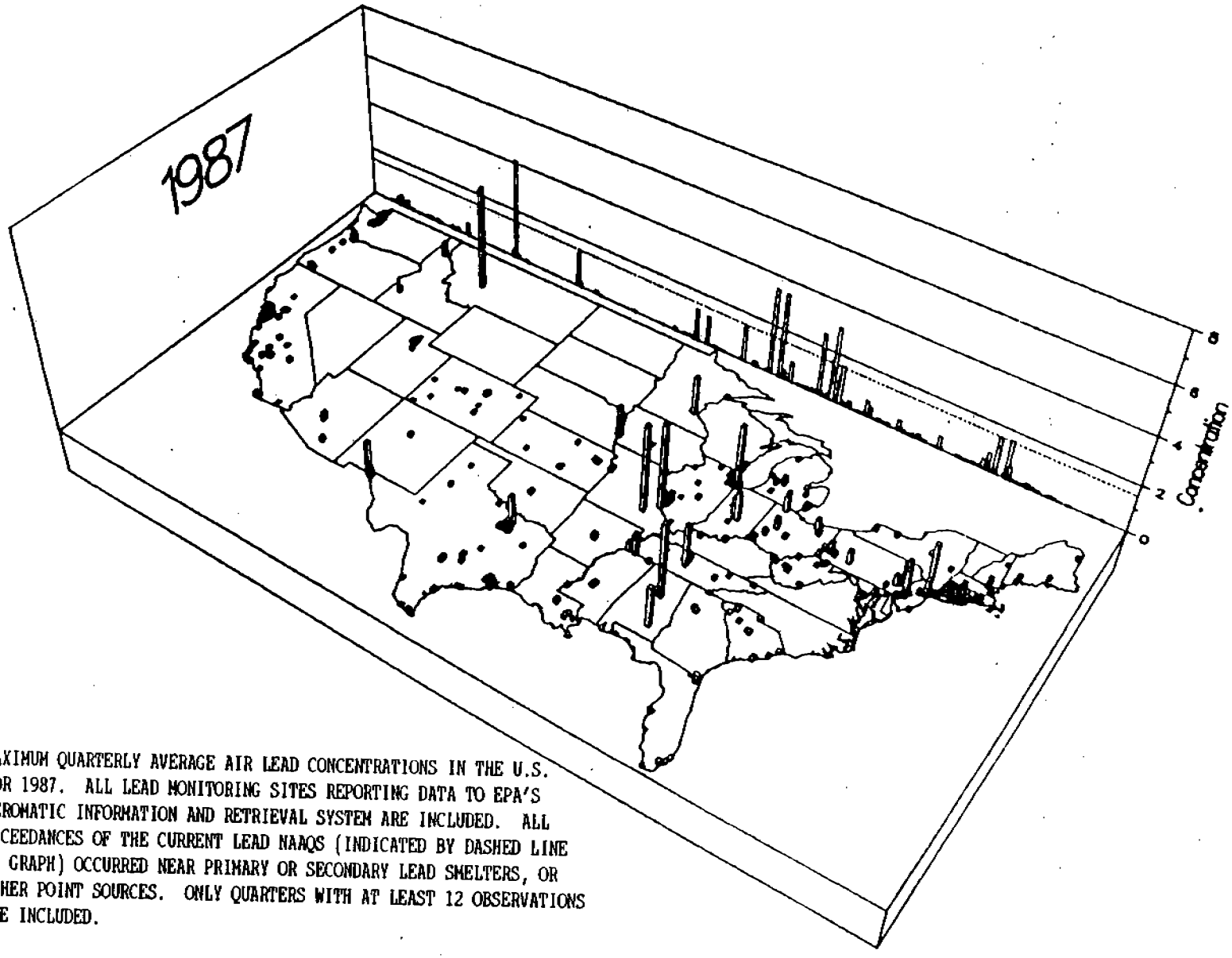

Figure 2-4. MAXIMUM QUARTERLY AVERAGE AIR LEAD CONCENTRATIONS IN THE U.S. FOR 1987. ALL LEAD MONITORING SITES REPORTING DATA TO EPA'S AEROMATIC INFORMATION AND RETRIEVAL SYSTEM ARE INCLUDED. ALL EXCEEDANCES OF THE CURRENT LEAD NAAQS (INDICATED BY DASHED LINE ON GRAPH) OCCURRED NEAR PRIMARY OR SECONDARY LEAD SMELTERS, OR OTHER POINT SOURCES. ONLY QUARTERS WITH AT LEAST 12 OBSERVATIONS ARE INCLUDED.

predominately made up of large (> 7 micrometers, or μm) lead particles resulting from materials handling, furnace upsets, and furnace charging and tapping operations (Landrigan et al., 1975; Jennett et al., 1977; Battye et al., 1985). Beyond the immediate area (≈2 km) of lead stationary sources, process emissions from stacks, predominant as lead sulfates and oxides with a size range between 1 and 10 μm, become the major source of lead in soils and air (Dorn et al., 1976; Roels et al., 1980; Davidson and Osborn, 1984). A recent study of controlled process emissions from three non-ferrous smelters (1 zinc, 1 lead, and 1 copper smelter) reported that the mass median aerodynamic diameters (MMAD) of process particulate emissions are near 1 μm or less (Bennett and Knapp, 1989).

Size-specific data collected near primary and secondary smelters and battery plants indicate approximately 25% of ambient lead particle mass is less than 2.5 μm MMAD, 20% is between 2.5 and 15 μm, 40% is between 15-30 μm, and 15% is larger than 30 μm (Cohen, 1987). It should be noted, however, that for every lead smelter, refiner, or manufacturer, the particle size distribution will be unique to that facility depending on the proportions and types of fugitive and controlled emissions present.

Because of fugitive emissions and process operating parameters, air quality levels in close proximity of stationary sources can vary significantly day-to-day. While daily sampling data in the vicinity of major sources is sparse, one monitor near (100 meters) a lead refinery in Omaha was operated on a daily basis during 1984. Figure 2-5 illustrates the day-to-day variation in observed air quality levels for the three month period of July, August, and September 1984.

Other months of the year displayed similar variations, but July-September was chosen as representative of a period of usual plant operations. It is interesting to note that despite the high daily peaks, the quarterly average air lead concentration

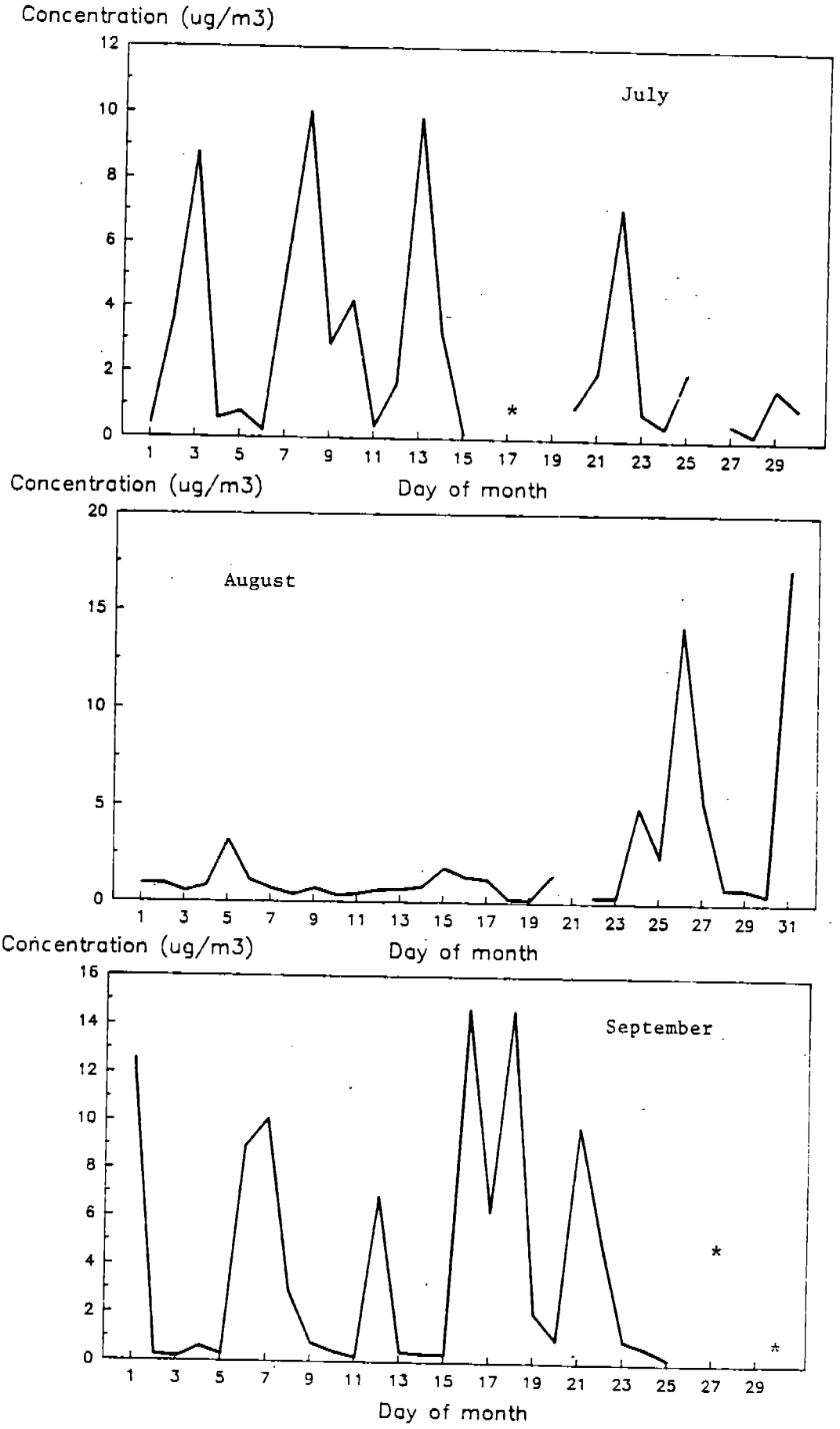

FIGURE 2-5. DAILY VARIABILITY OF AMBIENT LEAD CONCENTRATION AT OMAHA REFINERY, JULY, AUGUST, SEPTEMBER, 1984

* Denotes where data are discontinuous

for the period, composed of 1-in-6 day (1/6) samples, was 1.51 $\mu g/m^3$ which would demonstrate attainment of the current NAAQS. If all of the available daily data are used for this quarter, the average concentration is 2.84 $\mu g/m^3$. The air quality monthly averages, composed of 1/6 day sampling for this quarter are .832, .65, and 3.05 $\mu g/m^3$, respectively. However, when computing monthly averages, the 1/6 day average is not always less than an average computed from all available daily data. Several monthly averages from this data set show larger 1/6 day averages than averages comprised of daily samples. For example, the month of May had a monthly average of 5.07 based on 1/6 sampling and a monthly average of 2.44 based on daily sampling. Three other months that year displayed a similar but less extreme pattern. As this illustrates, the degree of daily variability in air lead levels around major lead point sources, coupled with the available data on particle size distributions, has important implications when considering the appropriate averaging period, form, and sampling methodology for the lead NAAQS. These issues are discussed more fully in Section IV.

III. CRITICAL ELEMENTS IN THE REVIEW OF THE PRIMARY STANDARD

To characterize and assess risks associated with alternative lead NAAQS, information is necessary on: a) sensitive populations; b) mechanisms of lead toxicity; c) health effects of concern; d) relationships between blood lead (i.e., "dose") and different health effects (i.e., "response"); and e) the effects of alternative lead NAAQS on blood lead distributions among the sensitive populations. As part of the current lead NAAQS review, OAQPS staff is estimating blood lead responses under different standards using methods that account for past, current, and future exposures to lead in food, water, soil, dusts, and air, and the cumulative effects of lead in the environment as well as in different tissues within the body. A separate staff report has been prepared to ensure that complex multi-media modeling methodologies are fully documented and reviewed (EPA, 1989a). The exposure methodologies described in that supplemental report have been used to predict, under alternative lead NAAQS, blood lead distributions in populations living near lead point sources. Results of three "case studies" are presented in Section IV.C. This section summarizes information on the other critical elements needed to determine a primary lead NAAQS.

A. Sensitive Population Groups

Lead is harmful to any exposed organism. At least three populations have been identified as especially sensitive: pre-school age children, pregnant women--as exposure surrogates for the fetus, and middle-aged men. Several factors predispose young children to lead-related risks: 1) normal mouthing behavior (e.g., finger licking and immature dietary habits), as well as abnormal ingestion of non-food items ("pica"), which can result in excessive ingestion of lead-contaminated soils and dusts; 2) greater lead absorption and retention rates; 3) greater prevalence of nutritional deficiencies which enhance

gastrointestinal lead absorption; 4) relatively greater proportion of lead body burden in labile pools (e.g., soft tissues) rather than in slow exchange pools (e.g., dense bone matrix) compared to adults; 5) a less developed blood-brain barrier that can allow greater entry of lead into the brain; and 6) an inherently greater physiological sensitivity of developing tissues and organs, as indicated by heightened hematological and neurological responses to lead among children.

Physiological sensitivity to lead is also high during fetal development when the central nervous system is undergoing its most pronounced growth. Persistent effects on neurological function have been observed following in vitro lead exposure in experimental animals. Early developmental impairments associated with fetal exposure have been found in several human longitudinal studies (see Section III.D.2). The pregnant woman is considered sensitive not only because of risks of delivery complications, but because she is the exposure vehicle for the fetus since lead is readily transferred across the placenta. As discussed in the lead exposure staff report (EPA, 1989a), blood lead estimates for pregnant women will not be made under alternative lead NAAQS in this review. This decision was made jointly by EPA staff and the CASAC subcommittee on the lead NAAQS exposure modeling (see Appendix E; EPA, 1989a) because of the lack of biokinetic data for pregnancy that could be used to estimate the distribution of lead among tissues (including fetal) during this complex and dynamic metabolic period. As discussed in Section IV.C., after accounting for the relative contributions to the fetus of maternal bone lead stores versus contemporaneous environmental exposures to young children, it appears reasonable to consider children as the most sensitive group for purposes of this review.

Blood lead has been found in some recent studies to be a small, but significant factor in predicting blood pressure in adult men (see Section III.D.5.), and to a lesser extent in adult women (Schwartz, 1989), including pregnant women (Rabinowitz et

al., 1984). In the largest of these studies, the association was strongest in white males, ages 40-59 years (Pirkle et al., 1985). Because black men are in general more susceptible to blood pressure changes, the impacts of alternative lead NAAQS on blood lead distributions for both white and black middle-aged men will be presented.

Post-menopausal women also appear to be at increased risk due to major changes in mineral metabolism and in bone lead mobilization (Silbergeld et al., 1988); at this time, there are insufficient data to quantify their risks under alternative standards.

Estimated numbers of the three sensitive population subgroups and total populations living around major, operating lead point sources are given in Table 3-1. Populations living within 5 kilometers (km) of 5 primary lead smelters and 1 primary refinery, within 2 km of 23 secondary lead smelters, and within 1 km of 87 lead-acid battery plants were estimated using U.S. Census Bureau-defined block groups or enumeration districts (Battye, 1988b). These distances were selected to include all areas affected by emissions resulting in air lead levels of at least 0.25 $\mu g/m^3$ from the different sources, and not necessarily the high-impact areas. In the exposure modeling discussed in Section IV.C, only populations exposed to air-lead levels at least as high as 0.4 $\mu g/m^3$ are analyzed.

Many more Americans can be identified as especially susceptible to lead toxicity because of excessive exposures to lead in paint, drinking water, and contaminated soil from historical deposition. It is estimated that in 1980, between 6.2 and 13.6 million children under age 7 lived in homes containing hazardous levels of lead in paint surfaces, as defined by CDC, with between 235,000 to 840,000 of them residing in unsound housing conditions (e.g., peeling paint, cracked plaster) (Pope, 1986). Lead-based paint, in combination with poverty, poor

TABLE 3-1. POPULATIONS LIVING NEAR MAJOR U.S. LEAD POINT SOURCES*

SOURCE TYPE (Number Operating)	Total Population	Children[a]	Women of Child-Bearing Age[b]	Adult Men[c]
Primary Smelters and Primary Refinery (6)	136,265	14,649	32,700	13,052
Secondary Smelters (23)	114,301	12,165	27,471	10,965
Battery Plants (87)	322,000	34,269	77,400	30,890

*Distances given in text. Point sources operating as of February, 1988.
[a]Children 0-6 years of age.
[b]In any given year, pregnant women comprise about 7% of all women of child-bearing age (15-44 years).
[c]Adult men 40-59 years of age are focused on because the relationship between blood pressure and PbB appears strongest in that age group. Significant associations have been found, however, for all ages of adult men and women (>20 years of age).

nutrition, and parental stresses and limitations, will continue to be the major source of lead toxicity during the coming decades (Chisolm, 1984; Schneider and Levander, 1986). In addition, as many as 290,000 children may receive enough lead from drinking water via either old plumbing or new lead-soldered plumbing to elevate their blood lead levels to toxic levels (ATSDR, 1988). The numbers of children exposed to potentially hazardous levels of lead in contaminated soils and dusts from historical deposition is difficult to quantify, but likely represents a significant fraction of those living near busy roadways, old housing, and old industrial facilities.

Even the most stringent lead NAAQS cannot be expected to sufficiently reduce health risks in these groups exposed excessively to "non-air" sources of lead and no attempt will be made in this paper to predict their exposures under different air lead scenarios. To abate existing hazards and regulate high intensity exposure sources, better interagency (EPA, FDA, HUD, HHS) coordination to address total lead exposure from multiple sources is needed, as well as a commitment for housing inspection and enforcement, parental education, incentives for property owners, and continued lead screening and research programs.

Although the potential effects of alternative lead NAAQS on some of the other sensitive groups are not evaluated quantitatively, risks related to lead exposure among these groups will be considered in establishing the margin of safety.

B. Mechanisms of Toxicity

The toxicological impact of environmental lead can be the cumulative product of continuous low-level exposure, or of single or repeated acute exposures. Adverse effects are due essentially to the mobile fraction of absorbed lead within the body. A major determinant of toxicity is the distribution of lead among binding proteins and compartments that contain susceptible enzyme systems or other target sites (Raghavan et al., 1981; Silbergeld, 1983).

On a larger scale, the selective accumulation of lead in the heart, kidney cortex, liver, and particularly in the brain during the early stages of pre- and post-natal life may be associated with the sensitivity of these organs to lead. The effects of lead on subcellular structures and processes result in biochemical derangements common to, and affecting, many tissues and organ systems. These biochemical alterations can be linked to the diverse types of lead-based functional disruptions of organ systems that operate in a coordinated, interdependent way.

One molecular basis underlying lead's toxicity in various human tissues is believed to be its ability as a metallic cation to bind with specific biochemical ligands, such as sulfhydryl, amino, and carboxyl groups, which are present in biomolecular substances crucial to normal physiological functions (Moore et al., 1980). Another fundamental mechanism and early manifestation of lead toxicity common to diverse cell types is related to perturbations in intracellular calcium ion homeostasis (Pounds et al., 1982). Lead alters calcium mediated cellular processes and may mimic calcium in binding to various regulatory proteins (Haberman et al., 1983). These disturbances in turn interfere with a constellation of biochemical events, summarized below, which appear to contribute to the more obvious manifestations of lead toxicity.

1. Alteration of enzyme activity

Lead inhibits at least two enzymes in the heme biosynthetic pathway, delta-aminolevulinate dehydrase (ALA-D) and ferrochelatase (Chisolm, 1981), as well as several enzymes and cofactors involved in maintaining the structural integrity of red blood cells and protecting them against oxidation -- Na^+, K^+-activated adenosine triphosphatase (Na^+, K^+ - ATPase), pyrimidine-5'-nucleotidase (Py-5-N), superoxide dismutase, and glutathione (Hasan et al., 1967; Secchi et al., 1973; Angle et al., 1975; Valentine et al., 1976; Levander et al., 1980; Gelman et al., 1978). Altered synthesis of tetrahydrobiopterin and activity of protein kinase C and brain adenyl cyclase (associated with neurochemical receptors; see below) has also been reported

with lead *in vitro* and *in vivo* at low concentrations (Purdy et al., 1981; McIntosh et al., 1985; Nathanson and Bloom, 1975; Markovac and Goldstein, 1988a,b).

2. Altered cellular energy metabolism and ion transport

Energy metabolism occupies a central position in all biologic processes. Substantial interference with one or more steps in cellular energetics can have immediate and severe effects on the usual functioning of a cell, tissue, or organ. Mitochondrial structure and a variety of its functions in energy metabolism are very sensitive to lead, particularly in rapidly developing tissues in the young (Bull et al., 1979). Effects including uncoupled oxidative phosphorylation (Goyer and Moore, 1974), inhibited substrate oxidation, and changes in mitochondrial membrane permeability and transport of ions, (especially calcium, sodium, and potassium), occur at levels of lead as low as 15 micromolar in intact cellular systems (Holtzman et al., 1977; Bull, 1980; Van Rossum et al., 1985).

3. Competition with ions for essential binding sites and altered neurochemistry

Lead absorption, distribution, and retention is known to vary depending on dietary intake of calcium, iron, copper, and zinc, as well as other nutrients (e.g., protein, fat, vitamin D) (Mahaffey and Michaelson, 1980). In addition, increased susceptibility to the toxic effects of lead on heme synthesis and on neurological function has been associated with deficiencies in calcium, iron, copper, and zinc (Mahaffey-Six and Goyer, 1970, 1972; Klauder and Petering, 1977; Cerklewski and Forbes, 1976). These metabolic interactions can be expected among elements that share common chemical properties and compete for common metabolic binding sites, such as the mucosal proteins responsible for absorption and transport across the intestinal wall, and on specific intracellular enzymes.

Lead-induced alteration of cellular calcium homeostasis has been observed at lead concentrations as low as 50 micromolar, either by direct competition at receptor binding sites (Barton et

al., 1978; Ong and Lee, 1980; Habermann et al., 1983), or indirectly by reducing energy production and impairing mitochondrial and cell membrane transport "pumps" (Pounds et al., 1982). This could disturb multiple cell functions of different tissues that depend upon calcium as a messenger of hormonal and electrical stimuli, or as a modulator of cyclic nucleotide metabolism (Rasmussen and Waisman, 1983; Rosen, 1983). For example, low levels of lead inhibit the calcium-mediated regulation of pyruvate kinase activity essential to hepatic glycolysis (Pounds et al., 1982), and some calcium-dependent neurotransmission which regulates the propagation of nerve impulses in the brain (Silbergeld et al., 1977; Silbergeld and Adler, 1978), as well as peripheral neuromuscular junctions (Cooper et al., 1984). A wide range of linkages between lead's impact on calcium and energy metabolism, and altered functional activity and developmental delays in the kidney, liver, brain, cardiovascular system, and smooth muscle have been proposed (Bull et al., 1979; McCauley et al., 1979; Silbergeld, 1983; Pounds et al., 1982).

Besides competition with calcium at synaptic binding sites, other mechanisms by which lead at low doses may alter the functioning of neurotransmitter pathways (see CD, Table 12-7) include: 1) inhibition in the brain of the enzymes (Na,K)-ATPase, which helps maintain the ion distribution about the cellular membrane required for neuronal activity (Vallee and Ulmer, 1972), and adenyl cyclase, which regulates cyclic AMP metabolism and synaptic transmission (Nathanson and Bloom, 1975); 2) inhibition of sodium-dependent neurotransmitter uptake (Silbergeld and Goldberg, 1975); 3) impairment of cerebellar and cerebral energy metabolism (Holtzman et al., 1978; Bull et al., 1979); 4) altered metabolism of tetrahydrobiopterin, which helps control the synthesis of the neurotransmitters dopamine and norepinephrine (Purdy et al., 1981; McIntosh et al., 1985); 5) altered GABA neurotransmission, linked to either inhibition of heme synthesis in brain and an accumulation of ALA, altered glutamate metabolism, or lead-induced increase in zinc concentrations in the brain (Sassa et al., 1979; Silbergeld and

Lamon, 1980; Regunathan and Sundaresan, 1985; Baraldi et al., 1985); 6) reduced heme levels in the liver that appear to indirectly alter associated activity in the brain of the amino acid, tryptophan, and the transmitter to which it contributes, serotonin (Litman and Correia, 1983); 7) altered levels of endogenous opiate (e.g., endorphin) and increased sensitivity of brain opiate receptors which may directly affect motor functions (Memo et al., 1981; Baraldi et al., 1985); 8) increased axonal growth and innervation in adrenergic neural pathways in the brain (Freedman et al., 1988); 9) retarded development of other dendritic and axonal connections (Petit and Alfano, 1983) and of neural support cells (Ohnishi and Dyck, 1981; Scott and Lew, 1986).

Most of the above in vitro findings were elicited by micromolar concentrations of lead. Recently, picomolar concentrations of lead were reported to mimic calcium and activate brain protein kinase C, a regulatory enzyme localized in presynaptic terminals and brain microvessels and critical to neurotransmission, neuronal growth and differentiation, and the integrity of the blood-brain barrier (Markovac and Goldstein, 1988a,b). Although this enzyme is only one of several potential mediators of lead toxicity, this finding is important given that cellular concentrations of lead would be expected to be in the picomolar range in humans with typical blood levels today (i.e., 5-25 µg/dl) (Markovac and Goldstein, 1988a). Lead-induced activation of membrane-bound protein kinase C in red blood cells has also been hypothesized to mediate the enhanced vascular reactivity, and in turn, increased blood pressure, associated with lead exposure (Chai and Webb, 1988).

These different effects on neurotransmitter function may reflect either a different accumulation of the metal within distinct anatomical regions or differences in the mechanisms regulating synthesis, release and uptake of the neurotransmitters involved in various brain areas (Collins et al., 1984; Lucci et al., 1981). It is apparent, however, that the type of

neurotransmitter receptor changes induced by lead is determined by the developmental phase during which exposure occurs (Roussouw et al., 1987).

In summary, it remains uncertain whether a common underlying mechanism is involved in the diverse functional impairments produced by lead. It does appear, however, that lead affects biological systems directly rather than through metabolic transformation, and that if present, there may be no biological threshold for effects of lead ions at subcellular or cellular sites of action. The factors that determine the distributions and ultimate availability of lead at these many sites are poorly understood. Thus external exposure levels or internal circulating levels (blood lead concentrations) of lead sufficient to achieve subcellular or cellular concentrations associated with biochemical changes described above remain to be defined.

C. Effects of Concern

Lead is a poison with no known normal function in the body. Lead produces physiological, and ultimately, pathological effects in a variety of tissues and organ systems across a broad range of exposure levels. Evidence for such effects is drawn from in vitro, animal toxicological, and human clinical and epidemiological studies. Based on these data, summarized in the CD (Chapter 12), the 1986 CDA and the 1990 CDA Supplement, relatively low-level effects in the following areas are of primary interest:

1) heme biosynthesis and related functions
2) neurological development and function
3) reproduction and physical development
4) kidney function
5) cardiovascular function

Lead also affects immunological, liver, gastrointestinal, and endocrine functions, and at high dosages produces tumors in

laboratory animals. Information on these effects is generally limited to high exposure levels. The major implications of the available literature and dose-response information related to each of the key effect areas listed above, as well as the potential carcinogenicity of lead, are summarized in Section III.D. as they relate to assessing the risks associated with alternative lead NAAQS.

D. Dose-Response Information

The amount of lead measured in whole blood (PbB) has been the most widely used indicator of lead exposure in the many studies of health effects associated with lead. Although blood lead is only an indirect surrogate of toxicologically active dosages at target sites, and may under-represent total body burden of lead especially after high exposures, it does provide a reliable index of fairly stable exposures and can respond relatively rapidly to short-term changes in lead intake. Future research is expected to increasingly rely on serial blood measurements in combination with <u>in situ</u> bone lead analysis as indices of long-term integrated exposures.

Tables 3-2 and 3-3 summarize the lowest observed effect levels (in terms of PbB levels) that have thus far been credibly associated with health effects of concern observed in children and in adults, respectively. The tables are adapted from Tables 13-7 and 13-8 in the 1986 CD, and have been updated to include more recent data, as evaluated in the 1986 CDA and its 1990 supplement, as well as the 1988 ATSDR Report to Congress. Because of variations in individual biological susceptibility, nutritional status, exposure patterns, and other factors, many people would not experience the stated effects until higher PbB levels while others may respond to even lower levels. Lead affects many levels of physiological and anatomical organization within the body across a wide range of exposure levels. These effects range from biochemical changes in energy metabolism and synaptic neurotransmission, with no apparent threshold on a

TABLE 3-2. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN CHILDREN

Lowest Observed Effect Level (PbB)*	Heme Synthesis and Hematological Effects	Neurological Effects	Effects on the Kidney	Developmental Effects
80-100 ug/dl		Encephalopathic signs & symptoms	Chronic nephropathy (aminoaciduria, etc.)	
70 ug/dl	Frank anemia			
60 ug/dl		Peripheral neuropathies		
		↓		
50 ug/dl		?		
40 ug/dl	Reduced hemoglobin synthesis	Peripheral nerve dysfunction (slowed NCV's)		
	Elevated coproporphyrin	CNS cognitive effects (IQ deficits, etc.)		
	Increased urinary ALA	↓		
30 ug/dl		?	Vitamin D metabolism interference	Reduced gestational age & birthweight
15 ug/dl	Erythrocyte protoporphyrin elevation	Altered auditory, electrophysiological responses	↓	Deficits in mental development, growth rate
	↓	↓		↓
10 ug/dl	ALA-D inhibition		?	?
	↓	?		
	Py-5-N activity inhibition			
	↓			
	?			

*PbB = blood lead concentration

Updated from CD Table 13-7

TABLE 3-3. SUMMARY OF LOWEST OBSERVED EFFECT LEVELS FOR KEY LEAD-INDUCED HEALTH EFFECTS IN ADULTS

Lowest observed effect level (PbB)*	Heme Synthesis and Hematological Effects	Neurological Effects	Effects on the Kidney	Reproductive Function Effects	Cardiovascular Effects
100-120 ug/dl		Encephalopathic signs and symptoms	Chronic nephropathy		
80 ug/dl	Frank anemia				
60 ug/dl				Pregnancy complications	
50 ug/dl	Reduced hemoglobin production	Overt subencephalopathic neurological symptoms		Altered Testicular function	
40 ug/dl	Increased urinary ALA and elevated coproporphyrins	Peripheral nerve dysfunction (slowed nerve conduction)		Pre-term delivery	
30 ug/dl					Elevated blood pressure
25-30 ug/dl	Erythrocyte protoporphyrin (EP) elevation in males			?	
15-20 ug/dl	Erythrocyte protoporphyrin (EP) elevation in females				?
<10 ug/dl	ALA-D inhibition				

*PbB = blood lead concentration
Updated from CD Table 13-8

subcellular molecular level, to severe, irreversible central nervous system damage manifested by mental retardation, encephalopathy (degenerative brain disease), and possibly, death at PbB levels starting between 80 and 100 μg/dl in the most highly susceptible children (EPA, 1986a, p. 12-69). Other overt neurological damage such as peripheral neuropathies, have been observed at PbB levels possibly as low as 40-60 μg/dl (EPA, 1986a, p. 12-108). Clearly adverse effects occur in other organ systems at these elevated levels (60-100 μg/dl) including chronic nephropathy, gastrointestinal symptoms, and frank anemia, which represents an extreme manifestation of reduced hemoglobin synthesis. The focus here will be on the most sensitive targets of low-level lead toxicity: in children, heme synthesis and related functions, neurological function, and mental and physical development; and, the cardiovascular system in adults. Potential carcinogenicity of lead will also be discussed. The PbB levels of concern in evaluating a range of alternative lead NAAQS are discussed in Section III.E.

1. Heme Biosynthesis and Related Functions

Other than some changes in neurochemistry discussed in Section III.B., hematological changes are generally the earliest effects seen in lead exposure. Under normal circumstances, heme biosynthesis is a highly efficient and coordinated pathway, which produces only sufficient amounts of intermediates and, ultimately, heme to service requirements for hemoglobin -- the blood pigment responsible for transporting oxygen to the tissues -- as well as a multitude of functions mediated in most cells by heme-containing proteins. These hemoproteins include myoglobin, the hemoglobin of muscle, and the mitochondrial respiratory pigments, cytochromes, responsible for cellular energetics. As summarized in Table 3-4, moderately elevated lead exposure has been demonstrated to disturb the biosynthetic sequence so as to produce large quantities of redundant intermediates that must then be excreted. More severe lead intoxication may result in the development of anemia due to

TABLE 3-4. SUMMARY OF LEAD'S EFFECTS ON HEME BIOSYNTHESIS AND RELATED SYSTEMS IN CHILDREN

PbB (ug/dl)[1]	Effect	References
≤10-15	Inhibition of ALA-D, Py-5-N, red blood cell ATPase activity	Hernberg and Nikkanen, 1970; Secchi et al., 1973; Wada et al., 1976; Angle and McIntire, 1978; Valentine and Paglia, 1980
≥12	Reduction in vitamin D hormone synthesis	Rosen et al., 1980
~12	Elevated EP in children with iron deficiency	Marcus and Schwartz, 1987
15-18	Accumulation of EP in children with mix of iron status	Roels et al., 1976; Piomelli et al., 1977; 1982; Hammond et al., 1984; Rabinowitz et al., 1986
>20	Impaired globin synthesis	White and Harvey, 1972; Dresner et al., 1982
~23	Elevated EP in children with high iron status	Marcus and Schwartz, 1987
25-30	Significant EP elevation above normal	Roels et al., 1980; Piomelli et al., 1982
>33	Significant interference with vitamin D hormone synthesis comparable to that seen in renal diseases	Rosen and Chesney, 1983; Chesney et al., 1983
18-40	Accumulation of underutilized ALA; possible interference with neuro-transmission	Meredith et al., 1978; O'Flaherty et al., 1980; Nicoll, 1976; Brennan and Cantrill, 1979; Silbergeld et al., 1980, 1982
~40	Reduction in hemoglobin levels	Betts et al., 1973; Rosen et al., 1974; Adenbojo, 1974; Pueschel et al., 1972;
?	Impairment of cytochrome synthesis and function (e.g., liver detoxification cellular energy metabolism)	Alvares et al., 1975; 1976, Meredith et al., 1977; Saenger et al., 1984; Holtzman and Shen Hsu, 1976; Bull et al., 1979
?	Alterations in heme-based neurochemical synthesis and activity and neural tissue development	Litman and Correia, 1983; Whetsell and Kappas, 1981; Whetsell et al., 1984

[1]These levels represent lowest observed effect levels in a significant fraction of children studied. In some cases, no threshold has been detected, as noted by < or > signs. Question mark signifies that the effect has been observed in vitro or in vivo in animals models and extrapolating dosages to children is not not possible at this time.

reduced hemoglobin production and shortened red blood cell survival. Because heme synthesis is a continuous process, most of these effects are reversible upon removal or reduction of lead. However, given: a) there may be long-term functional consequences of even transitory changes in developing tissues in children; b) heme's pervasive role in many organ systems and physiological processes; and c) the sensitivity of heme production to lead, lead's interference in the heme synthetic pathway may have long-lasting implications that must be carefully considered.

As discussed in the CD (Section 12.3), lead interferes with heme synthesis at several points in its metabolic pathway:

1) Activity of the enzyme ALA-D (porphobilinogen synthase), which catalyzes the conversion of ALA to porphobilinogen, is inhibited in red blood cells at PbB levels below 10-15 µg/dl with no clear threshold (Hernberg and Nikkanen, 1970);

2) Accumulations of ALA, which result from inhibited ALA-D activity, have been noted in plasma and urine at PbB levels of 40 µg/dl, and possibly as low as 18 µg/dl. Inhibition of ALA-D activity, and increases in non-utilized ALA appear to occur in brain, kidney, and the liver at roughly the same PbB levels associated with ALA accumulations in plasma (Millar et al., 1970; Secchi et al., 1974; Silbergeld et al., 1982);

3) Lead impairs the transmitochondrial transport of iron and instead of producing heme, the mitochondria accumulate its precursor, protoporphyrin which, lacking iron, is incapable of performing its essential respiratory function. As a result of lead intoxication in newly forming erythrocytes, protoporphyrin (referred to as erythrocyte protoporphyrin or EP) takes the place of heme in the specific pocket of the hemoglobin molecule. As the red blood cells remain in the circulation, zinc is rapidly chelated at the center of the molecule in the site normally

occupied by iron (Piomelli et al., 1982). The resulting zinc protoporphyrin (ZPP) is tightly bound in the available heme pocket for the life of the erythrocyte, normally 120-130 days (Lamola et al., 1975). Impairment of iron utilization for heme synthesis by lead is enhanced by iron deficiency. Persons with both low iron status and PbB levels above 30 µg/dl were approximately 6.5 times as likely to have elevated EP than those with normal iron status in the same PbB range (Mahaffey and Annest, 1986). The interaction of iron status and lead in elevating EP in children should be considered. Several studies have found progressive increases in EP with increasing PbB with an apparent threshold between 15 and 18 µg/dl (Roels et al., 1976; Piomelli et al., 1982; Rabinowitz et al., 1986). Significant EP elevations greater than one and two standard deviations above normal were found in 50% of children with PbB levels of 25-30 and 35 µg/dl, respectively. Some of these studies selected children so as to minimize the number with iron deficiency, although direct data on nutritional status were not available and it is likely that children with different iron stores were grouped together. Data on U.S. children surveyed in NHANES II were reanalyzed to more directly examine the impact of iron status on the dose-response relationships between PbB and EP (Marcus and Schwartz, 1987). While no actual threshold exists in the fitted, non-linear model, the typical estimated EP response increases sharply at about 12 µg/dl in iron-deficient children, and at about 23 µg/dl for children with high iron stores.

The health significance of EP or ZPP accumulation is that it indicates that heme or hemoprotein synthesis in many tissues has been impaired as a result of lead's entry into mitochondria (EPA, 1986a, p. 12-46). Previously, EP elevations at PbB levels around 30 µg/dl were considered to be of concern based on functional disruptions in hemoglobin synthesis at 40 µg/dl and neurobehavioral effects above 50 µg/dl (EPA, 1977). Recent data, however, have provided more information on the extensive impact

of lead on the body heme pool and associated disruptions of many physiological processes (see Figure 3-1). With increasing lead exposure, impairment of heme and hemoprotein synthesis intensifies in different organ systems which can result in reductions in oxygen transport, changes in cellular energetics, interference with neurotransmitter synthesis and function, reduced detoxification of certain drugs and other foreign agents in the liver due to inhibition of cytochrome P-450, impairments in the biosynthesis of 1,25-dihydroxyvitamin D (1,25-OH_2-D) in the kidney, and possibly impairment of the immune system (EPA, 1986a, p. 13-30).

Most of these linkages between the biochemical effects of lead on heme synthesis, and effects on other functions such as neurotransmission, are primarily based on animal or <u>in vitro</u> experimental data. It is, therefore, difficult to determine a PbB level of concern for heme-related disturbances in humans. Nevertheless, the common biochemical processes operating across mammalian species suggest the abnormalities in heme synthesis caused by low level lead exposure in humans may also indicate some risk of broader functional impairments.

Of the functional consequences associated with heme reductions and lead's interaction with those processes, perhaps the best quantitative data are available on the negative correlation between PbB levels and circulating levels of the vitamin D hormone, $1,25(OH)_2D$ (Rosen et al., 1980). Synthesis of this hormone, which is the major active form of vitamin D, is mediated by a heme-requiring cytochrome P-450 enzyme system (renal 1-hydroxylase) in the kidney. It is also controlled by the functional integrity of the renal mitochondria, by the ionic (calcium, phosphorous) environment of the extracellular fluid, and by the active uptake of calcium by mitochondria (EPA, 1986a, p. 12-38). Given lead's effects on mitochondria, cellular energetics, cytochrome P-450 function, and ferrochelatase activity in kidneys, it is not surprising that lower $1,25(OH)_2D$

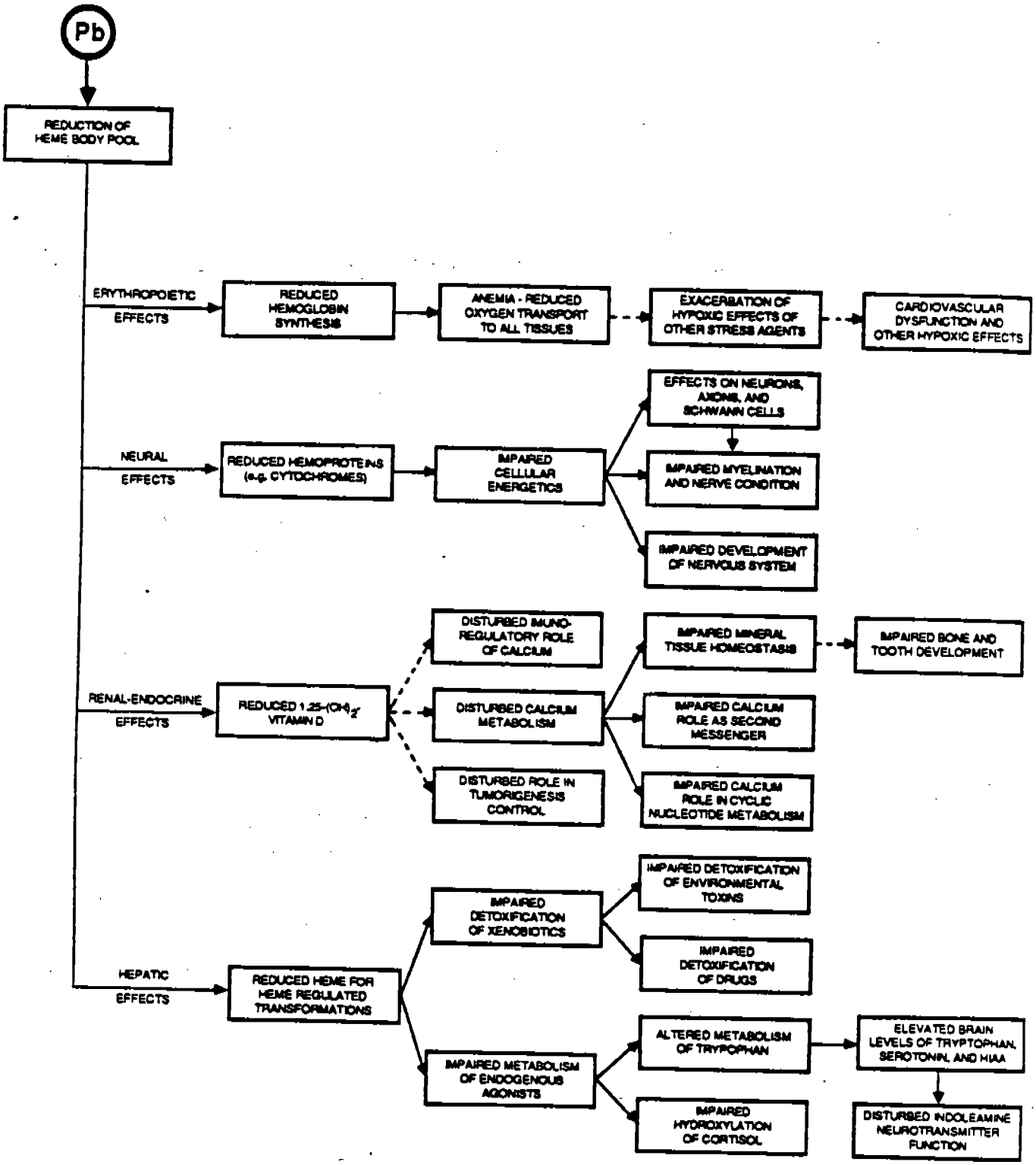

Figure 3-1. Multi-organ impact of reductions of heme body pool by lead. Impairment of heme synthesis by lead results in disruption of wide variety of important physiological processes in many organs and tissues. Particularly well documented are erythropoietic, neural, renal-endocrine, and hepatic effects indicated above by solid arrows (——►). Plausible further consequences of heme synthesis interference by lead which remain to be more conclusively established are indicated by dashed arrows (--►).

Source: Criteria Document (Figure 13-4).

levels occur at PbB levels corresponding to those associated with the onset of EP accumulation in red blood cells. A strong negative correlation between vitamin-D hormone and PbB levels was found over a range of 12-120 µg/dl (Mahaffey et al., 1982) with no apparent threshold. Above 33 µg/dl, the reductions in vitamin D hormone were comparable to these observed in children lacking two-thirds of normal renal function.

The CD concludes that it appears likely that lead-induced reductions in heme underlie this association, and that impaired production of $1,25(OH)_2D$ can have profound and pervasive effects on tissues and cells of diverse type and function throughout the body (EPA, 1986a, p. 12-51). Altered levels of $1,25(OH)_2D$ may affect calcium homeostasis and thus calcium-dependent processes essential to several enzyme systems, the transport of and response to various hormonal and electrical stimuli, and cyclic nucleotide metabolism. In addition, lead may affect the role of $1,25(OH)_2D$ in cell differentiation/maturation, immunoregulation, pancreatic function (e.g., insulin secretion), and mediation of tumorigenesis (EPA, 1986a, pp. 12-40 to 12-42).

At higher levels, lead's interference with heme synthesis and other red blood cell functions (e.g., inhibition of Py-5-N activity which affects membrane stability) may result in anemia. A PbB threshold for apparent reductions in hemoglobin levels in children has been commonly cited at 40 µg/dl (WHO, 1977) although this has not been conclusively established (EPA, 1986a, p. 12-29). Judgments of experts were encoded in 1985-86 in an attempt to address the uncertainty in the dose-response relationship between lead absorption and hematologic dysfunction. These judgments are described in Wallsten and Whitfield (1986) and summarized in Appendix A. Three of four experts assigned at least a 50% chance that some children with a PbB level of 35 µg/dl ($\simeq$5-11%) would have lead-induced anemia and that there would be some children at small risk at even lower levels. A fourth expert felt there was no measurable lead-induced hemoglobin effects at PbB levels below

45-55 µg/dl. Recent analysis of data collected in 1974 from Idaho children living near a lead smelter and rural control areas indicate that hematocrit levels were depressed below normal (an index of anemia) in one-year olds beginning at a PbB level of about 20 µg/dl, and at about 40-50 µg/dl in older children (Schwartz et al., 1989). Although anemia is a serious clinical manifestation, the inhibition of heme synthesis at lower PbB levels has much wider implications for a multitude of organs and physiological systems.

2. Neurological Effects of Lead

The nervous system is a critical target for low-level lead effects. Alterations in neurotransmission and brain mitochondrial function are evident within minutes of exposure for submicromolar lead concentrations in vitro and in vivo. Although the functional significance is difficult to assess and PbB levels at which such effects occur in humans have not yet been determined, these neurochemical changes (e.g., inhibition of acetylcholine release and Na, K-ATPase activity) exhibit continuous dose-response relationships which may form the bases of delayed brain development and disrupted neurobehavioral function (Silbergeld, 1983).

The effects of lead on the nervous system, summarized in Table 3-5, are both structural and functional, involving various regions of the brain and spinal cord (i.e., the central nervous system) as well as the motor and sensory nerves leading to specific areas of the body (i.e., the peripheral nervous system). These effects can result in deterioration of intellectual, sensory, neuromuscular, and/or psychological functions.

a) Acute Effects

Acute encephalopathy (degenerative brain disease) is the most severe consequence of lead intoxication and can abruptly progress to delirium, convulsions, coma, and ultimately death (Cumings et al., 1959). Acute encephalopathy in adults usually

Table 3-5. SUMMARY OF LEAD'S EFFECTS ON THE NERVOUS SYSTEM

Effect	Exposure	References*
Biochemical		
In vitro impairment in rat brain of: synthesis on tetrahydrobiopterin (neurotransmitter cofactor), adenyl cyclase; Na, K-ATPase activity, energy metabolism; activation of protein kinase C	0.001 - 5 uM lead solution	Purdy et al., 1981; Goddard and Robinson, 1976; Taylor et al., 1978; Gmerek al.,1981; Markovac and Goldstein, 1988a,b
Delayed development of rat brain energy metabolism and respiration (in vivo)	0.02% lead salt in drinking water	McCauley et al., 1979; Bull et al., 1977; Bull, 1983
Altered synthesis, release, and/or uptake of several neutotransmitters and cofactors in vivo (dopamine, norepinephrine, serotonin, GABA, tetrahydrobiopterin)	0.2 - 2.0% lead salt in drinking water	Shellenberger, 1984*; Litman and Correla, 1983; McIntosh et al., 1985; Baraldi et al. 1985
Morphological and Functional Development		
Impaired myelin, glial cell development in rat brain.	0.05 - 2.0% lead in diet	Reyners et al., 1979; Widebank et al., 1980; Stephens and Gerber, 1981
Delayed synaptogenesis and neuronal development in young, rat brain	0.1 - 2.0% lead in diet	Petit et al., 1983;* Costa and Fox, 1983; Bull et al., 1983; Roussouw et al. 1987
Delayed development of reflexes and locomotor activity; alterations in social interactions; some persistent learning and behavior deficits,in rats and monkeys exposed in utero or post-natally	>0.001% lead in diet	Brown, 1975; Overmann et al., 1981; Hastings et al., 1979; Bull et al., 1983; Bushnell and Bowman, 1979; Bushnell & Levin, 1987; Cory-Slechta et al., 1985; Rice, 1984, 1985; Winneke et al., 1982b; Barrett and Livesey, 1983
Deficits in early mental development in infants	mean maternal and neonatal PbB 10-15 ug/dl, possibly below	See Table 3-6
Electrophysiological		
Altered electrical activity, neurotransmission in isolated neurons (in vitro)	>1 - 5uM lead solution	Sillman et al., 1982; Taylor et al., 1978; Olson et al., 1984; Cooper et al., 1984; Silbergeld and Adler, 1978
Altered visual and electrical evoked responses, visual acuity, and spatial resolution in young rats, monkeys	0.2% lead in drinking water/diet	Bushnell et al., 1977; Fox et al., 1982; Winneke, 1980
Subtle, alterations of brain electical activity (EEG patterns), auditory function in young children; inconsistent findings on slow-wave potential, visual and auditory evoked potential.	No apparent threshold down to 15 ug/dl PbB and possibly below	Otto et al., 1981, 1982; Otto, 1985; Robinson et al., 1985; Benignus et al., 1981; Burchfiel et al., 1980; Winneke et al., 1984; Schwartz and Otto, 1987
Depressed conduction velocities in sensory and motor nerves of adults and children (conflicting results at similar exposure levels)	>20-30 ug/dl PbB	Seppalainen et al., 1975, 1979, 1983; Schwartz et al., 1988 (Spivey et al., 1980; Triebig et al., 1984)
Motor Nerve Function		
Small deficits in perceptual-motor integration, fine motor coordination and balance in young children	50 - 60 ug/dl PbB, possibly as low as 30 - 40 ug/dl or lower	de la Burde and Choate, 1972, 1975; Landrigan et al., 1975; McBride et al., 1982; Needleman et al., 1979, 1984; Winneke et al., 1982, 1983; Bhattacharya et al., 1988
Conflicting results at similar exposure levels		Rummo, 1974; Rummo et al., 1979; Perino and Ernhart, 1974; Kotok et al., 1977; Winneke et al., 1984

TABLE 3-5. SUMMARY OF LEAD'S EFFECTS ON THE NERVOUS SYSTEM (CONT'D)

Behavioral Disorders		
Symptoms associated with neuropsychiatric disorders (hyperactivity, mental retardation) in children	Effect level not adequately defined	Baloh et al., 1975; Gittleman & Eskenazi, 1983; David et al., 1977, 1983, 1985: Beattie et al., 1975; Moore et al., 1982; Youroukos et al., 1978
Attention (reaction time) deficits and distractability in young children	>30 - 50 ug/dl PbB and possibly as low as 15 - 30 ug/dl	Winneke et al., 1983, 1984; Needleman et al., 1979, 1984; Yule and Landsdown, 1983; Hunter et al., 1983; Hatzakis et al., 1989
Auditory and Language Processing		
Abnormal processing of complex auditory stimuli in infant monkeys	Prenatal and neonatal PbB 50 - 80 ug/dl	Morse et al., 1987
Deficits in motor speech behavior, language comprehension, formulation behaviors, auditory processing and function in children	>30 - 50 ug/dl PbB; no threshold for auditory function	de la Burde and Choate, 1975; Needleman et al., 1979, 1984; Schwartz and Otto, 1987
Cognitive Function		
1 - 4 point deficits in IQ scores on verbal performance, visual-motor perception, short-term memory, general intelligence among young children	>30 - 50 ug/dl PbB; [possibly below 30 ug/dl in socially disadvantaged children]	de la Burde and Choate, 1972, 1975; Rummo, 1974; Rummo et al., 1979; Perino and Ernhart, 1974; Ernhart et al., 1981; Ernhart, 1983, 1984; Needleman et al., 1979, Needleman, 1984; Schroeder et al., 1985; Fulton et al., 1987; Hatzakis et al., 1989 [Harvey et al., 1983, 1984; Winneke et al., 1983; Schroeder and Hawk, 1987]
1 - 2 point, IQ differences due to lead at lower exposure levels in children	15 - 30 ug/dl PbB	Smith et al., 1983; Harvey et al., 1983, 1984; Yule et al., 1983; Yule and Landsdown, 1983; Winneke et al., 1984; Landsdown et al., 1986
Overt Toxicity		
Peripheral nerve damage among chronically exposed adults and children	>40 ug/dl	Lillis et al., 1977; Spivey et al., 1980; Haenninen et al., 1979; Zimmerman-Tansella et al., 1983; Erenberg et al., 1974
Encephalopathy, mental retardation, possibly death among children	>80 - 100 ug/dl	Gant et al., 1938; Smith et al., 1938; Chisolm and Harrison, 1956; Chisolm, 1965; Bradley and Baumgartner, 1958; Rummo et al., 1979

*In some cases, review articles are cited. Refer to CD for more comprehensive referencing

is manifested at PbB levels of approximately 100-120 µg/dl (Chisolm, 1965); this syndrome may be associated with PbB levels between 80 and 100 µg/dl in the most susceptible children (EPA, 1986a, p. 12-69) and can lead to permanent dysfunctions ranging from short attention span to mental retardation.

b) Peripheral Nerve Damage

Peripheral nerve damage (neuropathy) due to high lead exposure has been more commonly found in adults occupationally exposed to lead. Overt symptoms such as muscle tremor, palsy (e.g., "wrist drop") or weakness, muscle and joint pain, and gastrointestinal complaints have been observed in workers with PbB levels exceeding 40 µg/dl (e.g., Lilis et al., 1977; Spivey et al., 1980). Small reductions in conduction velocities of electrically-stimulated sensory and motor nerves (NCVs) have been observed in some apparently asymptomatic workers with PbB levels as low as 30-50 µg/dl (e.g., Seppalainen et al., 1983). It is difficult to draw conclusions from the many studies (more than 30 published) in light of contrasting, negative findings (Spivey et al., 1980; Triebig et al., 1984), as well as a lack of consistency in the nerves examined and in the statistical significance of the effects. Nevertheless, the preponderance of results have been positive, and the most consistently decreased NCVs appear to involve the median motor nerve in the arm. Although lead-induced impairment of nerve conduction may be reversible (peripheral nerves can regenerate), at least in part by a reduction in PbB levels through chelation therapy (Feldman et al., 1977; Araki et al., 1980), electrophysiologic dysfunction in adults is accompanied by alterations in neuromuscular performance (e.g. reduced grip strength and eye-hand coordination) and by subclinical tremor, and reduced visual sensitivity and reactivity (Repko et al., 1979; Baloh et al., 1979). Even small changes in nerve conduction thus may be early warning signals of progressively more serious neuropathy in otherwise undiagnosed lead intoxication (Feldman et al., 1977; Seppalainen and Hernberg, 1980).

Overt, lead-induced peripheral neuropathy has been documented in children with PbB levels above 60 µg/dl (Erenberg et al., 1974), possibly as low as 40 µg/dl (EPA, 1986a, p. 12-108). Unlike the data base for adults, no longitudinal data on nerve conduction are available for children which precludes clear conclusions regarding a threshold for lead-induced neuropathy. Schwartz et al. (1988) reanalyzed cross-sectional data and found a small effect on motor nerve conduction velocity in asymptomatic children at PbB levels beginning at 20-30 µg/dl, with about a 2% slowing in NCV associated with every 10 µg/dl increment in PbB.

c) Effects Associated with Chronic Low-Level Exposures

Besides the severe pathophysiological changes observed in the central nervous system (CNS) associated with childhood lead intoxication, various maladaptive behaviors, neuropsychological deficits, and neuro-anatomical changes have been associated with chronic exposures to relatively low concentrations of lead. Table 3-5 summarizes the numerous biochemical, morphological, and functional effects of lead at low dosages and exposures that have been found in developing nervous systems and the discussion below highlights the key dose-response information.

i) Brain Development: Prospective Studies

Lead readily enters the brain and appears to be selectively deposited in the hippocampus and cortex as well as in non-neuronal elements (e.g., glial cells, endothelial cells of brain capillaries) that are important in the maintenance of "blood-brain barrier" functions (Fjerdingstad et al., 1974; Stumpf et al., 1980). Once deposited, lead is retained in the brain for long periods of time even after external exposure ceases and PbB levels decline (Mykkanen et al., 1979; Goldstein et al., 1974).

The sensitivity of the brain during the period of maximal brain growth and differentiation in the first 2 years of life tends to magnify the severity of the long-term consequences of

any toxin encountered during that period (Dobbing, 1974). The immaturity of specific brain tissues (i.e., hippocampus, cerebellum and neocortex) at birth and their relatively late development suggests that post-natal lead exposure could interfere with mitosis, cellular migration, differentiation of dendritic and axonal processes, synaptogenesis, and myelin production, as well as exerting biochemical and cytotoxic effects (Campbell et al., 1982). While the developing nervous system may possess considerable reserve for functional compensation (involving plasticity, regeneration, and redundancy of neural pathways), specific processes affected by lead apparently may not be reversed, either because lead is not removed from brain cells (Silbergeld, 1983) or because of interruption or damage to neurostructural elements undergoing rapid development at the time of the lead insult.

Rat pups exposed to low levels of lead during the pre-natal or neonatal period show retarded development in cerebral energy metabolic pathways, delayed cerebral cortex synaptogenesis, and reductions in hippocampal morphometric, dendritic, and axonal development (See Table 3-5). These biochemical and morphological disruptions are paralleled by delays in the development of exploratory and locomotor activity, and by learning and behavioral deficits in young, lead-exposed animals (EPA, 1986a, Tables 12-4 and 12-5). Emerging findings from well-conducted, ongoing prospective studies indicating that low levels of <u>in utero</u> or neonatal lead exposure are associated with disturbances in early neurobehavioral development are therefore not surprising.

These studies are reviewed in the CDA and CDA Supplement. Prospective studies have several advantages over cross-sectional or retrospective studies. For example, lead exposure histories can be ascertained and potential confounding variables are better controlled. In addition, efforts were made by the different investigators to use comparable study designs, analytical techniques, and covariate and outcome measures. The study groups

inevitably had different exposure/environmental/socioeconomic profiles, which probably accounts in part for contrasting findings. Numerous combinations of blood lead measures (e.g., maternal, umbilical cord, 3-,6-,12-,24-months, etc.) and mental and psychomotor test measures (e.g., Bayley Mental and Physical Development Indices - MDI and PDI, General Cognitive Index-GCI, etc.) were tested for associations after adjustment for numerous covariates. The many results from the individual studies differ in terms of temporal associations, or lag periods between exposure and outcome measures, statistical significance, and in some cases, direction of effect (PbB positively correlated with some neurological scores in some studies). A generally consistent pattern, however, is evident from these studies linking low-level lead exposure during early development and later neurobehavioral performance. Table 3-6, adapted from Table 13 in the CDA Supplement, summarizes for the most completely documented studies so far, the strongest relationships between different PbB and outcome measures. Other more recent studies provide preliminary results or incomplete analyses that are given less weight in the CDA Supplement (Rothenberg et al., 1989; Graziano et al., 1989a,b; Moore et al., 1989; Fergusson et al., 1988; Winneke et al., 1985 a,b).

Considering the difficulties in assessing neurological function in infants and young children, the different measures used in the prospective studies are generally considered the most reliable and sensitive indicators available. The MDI, for example, reflects the infant's attentiveness and responsiveness to stimuli, rudimentary problem solving, and display of early communicative behavior. While the predictive ability of the MDI is debatable, the correlation between infant MDI scores and childhood test scores are, in general, moderately high, positive, and statistically significant (Davis and Svendsgaard, 1987).

Based on an assessment of earlier results from the Boston, Cincinnati, Cleveland, and Port Pirie studies, the 1986 CDA

TABLE 3-6. SIGNIFICANT EXPOSURE/EFFECT RELATIONSHIPS FROM KEY PROSPECTIVE STUDIES

Study	PbB Measure	PbB Level (ug/dl)	Affected Measure*	Comment
Boston (Bellinger et al., 1985, 1986a,b, 1987, 1988, 1989)	Cord	10-25 (6-7 in "low" SES)	6-,12-,18-,24-month MDI	MDI not related to postnasal PbB. No cord PbB effect at 5 yrs; but risk of persistent effect higher with prenatal PbB >10 ug/dl
	2-yr	mean = 6.8	5-year GCI	
Cincinnati (Dietrich et al., 1986, 1987; 1989a,b; Bornschein et al., 1989; Shukla et al; 1987; Bhattacharya et al., 1988)	Maternal	12-13	3- and 6-month MDI, mediated by birthweight and gestational age	Effect of maternal PbB could range between 7 and 18 ug/dl. No effect of pre- or postnatal PbB by 2 yrs
			Postnatal growth rate	
	Postnatal/10 day	1-29	12-month MDI	
	2-yr	9-49		
			6-yr postural sway	
Cleveland (Wolf et al., 1985; Ernhart et al., 1986, 1987; Morrow-Tlucak and Ernhart, 1987)	Cord	mean = 6.9	12-month MDI via muscle tonus	No effect on birthweight or postnatal growth
			soft signs	
			2-yr language acquisition	
	Maternal/ delivery	mean = 6.8	6-month MDI, PDI, KID	
	6-month	mean = 10.1	6-month KID	
Port Pirie (Vimpani et al., 1989; Baghurst et al., 1987; Wigg et al., 1988; McMichael et al., 1986, 1988)	6-month	avg. = 14	2-yr MDI	Effects on 2-yr MDI marginally significant (p=0.07)
	6-,24-,36-month, and integrated postnatal	avg. = 14-21	4-yr GCI	
	Maternal	>14	Pre-term delivery	
Sydney (Cooney et al., 1989a,b,; McBride et al, 1989)	Maternal/Cord	avg = 8.1-9.1		No consistent significant associations with MDI, PDI, GCI
	6-48 months	avg = 10-16		

*Numerous combinations of PbB measure (e.g., cord, 3-, 6-month, etc.) and outcome measure were tested in these studies; only those found to have significant, negative correlations are listed here (see CDA Supplement). Refer to text and CDA for descriptions of outcome measures: MDI and PDI are Bayley Mental and Physical Development Indices; KID is Kent Infant Development Scale; GCI is McCarthy Scales General Cognitive Index.

concluded that "these studies taken together suggest that neurobehavioral deficits, including declines in Bayley Mental Development Index scores and other assessments of neurobehavioral function, are associated with prenatal PbB exposure levels on the order of 10 to 15 µg/dl and possibly even lower, as indexed by maternal or cord PbB concentrations" (EPA, 1986b, p. A-48).

The updated assessment from those and other more recent studies in the CDA Supplement concludes that:

> "Various lines of evidence still relate neurobehavioral effects to blood lead levels of '10-15 µg/dl, and possibly lower,' as was previously concluded in the 1986 CDA. Further analyses from the Boston study, which has provided the most direct information bearing on dose-response relationships for neurobehavioral effects, not only supported the 10-15 µg/dl level of concern but indicated that MDI deficits can be detected in relation to cord blood lead levels of 6-7 µg/dl in "lower" SES children (Bellinger et al., 1988). Since the Boston cohort was mostly middle to upper-middle class, "lower" SES merely refers to less than the highest SES levels and is probably in fact much closer to the median of the U.S. population. Although the postnatal lead exposure levels were somewhat higher in the Port Pirie study, analyses of the relationship between postnatal blood lead levels and covariate-adjusted MDI scores provided 'no evidence of a threshold effect' (Wigg et al., 1988). Indeed, restricting the analysis to children with blood lead levels below 25 µg/dl in the Port Pirie study yielded an even stronger association between covariate-adjusted McCarthy GCI scores and integrated postnatal blood lead measures (McMichael et al., 1988)" (EPA, 1990, p. 53).

Recent data from these studies suggest that effects of early lead exposure may be attenuated. Sizable increases in postnatal PbB levels were noted in the Cincinnati, Cleveland, and especially in the Port Pirie studies, but not in the Boston study. None of the first 3 studies showed a significant association between pre- or post-natal PbB and MDI scores at or past 2 years of age. Results from the Boston study suggest that the association between prenatal lead exposure and development only persisted beyond age 2 if postnatal exposure remained at

levels above 10 µg/dl (Bellinger et al., 1989). In the Port Pirie study, the strongest relationship was between MDI and integrated postnatal average lead exposure, suggesting that it is cumulative exposure from pre-birth and early childhood that is critical in affecting subsequent mental development (Vimpani et al., 1989).

Future reports from these studies will perhaps provide insight into the causal linkages involved and help clarify uncertainties, including: (a) which period of exposure (pre- or post-natal, cumulative versus concurrent) is most critical under different conditions; (b) the persistence of the effects given the nervous system's ability of adapting to and even compensating for early developmental insults; and (c) the possibility that important effects are obscured by indirect measures of target dose levels or rapid post-natal changes in lead exposure (see CDA Supplement, pp. 57 to 62). Until then, it must be assumed that any disturbance in a child's developmental potential, even if reversible, can have long-lasting secondary effects. For example, otitis media itself may be transient and fully reversible, but secondary effects on language development in young children may be much longer lived (EPA, 1990, p. 62). Further, the potentially large public health implications of even small neurobehavioral deficits associated with PbB increments warrants minimization of lead exposure from any source. For example, the CDA Supplement notes that the Boston, Cincinnati, and Port Pirie studies found that Bayley MDI scores declined by 2-6 points for approximately every 10 µg/dl increase in PbB level (EPA, 1990, p. 62). An overall 4-point downward shift in a normal distribution of scores such as the MDI or GCI would result in 50% more children scoring below 80 on these exams (Davis and Svendsgaard, 1987).

ii) Behavior and Motor/Communication/Cognitive Functions

1. Animal Data

A variety of behavioral changes, abnormalities and/or developmental delays in motor ability, and deficits in learning, have been observed in young animals following early lead exposure (see Table 3-5). It has been suggested that the animal experiments indicate that lead exposure during early development is associated with an underlying tendency to respond excessively (a behavioral "overreactivity"), whether or not such response is appropriate. This overreactivity facilitates active avoidance and other simple learning tasks but is disruptive in demanding, difficult discrimination learning and complex neuropsychological performance (Overmann, 1977; Winneke et al., 1982; Rice, 1985; Alfano and Petit, 1985).

Interpretation of the animal data is limited given: a) inconsistent measures and results across studies; b) uncertainties in comparing "learning" impairments and behavioral measures (e.g., locomotive activity) across species; c) possible confounding effects of nutrition, route of exposure, litter size, maternal care, and differential species and strain-sensitivity (CD, pp. 12-110 to 12-117); and d) uncertainties in relating external and internal exposure indices across species. Despite these limitations, it is likely that lead-induced effects observed in animal studies at least qualitatively parallel altered neurobehavioral function seen in children.

2. Cross-Sectional Data on Children

Since 1979, when Needleman et al. reported small but significant deficits in IQ, attention span, and auditory and speech processing in apparently normal children at lower exposure levels than had previously been suspected, over 20 cross-sectional studies from 9 countries have been published along with numerous reviews (e.g., Rutter, 1980; Bellinger and Needleman, 1982; Smith, 1985; EPA, 1986a, 1989b).

Determining the subtle interactive effects of low level lead exposure on children's neuropsychological development in relation to social (especially caregiving), genetic, nutritional, and other influential variables over time, while controlling for experimental and analytical biases has proved to be difficult. Problems encountered in the conduct and interpretation of childhood lead studies are discussed in the CD (pp. 12-53 to 12-56).

Based on five methodological criteria (adequate markers of lead exposure, sensitive measures of neurobehavioral function, appropriate subject selection, control of confounding covariates, and appropriate statistical analysis), the criteria document has identified a group of neurobehavioral studies that "were conducted rigorously enough to warrant at least some consideration here" (EPA, 1986a, p. 12-72).

There have been mixed findings regarding lead's association with children's scores on standardized IQ tests, which measure some combination of literacy, information, academic capacity, and intelligence (Flynn, 1984). Several well-controlled studies have found effects that are clearly statistically significant, whereas others have found "non-significant" but borderline effects. It is important to note that: 1) the definition of "statistical significance" ($p < 0.05$) is somewhat arbitrary and should not be used to totally exclude results that may have important public health implications; and 2) given the likely subtle nature of the behavioral or neural effects probable at low levels of lead exposure, the differential maturation patterns and sensitivities among different brain processes, and the many other factors that play a larger role in an individual's developmental trajectory, one would not expect to find striking differences in every study, especially in those that use standardized but non-specific measures of intelligence or academic capacity.

The criteria document concludes that:

"none of the available studies on the subject, individually, can be said to prove conclusively that significant cognitive (IQ) or behavioral effects occur in children at PbB levels < 30 µg/dl. Rather, the collective neurobehavioral studies can probably now be most reasonably interpreted as being clearly indicative of likely associations between neuropsychologic deficits and low level lead exposures in young children resulting in PbB levels ranging to as low as 30-50 µg/dl. The magnitude of average observed IQ deficits appears to be approximately 5 points at mean PbB levels of 50-70 µg/dl and about 4 points at mean PbB levels of 30-50 µg/dl (CD, p. 13-35). Although such IQ deficits are relatively small on average, such shifts in the mean can make a substantial difference in the percentage of children with IQ's in the extremes of the population distribution (i.e., below 80 and above 125) and may impact the intellectual development, school achievement, and social development of the affected children sufficiently so as to be regarded as adverse" (EPA, 1986a, p. 13-36).

Figure 3-2 illustrates that an apparently small shift (4 points) in IQ in the mean of a normal distribution may result in

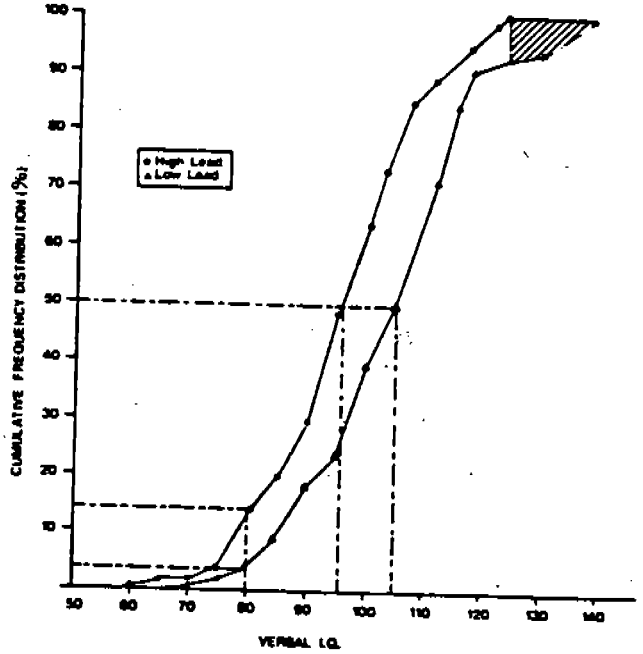

FIGURE 3-2. CUMULATIVE FREQUENCY DISTRIBUTION OF VERBAL IQ SCORES IN SUBJECTS WITH LOW OR HIGH LEAD LEVELS (Source: Needleman et al., 1982)

a nearly four-fold increase in the likelihood of children having severe deficits (IQ < 80), along with an approximately three-fold reduction in the likelihood of children attaining superior function (IQ > 125).

Associations at lower exposure levels have been more difficult to disentangle from other factors. In European children estimated to have PbB levels between 15 and 30 µg/dl, small deficits in IQ and attentiveness have been observed, although no consistent, statistically significant associations have been found (Smith et al., 1983; Harvey et al., 1983, 1984; Yule et al., 1984; Hunter et al., 1983; Winneke et al., 1983, 1984). The criteria document concluded from these studies that "the possibility of small neuropsychologic deficits being associated with lead exposure in apparently asymptomatic children at the exposure levels studied (i.e., 15-30 µg/dl) cannot be completely ruled out, given the overall pattern of results obtained with the cross-sectional study designs employed by Winneke and the British investigators. Small, 1-2 point differences in IQ, seen in some of their studies between control and lead exposure groups might in fact be due to lead effects masked by much larger effects of socioeconomic factors, home environment, or parental IQ" (EPA, 1986a, p. 12-98).

Four recent cross-sectional studies have found continuous exposure-response relationships across the following measured PbB ranges: 7.4 - 63.9 µg/dl, mean = 23.7 µg/dl (with IQ and reaction time performance; Hatzakis et al., 1989); 3.3 - 34.0 µg/dl, mean = 11.5 µg/dl (with British Ability Scales of perceptual, short-term memory, and language functions; Fulton et al., 1987); 6 - 59 µg/dl (with IQ; Schroeder et al., 1985); 6 - 47 µg/dl, mean = 20.8 µg/dl (with IQ; Schroeder and Hawk, 1987). The latter 3 studies found linear relationships with no detectable thresholds. The cohort of 3-7 year-old, low SES children studied by Schroeder et al. (1985) were followed up 5 years later after PbB levels declined (all were below 30 µg/dl); after covariate adjustment, the relationship between PbB and IQ was not significant.

Smaller cross-sectional studies recently reported either consistent findings at moderate-high exposure levels (Faust and Brown, 1987; PbB levels between 30 and 60 µg/dl), or no significant associations among children with lower exposure levels, for example: 5.4 - 21.5 µg/dl, mean = 10.8 µg/dl (with Bayley MDI; Wolf et al., 1987); mean PbB = 11.5 µg/dl (with IQ; Vivoli et al., 1989).

Given the experimental problems encountered in studying subtle, low-level lead effects on children's neurobehavior, it is important to recognize the limits of evaluating studies in isolation. Although results from several studies failed to attain statistical significance individually at the $p = 0.05$ level, in nearly all studies children with higher lead exposures consistently showed lower mean IQs (after covariate adjustment). Simply tallying "positive and negative" studies according to whether the observed association achieved some "arbitrary level of significance" in an attempt to seek a consensus summary is misleading (Pocock and Smith, 1987; Needleman and Bellinger, 1989). For example, two apparently contradictory studies (Fulton et al, 1987, discussed above; and Pocock et al., 1987, who found no significant association between tooth lead and IQ) were compared in terms of their regression coefficients and confidence intervals and were shown to have considerable overlap (Pocock and Smith, 1987). Needleman and Bellinger (1989) integrated recent studies on lead-IQ relationships in children (<12 years of age) into a meta-analysis whereby each study is treated as a subject in a study of studies, and then combined effects are computed. Criteria for selection of the studies were based on adequate information regarding statistical analyses and methodology. Thirteen studies were included; the joint probability was found to be less than 3 in a trillion (2.97×10^{-12}) that the observed pattern of results (lower IQ in higher lead exposure groups) could have been due to chance if there were really no effect. Only if the studies were consistently biased towards finding an effect would the robustness of this result be questionable.

Actually, these studies subtract out variance due to lead (i.e., "overcontrol"). For example, adjusting for covariates such as maternal IQ or maternal caregiving, which negatively correlate with prior lead exposure, likely removes some "transgenerational" influences of lead (Needleman and Bellinger, 1989).

Results of encoding experts' probability judgments on lead-induced IQ decrements, summarized in Appendix A, provide additional insight. The encodings were done in 1984 and 1985 before several key studies were published. According to five of the six experts, risks of small but measurable IQ deficits exist at PbB levels as low as 15 μg/dl in children living in households with incomes in the lowest 15th percentile. Three of the experts felt that there would be some risk of very small lead-induced IQ deficits in low SES children with PbB levels as low as 5 μg/dl.

In addition to IQ decrements, PbB levels in the 30-50 μg/dl range, and possibly lower, may be associated with deficits in auditory and language processing, motor coordination, postural equilibrium, appropriate social behavior, and the ability to focus attention (de la Burde and Choate, 1972, 1975; Needleman et al., 1979; Winneke et al., 1983; Bhattacharya et al., 1988). The degree to which lead's effects on neuropsychological performance at these levels persist into later life remains to be established. One study followed the academic performance of a subset of the children initially evaluated by Needleman et al. (1979) and found that grade retention was clearly associated with past dentine lead levels, while the relationship between other outcomes and past dentine levels were either marginally - (e.g., IQ scores, classroom behavior) or statistically non-significant (e.g., teacher ratings) (Bellinger et al., 1984).

iii) Electrophysiological Effects and Altered Auditory Function

As discussed earlier, in addition to its varied effects on neuronal development and chemically-mediated synaptic transmission, lead impairs peripheral nerve conduction

velocities, at levels possibly as low as 20-30 µg/dl. Similarly, lead exposure affects brain morphology and metabolism, interferes with neurotransmission in central nervous system tissue (e.g., cerebellum, retina) (Palmer et al., 1981; Fox and Sillman, 1979; Sillman et al., 1982), and depresses conduction velocities in the visual pathways of rats accompanied by persistent decreases in visual acuity and spatial resolution (Fox et al., 1977; Cooper et al., 1980; Winneke, 1980; Impelman et al., 1982; Fox and Wright, 1982). Neurological assessments of adult workers indicate that a wide range of lead levels may be associated with impaired function in the visual-motor and auditory systems (Repko and Corum, 1979; Haenninen et al., 1978).

Electrical activity in the brain, determined by electroencephalograms (EEG), is disrupted in animals and humans suffering from lead intoxication (Cooper et al., 1980). More subtle abnormalities in brain wave patterns have been associated with PbB levels in children (along with IQ decrements; Burchfiel et al., 1980) in the range of 30-50 µg/dl, with no evident threshold down to 15 µg/dl, or somewhat lower (Benignus et al., 1981; Otto et al., 1981, 1982, 1985). The functional significance of many of the electrophysiological changes observed below 30 µg/dl (i.e., slow wave potentials, synchronized EEG amplitudes, visual evoked potentials) has not been established, although some changes persisted for at least two years (Otto et al., 1982). Inconsistent or unexpected findings across studies at PbB <30 µg/dl (e.g., decreased evoked potential latencies with increased PbB) (Winneke et al., 1984; Otto et al., 1985; Baumann et al., 1987) require clarification but may indicate hyper-excitability of the peripheral and central nervous system. This would be compatible with symptoms of cognitive impairment associated with lead such as attention deficits, learning disorders, and developmental delays.

The effects on hearing or nerve conduction in the auditory pathway that have been related to lead exposure in children may also be indicative of subtle, but potentially important

neurological impairment. Slowed nerve conduction in the auditory pathway (i.e., increased latencies of brainstem auditory evoked potentials [BAEP]) was directly related to increased PbB levels in children 6-12 years old across the range of 6 to 59 µg/dl (Otto et al., 1985). Attempts to replicate these findings in an independent group of children 3 to 7 years old found that the latency of BAEP waves, as well as hearing threshold at 2000Hz, increased with the maximal PbB levels found in the children's medical records, from 6 to 56 µg/dl (Otto, 1985; Robinson et al., 1985).

Probability of elevated hearing thresholds in 4 different frequencies (500-400Hz) increased significantly with increasing PbB in an analysis of 4,500 children and adolescents (4-19 years of age) studied in NHANES II (Schwartz and Otto, 1987). An association with PbB was apparent across the entire exposure range down to the lowest levels measured (4 µg/dl) after adjustment for covariates including history of recent and chronic ear infections or other disorders. The age at which a child first sat, walked, and spoke also appeared to be associated with PbB levels above 11.5 µg/dl.

Given that lead exposure may impair hearing and the peripheral segment of the auditory pathway, and that a hearing loss occurring in early childhood that remains undetected may result in speech and learning impairments as the child develops, the implications of these findings should be pursued as part of understanding lead's putative role in subtle performance deficiencies among pre-school and school-age children. The preliminary nature of these auditory function results must be emphasized, however, and until comprehensive longitudinal, audiometric, electrophysiological, and speech measurements in children are done, it will be difficult to resolve this issue.

In summary, there have been some inconclusive findings and contrasting interpretations regarding lead's effects on specific

neurobehavioral indicators and functions (e.g., verbal performance, emotional reactivity, perceptual-motor integration, short-term memory, attention, electrical activity in the brain) and the mechanisms involved. The overall evidence, however, indicates that lead is associated with neurological impairment in some children with PbB levels between 30 and 50 µg/dl and that effects on certain behavioral and electrophysiological measures which may have some small, but potentially important and persistent effects on neurological function, support a continuous dose-effect gradient down to exposure levels as low as 15-30 µg/dl PbB, or perhaps, somewhat lower (CD, p. 12-157).

The CDA supplement concludes that "a blood lead concentration of 10-15 µg/dl, and possibly lower, remains the level of concern for impaired neurobehavioral development in infants and children. Given the fact that such effects have been associated with blood lead measures in pregnant women, umbilical cords, and infants up to at least 2 years of age, there is no apparent distinction at present as to whether this level of concern applies to only fetuses or infants or preschool-age children. Thus, a blood lead level of 10-15 µg/dl, and possibly lower, ought to be avoided in pregnant women, fetuses, infants, and young children, although it is recognized that pregnant women per se are not necessarily a population at risk" (EPA, 1990, p. 55).

3. Effects on Reproduction and Physical Development

Lead compounds have been used as an abortifacient and severe lead poisoning has been shown to be accompanied by miscarriages, stillbirths, and reduced fertility (Oliver, 1911). In female animals, relatively low-level lead exposure has been shown to affect pubertal progression and hypothalamic-pituitary-ovarian-uterine functions, as evidenced by ovarian abnormalities (Hilderbrand et al., 1973; Der et al., 1974), and delays in vaginal opening (Grant et al., 1980; Kimmel et al., 1980) and first conception (Maker et al., 1975). In addition, the ability

of the placenta to support fetuses is compromised in mice exposed to relatively low lead levels (Maisin et al., 1975; Jacquet et al., 1976). Newborn rodents and monkeys whose mothers were exposed to lead during pregnancy showed compromised growth (Reiter et al., 1975), congenital malformations in the spinal cord (Carpenter and Ferm, 1977; Jacquet and Gerber, 1979) and delayed neurological development (see previous section).

Pregnant women who lived in homes with excessive drinking water lead concentrations (>800 ppm) bore a significantly higher proportion of retarded infants (Beattie et al., 1975). Premature births, lower birth weight, and premature rupture of membranes have been associated with maternal PbB of 30-40 µg/dl and above in women who worked in or lived near lead smelters (Fahim et al., 1976; Nordstrom et al., 1978). Women in another smelter community, all with PbB at 14-20 weeks gestation below 32 µg/dl, also had increased risk of pre-term delivery (<37th week) as well as late fetal death (beyond 20th week of pregnancy) (McMichael et al., 1986). Mothers whose pregnancies terminated actually had lower PbB levels than average suggesting the possibility of greater lead transfer to the fetus in those cases, consistent with earlier findings (Wibberly et al., 1977).

In newborn children with umbilical cord PbB levels >6.3 µg/dl, an increased incidence in minor (but not major) congenital anomalies (e.g., benign cysts and minor skin defects) was reported after covariate control, although no single anatomic defect was individually associated with lead (Needleman et al., 1984). The longitudinal study of Ernhart et al. (1986), involving a smaller group, failed to find such an association, with average maternal and cord PbB levels of 5.8 and 6.5 µg/dl, respectively.

Significant reductions in gestational age and birth weight have been found to be related to increased maternal or cord PbB in some prospective studies (Moore et al., 1982--mean PbB 12-14 µg/dl; Rothenberg et al., 1989--mean PbB = 15 µg/dl;

Dietrich et al., 1984--apparent threshold at about 13 µg/dl) whereas other studies have reported non-significant, or inconsistent effects (Bellinger et al., 1986a; Ernhart et al., 1986; McMichael et al., 1986). Differences in the age of the mothers, racial make-up, sample sizes, and lead exposure levels, as well as analytical approaches, could underlie the varying results of these different studies (EPA, 1990, p. 57).

As discussed earlier, Dietrich et al. (1984) concluded that the neurobehavioral deficits associated with fetal lead exposure were in part mediated by the observed reductions in gestation and birth weight. Based on subsequent, preliminary analyses of this cohort, these investigators suggest that high prenatal lead exposure (>8 µg/dl) interacts with high postnatal exposure to yield lower than expected growth rates during the first 15 months (Shukla et al., 1987; Bornschein et al., 1989). Although preliminary, these findings lend support to cross-sectional analyses finding small but significant decreases in stature with increased PbB. Schwartz et al. (1986) found that at 59 months, the mean PbB of children surveyed in NHANES II (≈ 16.0 µg/dl) was associated with about a 1.5% reduction in height, weight, and chest circumference, with no apparent threshold across the measured PbB range (5-35 µg/dl). Dentine lead was significantly associated with growth in Danish children between 6 and 10 years of age with low level exposure (Lyngbye et al., 1987). Lauwers et al. (1986) studied children with higher exposures who lived in a lead smelter area and found reduced growth at PbB levels above 40 µg/dl. Despite the uncertainties regarding dose-response relationships, these findings on childhood growth are highly plausible given lead's interactions with heme-dependent enzymes, calcium metabolism, bone formation, and hormonal control (e.g., Rosen et al., 1980; Rosen, 1983; Sandstead et al., 1969).

Male reproductive function is also affected by lead. Sperm abnormalities, reduced fertility, and altered testicular function have been observed in lead-exposed animals and in some industrial workers with PbB levels above 40-50 µg/dl (EPA, 1986a, pp. 12-219).

Although there are inconsistencies, available data suggest that low level exposure to mothers and fathers, may increase the risk of early developmental delays and deficits and reproductive abnormalities. OSHA concluded in 1978 that men and women planning to have children should maintain PbB at or below 30 µg/dl. The 1990 CDA Supplement concludes that "it is difficult, however, to derive a definitive dose-response relationship for fetal outcomes from the available data, although some indications point to a level of concern starting in the region of 10-15 µg/dl. The average maternal blood lead levels in the studies where the pre-term delivery effect was clearest (Port Pirie and Glasgow) were in the 10-15 µg/dl range, in contrast to somewhat mixed findings in the Cincinnati, Boston, and Cleveland studies where the maternal or cord blood lead levels averaged below 10 µg/dl. A similar pattern seems to hold for birth weight as well. The strongest evidence of a birthweight effect comes from the Cincinnati study, with some of their analyses suggesting that this effect could start in the region of 12-13 µg/dl, but possibly extending from 7 to 18 µg/dl. However, other studies provide no support for this conclusion, and so it is considered an open issue awaiting more definitive resolution" (EPA, 1990, pp. 57-58).

4. Effects on the Kidney

Excessive exposure to lead can cause renal disease (see CD, Section 12.5). At low dosages, lead disturbs heme-mediated generation in the kidney of the hormonal metabolite of vitamin D, critical to calcium metabolism (see Section III.D.1). Lead also affects renal mitochondrial structure (e.g., swelling) and other functions (e.g., altered respiratory rates, oxidative phosphorylation and synthesis of proteins and nucleic acids) (Goyer, 1968; Fowler et al., 1980, 1981 a,b; Silbergeld et al., 1982). Lead's interference with these biochemical processes in the kidney, particularly energy metabolism, might account for the transient decreases in renal tubular reabsorptive processes, as indicated by hyperaminoaciduria, glycosuria, and hyperphosphaturia, at PbB levels ranging from 40 to more than

100 µg/dl, and possibly as low as 30 µg/dl (See CD, Sections 12.5.2 and 12.5.3; p. 12-170). The effects of chronic, low-level lead exposure on renal dysfunction in children have not been adequately studied, mainly because there is no good method to easily detect an early renal effect of lead.

There is limited evidence that elevated lead absorption contributes to renal disease in association with gout and hypertension (Emmerson, 1973; Batuman et al., 1981; Wedeen, 1982). The mild hypertension associated with chronic low-level lead exposure however, may be related to lead's ability to directly alter vascular reactivity (Webb et al., 1981; see following section).

5. Effects on the Cardiovascular System

Symptoms consistent with cardiac disease, such as degenerative changes in heart muscle (Kline, 1960), abnormal electrocardiograms (ECG) (Silver and Rodriquez-Torres, 1968) and increased cerebrovascular mortality (Dingwall-Fordyce and Lane, 1963; McMichael and Johnson, 1982; Fanning, 1988) have been associated with high human lead exposures. Cardiotoxicity has been reproduced in experimental animals acutely exposed to high concentrations of lead. Effects include depression in contractility, increased susceptibility to norepinephrine-induced arrhythmias (exaggerated in neonates), and decreased cardiac protein phosphorylation (Kopp et al., 1980; Williams et al., 1977 a,b). It appears that effects may persist in immature rats even after cessation of lead exposure (Williams et al., 1977b).

Chronic administration of lead resulting in PbB levels as low as 40 µg/dl caused structural changes in the myocardium of mice, and ECG abnormalities that are likely due to nerve conduction disturbances (Khan et al., 1977, Kopp et al., 1980). Besides affecting cardiac output, low levels of lead exposure have produced increased vascular responsiveness to contractile agents such as noradrenaline, and sustained elevations in

systolic blood pressure in rats with PbB levels around 40 µg/dl (and possibly lower) (Webb et al., 1981; Victery et al., 1982; Perry and Erlanger, 1979; Aviv et al., 1980; Kopp, 1980). These changes may be linked to depressed energy metabolism (Kopp, 1980), or to altered nerve transmission by increased intracellular calcium concentrations (mediated by impaired sodium-potassium cotransport or activation of protein kinase C) resulting in increased vascular reactivity in arteriolar smooth muscle to vasoconstrictive agents such as norepinephrine and angiotensin (Victery et al., 1982; Rasmussen, 1983; Skocynska et al., 1986; Chai and Webb, 1988; Moreau et al., 1988; Weiler et al., 1988). These studies suggest possible mechanisms by which lead may contribute to hypertension in humans.

Excessive amounts of mobilizable lead have been measured in patients with hypertension (Batuman et al., 1983) and evidence of increased hypertension has been found among men occupationally exposed to high levels of lead (> 50-60 µg/dl) (Inglis et al., 1978; Lilis et al., 1977; Kirkby and Gyntelberg, 1985; de Kort et al., 1987; Cooper, 1988), although there have been contrasting findings in similar populations (Richet et al., 1966; Cramer and Dahlberg, 1966; Parkinson et al., 1987; Selevan et al., 1988). After covariate adjustment, lead exposure has been associated with hypertension prevalence (Beevers et al., 1976; Kromhout and Coulande, 1984) and small increases in blood pressure in some community studies (Moreau et al., 1982; Pocock et al., 1984; Pirkle et al., 1985; Weiss et al., 1988; Neri et al., 1988; Sharp et al., 1988; Schwartz, 1989), but not in others (Staessen et al., 1984; Elwood et al., 1988; Grandjean et al., 1989). Rabinowitz et al. (1984b) reported that umbilical cord PbB was significantly associated with both mother's blood pressure at delivery and the presence of pregnancy hypertension in a sample of 3200 live births in Boston with a mean cord PbB of 6.9 µg/dl.

Weiss et al. (1988) followed changes in blood pressure among 89 Boston policeman over 5 years. Despite the small sample, the

longitudinal nature of the data overcomes many limitations associated with cross-sectional studies and provides a sensitive measure to detect a subtle effect. Time-series and bootstrap analysis indicated a significant association between PbB above 30 µg/dl (but not below) and subsequent elevation in systolic (but not diastolic) pressure. Another longitudinal study of lead foundry workers also found a significant association but results are confounded by cadmium exposures (Neri et al., 1988).

Some of the largest cross-sectional studies, involving as many as 7300 adult men (Pocock et al., 1984; Pirkle et al., 1985; Schwartz, 1985a,b; 1986a,b; E.I. Dupont de Nemours, 1986a,b) and subsequent reanalyses, are focused on in the 1986 CDA (pp. A-10 to A-18) and 1990 CDA Supplement. The quantitative results of these studies are summarized in Table A-3 of the CDA and Table 1 of the CDA Supplement.

Although the investigators in these studies originally published divergent conclusions, reassessment using comparable statistical approaches (comparing covariate-adjusted regression coefficients) on these, as well as 2 other "negative studies" on over 1700 Welsh men and women (Elwood et al., 1988), revealed substantially overlapping confidence intervals and a consistent indication of at least a weak positive association (Pocock et al., 1988; Figure 1, CDA Supplement). Based on the their analysis, Pocock et al. concluded that a mean increase of 1.45 mm Hg in systolic blood pressure appears to occur for every doubling of PbB concentration. This supports the earlier conclusion in the 1986 CDA (p. A-17) that the analyses in Table A-3 (Table 1 in the CDA Supplement) represented the best estimates of the association (i.e., generally in the range of 2.0-5.0 mm Hg/log PbB for systolic and 1.4-2.7 mm Hg/log PbB for diastolic blood pressure). The consensus among leading experts at the 1987 International Symposium on Blood Lead-Blood Pressure Relationships was similar: that a doubling of PbB was associated with about a 1-2 mm change in blood pressure, on average (Victery et al., 1988).

The NHANES II analyses initially focused on white males aged 40 to 59 years to avoid the collinearity between blood pressure and blood lead evident at lower ages, and because data relating cardiovascular disease to blood pressure are less extensive for non-whites (Pirkle et al., 1985). Lead was found to be a significant, but weaker, predictor of blood pressure in additional analyses on all men ages 20-74, both black and white (Schwartz, 1988), and in adult women ages 20-74. A threshold below which blood lead was not significantly related to blood pressure could not be found in that study across a range of adjusted PbB levels between 7 and 34 µg/dl. It is of interest to note that the dose-response relationships found by Pirkle et al. (1985) suggest a large initial effect, leveling off at higher PbB levels, which is consistent with the biphasic blood pressure response to PbB levels found in rats (Victery et al., 1982) and with the saturable, lead-induced accumulation of calcium in cells (Pounds et al., 1982). This may account for the inconsistent epidemiologic findings in persons with mild to moderate elevations of blood lead.

Because of the complex inter-relationships among the multiple environmental, dietary, medical, socio-economic, and genetic factors that influence blood pressure, all of which may not be measurable, results from even the recent large studies must be interpreted cautiously. Nevertheless, the CDA Supplement concludes that the new information emerging since 1986 substantiates the main conclusions stated in the CDA at that time:

> "Sufficient evidence exists from both the four large-scale general population studies discussed above (NHANES II, BRHS, and the two Welsh studies) and numerous other smaller-scale studies to conclude that a small but positive association exists between blood lead levels and increases in blood pressure. Quantitatively, the relationship appears to hold across a wide range of PbB values, extending possibly down to as low as 7 µg/dl for middle-aged men, and furthermore, an estimated mean increase of about 1.5-3.0 mm Hg in systolic blood pressure appears to occur for every doubling of blood lead concentration in adult males and

> something less than 1.0-2.0 mm Hg for adult females. The plausibility of these relationships observed in epidemiologic studies of human populations being of a causal nature is supported by controlled experimental animal studies demonstrating increased blood pressure effects clearly attributable to lead, with an apparent biphasic dose-response relationship being involved." (EPA, 1990, pp. 22-23)

As noted by Tyroler (1988) and other discussants at the 1987 Symposium mentioned above, despite the seemingly small elevations in blood pressure when viewed from the clinical perspective of each individual, any increase in blood pressure carries with it increased risk (albeit very small) for stroke, heart attack, and/or associated mortality. Projections of potential lead effects on such outcomes were modeled by Pirkle et al. (1985). The CDA Supplement concludes that:

> "projections of potential lead effects on such outcomes, as were modelled by Pirkle et al. (1985) and discussed in the 1986 Addendum, are not unreasonable in view of the potentially very large public health impacts; however, much caution must be exercised in accepting the validity of any specific quantitative estimates derived from such projections in view of the uncertainties associated with the selection of the specific coefficients used for (1) blood-lead-blood pressure relationships and (2) relationships between blood pressure increases and more serious cardiovascular outcomes." (EPA, 1990, p. 23)

Recent reanalyses of NHANES II data help to illustrate the possibility of detecting indications of small increased risks in the general population. Schwartz (1989) found a direct relationship between PbB levels and electrocardiogram (ECG) abnormalities, indicative of left ventricular hypertrophy. Such ECG abnormalities represent an early indicator of cardiovascular disease that is much more common than frank myocardial infarctions. It remains to be determined to what extent these observations are due to a lead-induced increase in blood pressure or to some other lead-related pathogenic mechanism (EPA, 1990; p. 19).

6. Possible Genotoxicity/Carcinogenicity

Dose-related increases in renal tumors (Azar et al., 1973; van Esch et al., 1962; Hass et al., 1967) and tumors in endocrine organs (Zawirska and Medras, 1968) have been reported in rats administered dietary lead acetate or lead subacetate. Other studies have found no indication of tumors at either low doses or short duration exposures in rats and mice (Kanisawa and Schroeder, 1969; Stoner et al., 1976; Koller et al., 1985) or high doses in hamsters (van Esch and Kroes, 1969). Data on other chemical forms of lead are either lacking (e.g., lead chloride), or are limited, but suggestive of carcinogenic potential (lead phosphate via injection, Roe et al., 1965; lead oxide via tracheal instillation with benzo[a]pyrene, Kobayashi and Okamato, 1974; lead napthenate via skin painting, Baldwin et al., 1964). Evidence for tumors at other sites other than kidneys is uncertain (Hass et al., 1967; Blakely et al., 1987).

Since lead is capable of transforming cells directly in culture (DiPaolo et al., 1978; Casto et al., 1979) and affecting DNA-to-DNA and DNA-to-RNA transcription (Sirover and Loeb, 1976; Robinson et al., 1984), lead may serve as an initiator of carcinogenic activity. Lead's potential to induce chromosomal aberrations (CD, Table 12-21) may be indicative of its ability to initiate carcinogenic activity but contradictory results have been reported (EPA, 1986a, Table 12-22). In addition, lead may be a promoter of carcinogenesis, as indicated by its ability to increase DNA, RNA, and protein synthesis (Choie and Richter, 1974, a,b), and to enhance the development of renal tumors in rats previously treated with a known carcinogenic initiator (Hiasa et al., 1983; Shirai et al., 1984). Lead's sequestration in the form of "inclusion bodies" in kidney cell nuclei may be linked to its carcinogenic effects (EPA, 1986a, p. 12-244).

An evaluation of these results by EPA (1989b) concludes that: (a) the evidence for carcinogenicity of lead in animals is adequate, although positive responses were generally seen only at

high doses (above a cumulative dose of 1 gram); (b) because several different lead compounds including organic and inorganic ones have been shown to be capable of inducing kidney cancer, and all lead compounds tested are capable of increasing the body burden of lead, from a qualitative weight of evidence perspective, all lead compounds are considered to be potentially carcinogenic; (c) most experiments administered lead in the food, although positive results were reported using other routes. Although no inhalation cancer bioassays are available, there is ample evidence for the bioavailability of lead via inhalation. Lead is therefore considered to be potentially carcinogenic by any route.

Epidemiological studies of lead-exposed workers and children suggest lead may induce chromosomal aberrations that may be associated with certain forms of cancer (Grandjean et al., 1983; Dalpra et al., 1983). Little can be reliably concluded from the conflicting occupational findings on kidney tumor incidence and excess cancer mortality (e.g., Cooper and Gaffey, 1975; Cooper, 1985; McMichael and Johnson, 1982; Sheffet et al., 1982; Selevan et al., 1988; Cantor et al., 1986), although the significant elevations in respiratory and digestive tract cancer in workers exposed to lead and other agents warrant concern (EPA, 1986a, p. 12-225). These latter findings should not be over-interpreted given differences in age distributions among the populations studied and inadequate controls for factors such as smoking, diet, ethnicity, geographical location, and simultaneous exposures to other heavy metals such as arsenic and chromium, which are proven carcinogens. Furthermore, these studies provide no specific information on the long-term lead exposure levels or the lead compounds to which workers were exposed.

The criteria document concludes that:

"Since lead acetate can produce renal tumors in some experimental animals, it seems reasonable to conclude that at least that particular lead compound should be regarded and treated as a human carcinogen (as per recommendations of the International Agency for Research on Carcinogenicity). However, this statement is qualified by noting that lead has

been seen to increase tumorigenesis rates in animals only at relatively high concentrations, and therefore does not seem a potent carcinogen. In vitro studies further support the genotoxic and carcinogenic role of lead, but also indicate that lead is not potent in these systems" (EPA, 1986a, p. 12-289).

Since the IARC recommendations were published in 1980, an EPA assessment (EPA, 1990) recommends that lead be classified as a probable human carcinogen in a tentative weight-of-evidence "Group B2". Evidence on potential carcinogenicity from human studies is considered "inadequate" and the evidence from animal studies is considered "sufficient" according to EPA's guidelines for Carcinogen Risk Assessment (EPA, 1990). This classification includes all lead compounds since all can be absorbed from both the respiratory and gastro-intestinal tracts, and in some cases, from the skin. Although the mechanism through which lead induces chromosomal aberrations and mutations is unknown, the pattern of responses suggests that lead compounds may not directly damage the genetic material, but rather may act through an indirect mechanism, such as activation of cellular transformation or tumor promotion (EPA, 1989b).

Although there are animal dose-response data that could be used to describe the carcinogenic potency of lead, the Agency staff feels that any such calculation would be highly uncertain. A variety of complicating factors influence lead-induced cancer, such as the route of exposure, nutrition, and bioavailability of different chemical forms. The preliminary evaluation of lead carcinogenicity concludes that while pharmacokinetic models have been developed to assess non-cancer health effects in humans, comparative models across species would be needed to extrapolate from high-dose animal studies to project human cancer risks at low-level environmental exposures, and that sufficient information is not available to incorporate many of the factors into a credible exposure-response model for humans (EPA, 1989b). Based on qualitative characterization, this assessment placed lead in potency Group 3 ("low"), as defined in EPA guidelines for evaluating potential carcinogenicity (EPA, 1986b). Combining the

weight of evidence (B2) and the potency ranking, lead receives a "hazard" ranking of "low" relative to other potential carcinogens.

The potential carcinogenicity of lead raises concern; available data, however, do not indicate substantial risks that can be anticipated at current exposure levels. It is recommended that for purposes of revising the lead NAAQS, attention be focused on the non-cancer effects of lead which represent significant risks at relatively low exposure levels. However, the staff believes that the potential carcinogenicity of lead should be considered in determining an adequate margin of safety.

E. Summary of Health Risks Associated with Different Blood Lead Levels of Concern

This section presents a brief staff assessment of how the dose-response information summarized previously may be applied in determining PbB levels of concern for sensitive populations in assessing the relative protectiveness of alternative lead NAAQS.

Lead exposure across a broad range of exposure levels has been associated with a continuum of effects ranging from subtle molecular changes to clear pathological effects. The critical findings at low PbB levels are as follows:

(1) Inhibition of ALA-D and Py-5-N activity at 10-15 µg/dl and possibly below, with no evident threshold;

(2) Elevated EP levels at 12-23 µg/dl in children, depending on their iron status. Elevated EP indicates interference with heme or hemoprotein synthesis in many tissues, which can result in reductions in oxygen transport, changes in cellular energetics, interference with neurotransmitter synthesis and

function, reduced detoxification in the liver, and impaired vitamin D metabolism;

(3) Interference with vitamin D hormone synthesis in children with no apparent threshold down to the lowest levels measured (12 µg/dl);

(4) Reduced auditory function in children with no apparent threshold down to the lowest measured levels (4-6 µg/dl);

(5) Altered electrical brain wave activity with no evident threshold down to 15 µg/dl, and possibly lower;

(6) Deficits in IQ and other measures of cognitive function (e.g., attention span) in children at PbB levels above 30 µg/dl, and small deficits as low as 15 µg/dl (or possibly lower) in socially disadvantaged children;

(7) Slowed peripheral nerve conduction at PbB as low as 20-30 µg/dl in children;

(8) Deficits in mental developmental indices in infants with maternal or umbilical cord PbB levels as low as 10-15 µg/dl. The CDA Supplement concludes that a PbB concentration of 10-15 µg/dl, and possibly lower, remains the level of concern for impaired neurobehavioral development in infants and children (EPA, 1990, p. 55);

(9) Low birth weight and decreased gestational age, which may influence early neurological development, at maternal PbB levels above 12-14 µg/dl;

(10) Reduction in early childhood growth with no apparent threshold in one study across the range of 5-35 µg/dl; a threshold at 40 µg/dl was identified in another study;

(11) Small increases in blood pressure in adult men with no apparent threshold from cross-sectional data down possibly, to 7 μg/dl.

Evidence that lead is a potential, weak carcinogen is also of concern although the focus here will remain on the non-cancer effects at low exposure levels.

The lack of an apparent PbB threshold in several studies is supported by the fact that many of the biochemical changes, or mechanisms, that appear to underlie lead toxicity (e.g., altered enzyme activity, membrane receptors, calcium homeostasis) have been observed at the lowest experimental dosages administered, often with no discernible threshold. There is a great deal of uncertainty regarding the point at which subtle molecular changes individually or collectively, become significant enough that they should be regarded as constituting "adverse" effects for purposes of standard setting under the Clean Air Act. However, such effects clearly become more pronounced (and likely), and broaden to cause more severe disruptions of the normal functioning of many organ systems, as PbB levels increase. This continuum of effects, from biochemical responses, cellular dysfunction and morphological changes, to organ system alterations and clinical toxicity, makes it difficult to identify clearly what PbB level constitutes an appropriate "threshold", if any, below which there are no significant risks of adverse effects.

One approach would be to simply state, as the American Academy of Pediatrics does, that since lead has no biologic value, the "ideal" PbB level is 0 μg/dl (AAP, 1987). This may be a correct public health goal, and adopting it as the basis for revising the lead NAAQS would avoid the problems inherent in addressing the kinds of uncertainties discussed above. However, the Clean Air Act does not instruct the Administrator to eliminate all conceivable health risks that might result from atmospheric lead, regardless of their likelihood, extent, or

significance, simply because there are uncertainties in the relevant scientific data. Instead, it requires him to weigh the available evidence, including the uncertainties, and set NAAQS which, in his judgment, will protect public health against "adverse" effects with an adequate margin of safety. Accordingly, the staff believes it is appropriate to assess the implications for public health of potential effects at PbB levels above zero and to examine the degree of protection that would be afforded by alternative NAAQS.

The approach taken here is to identify those effects that individually or collectively represent an adverse pattern that should be avoided. For children, the collective impact of the effects at PbB levels above 15 µg/dl can be seen as representing a clear pattern of adverse effects worthy of avoidance. Such levels provide relatively little margin from those currently defined by CDC as requiring environmental or medical intervention (> 25 µg/dl along with elevated EP levels). At levels of 10-15 µg/dl, there appears to be a convergence of evidence of lead-induced interference with a diverse set of physiological functions and processes, particularly evident in several independent studies showing impaired neurobehavioral function and development. While the available data do not indicate a clear threshold at 10-15 µg/dl, but rather suggest a continuum of health risks down to the lowest levels measured, the effects of lead below this range become increasingly difficult to detect and their significance more difficult to determine. For purposes of comparing the relative protectiveness of alternative lead NAAQS, the staff has estimated the percentages of children with PbB levels above 10 and above 15 µg/dl (see Section IV.C).

While the dose-response information on blood pressure changes in men is less clear than the information on children, the same approximate range of PbB levels can also be considered for assessing risks among adult men. Percentages of middle-aged men with PbB levels above 10 and 12 µg/dl are estimated to compare relative protection afforded by alternative NAAQS.

Quantitative analyses of differences in prenatal lead exposures under alternative lead NAAQS are not done in this review (see Section III.A). Although fetal sensitivity to lead is high, it appears that young children are significantly more responsive to a lead NAAQS; therefore, the analyses that focus on young children likely provide appropriate estimates of relative risks among alternative standards. Risks associated with fetal lead exposures will be considered in determining an appropriate margin of safety.

To further focus the evaluation of alternative lead NAAQS in Section IV.C., the following factors should be considered: (1) young children are most exposed and absorb a greater proportion of lead; (2) lead accumulates and persists not only in the skeleton but in target organs such as the immature brain; (3) peak exposure generally occurs during the period of maximal neurological growth and differentiation such that any effects on the "hardwiring" of neural networks in the brain may be irreversible. Given these considerations, the staff recommends that of the different sensitive populations and PbB levels of concern, greatest attention be placed on the percentages of young children with PbB levels above 10 μg/dl.

IV. FACTORS TO BE CONSIDERED IN SELECTING A PRIMARY STANDARD FOR LEAD

This section, drawing upon the previous evaluation of scientific information from the criteria document and other information sources, outlines the key factors that should be considered by the Administrator in designating appropriate criteria for averaging time, sampling frequency, monitoring options, and in establishing the level of the lead primary standard. Preliminary staff conclusions and recommendations regarding the most appropriate policy options in each of these areas are presented.

A. Averaging Time

When the lead standard was proposed in 1977, the averaging time for the primary lead NAAQS was specified as a calendar month due to studies which showed an equilibration period of approximately 60 days before steady state PbB levels in adults adjust to changes in air lead concentration (Rabinowitz et al., 1973; Griffin et al., 1975). A month averaging time was considered appropriate because of the greater risk of exposure of young children (FR Vol. 42, No. 240, 1977). Subsequently, EPA promulgated the current NAAQS with a calendar quarter averaging time based on the conclusion that an air lead level of 1.5 $\mu g/m^3$ as a ceiling would be safe for indefinite exposure of young children, and that the slightly greater possibility of elevated air lead levels within the quarterly period was not significant for health (FR Vol. 43, No. 194, 1978). The risk of shorter term exposures to air lead concentrations elevated above a quarterly-averaged standard that might go undetected was considered in the 1978 standard decision to be minimized because 1) based on the ambient air quality data available at that time, the possibilities for significant, sustained excursions were considered small, and 2) it was determined that direct inhalation of air lead is a relatively small component of total airborne lead exposure (FR Vol. 43, No. 194, 1978).

Since promulgation of the lead NAAQS in 1978, the air lead problem has changed in scope from a nationwide, primarily auto emission problem to one related to point source emissions. Point source emissions accounted for 63 percent of total lead emissions in 1987 (EPA, 1989c) and will reach an even higher fraction as gasoline lead emissions continue to decline. Therefore, the 1978 standard decision rationale is no longer as directly relevant to the remaining issues surrounding air lead emissions. The following assessment of additional health and exposure information available since 1978 and other evidence suggests that a monthly averaging time would be more appropriate than a calendar quarter.

1. Biological Kinetics of Lead and Potential Health Impacts Associated with Short-Term (Days-Weeks) Exposures

Lead is absorbed from the environment through the lungs (direct inhalation) and through the gastro-intestinal tract (ingestion). See Chapter 10 of the CD and exposure report (EPA, 1989a) for complete discussions of lead biokinetics and multi-media exposure. Once lead is absorbed into blood plasma through the alveoli or through the gut lumen, it is quickly ionized and is distributed from plasma to the red blood cells, kidney, liver, skeleton, brain, and other tissues. The following discussion summarizes the most relevant information from studies on adults and on children.

a) Adult Data

The initial uptake of lead from plasma to the red blood cells is very rapid, occurring within a few minutes to tens of minutes (Campbell et al.; 1984; Chamberlain, et al., 1983; De Silva, 1981). Ingested lead appears in urine in less than one hour (Chamberlain et al., 1978). Analysis of data from studies on exposure to lead isotope tracers (Rabinowitz et al., 1973, 1976; Griffin et al., 1975; De Silva, 1981) show that lead is absorbed into peripheral tissues in adults within a few days (Marcus, 1985a,b,c; Chamberlain, 1985).

The relevance of the rapid transfer of lead via blood plasma into target tissues is difficult to assess. Most animal and human studies of lead toxicity use measures of lead exposure which reflect accumulations over time (such as blood and tooth lead), and thus do not readily allow effects of different exposure patterns to be distinguished. It is generally accepted, however, that acute exposures to very high lead levels (i.e. from ingestion of paint chips) can result in immediate changes in blood lead and overt toxicity. Data are available on the effects of intense inhalation exposures on a direct precursor of lead toxicity, impaired heme synthesis. PbB levels and ALA-D activity in workers experiencing occupational lead exposure (e.g., as high as 2-4 mg/m^3 air lead) for the first time were significantly altered after only a few days of exposure (e.g., from 12 to 40 µg/dl PbB in 3 weeks), and concentrations of urinary lead and urinary ALA changed significantly after about two weeks (Tola et al., 1973). Hemoglobin and hematocrit levels were significantly lower in the workers at the end of the observation period (about 3 months). After a brief massive exposure of a British worker, zinc EP became highly elevated within one week. Similar results were seen under controlled conditions in which single experimental lead exposures were followed by a rapid (10-20 days) and significant elevation in EP in adult men and women (Stuik, 1974; Cools et al., 1976; Schlegel and Kufner, 1979).

While lead uptake and the onset of potential toxicity may occur rapidly during increased exposure, there is long-term retention of lead in tissues, and reductions in exposure do not cause an equally rapid reduction in either body burden or toxicity. Accumulation of mobilizable pools of lead in the skeleton and other tissues create an endogenous source of lead that is only slowly eliminated. Even soft tissues such as kidney, liver, and the brain retain lead on the order of months, and lead in bone may be retained for many years. Thus, the rapid intake of lead during periods of increased exposure is of

critical concern in determining an averaging time for the lead NAAQS.

b) Data on Children

The experimental data cited above are all based on adults, mostly males, and while valuable, should not be directly extrapolated to children. Children are kinetically different from adults, with a proportionally larger volume of blood and a much smaller but rapidly developing skeleton (especially dense cortical bone which retains most of the adult body burden of lead). Children also absorb lead from the environment at a greater rate, as they have greater gastrointestinal absorption of ingested lead and a more rapid ventilation rate than do adults. Blood lead concentrations change substantially during childhood (Rabinowitz et al., 1984a). These changes reflect the washout of *in utero* lead and the exposure of the child to changing patterns of food and water consumption, and changes in exposure to leaded soil and dust in his or her environment. Thus, an important consideration in determining an averaging time for the lead NAAQS is how quickly a child responds to changes in exposure.

As noted earlier, clinical studies with adult male volunteers showed that PbB changed to a new equilibrium level after 2 or 3 months of exposure, with a half-life of lead in blood of 18-28 days (Rabinowitz et al., 1973, 1976; Griffin et al., 1975). Few direct measurements have been made on the equilibration period for blood lead in children, although the higher metabolic rates in children would be expected to produce a more rapid turnover rate of red blood cells, along with lead, in their blood compared to adults (Chamberlain, et al., 1978) and would thus be more sensitive to changes in lead exposure. Limited, but informative, data on lead biokinetics in children are available:

(1) Ryu et al. (1983) measured lead balance in infants exposed to controlled concentrations of lead in formula and in milk. Blood lead and lead content of food were measured at 28-

day intervals. Blood lead levels in these infants appeared to equilibrate so fast that no estimate of the kinetic parameters was possible.

(2) A preliminary estimate by Duggan (1983), based on earlier input-output studies in infants (Ziegler et al., 1978) gave a PbB half-life (= mean life * log(2)) of 4 to 6 days. Duggan's method has many assumptions and uncertainties. An alternative method, allometric scaling based on surface area, suggests that if a 70 kg adult male has a blood lead mean life of 30 days, then a 7 kg infant should have a blood lead mean life of about 8 days.

(3) A biomathematical model has been developed by Harley and Kneip (1985) and modified for use by OAQPS (EPA, 1989a). This biokinetic model is based on controlled lead exposure studies on infant and juvenile baboons, believed to constitute a valid animal model for human growth and development. Data on human growth patterns were subsequently used to calibrate the model. Validation and application of the model is discussed in the staff exposure report (EPA, 1989a) and in Section IV.C. Annual changes of kinetic parameters such as the transfer rates for blood-to-bone, blood-to-liver, liver-to-gastrointestinal tract, and growth of blood, tissue, and skeleton are included. The model predicts a mean residence time for lead in blood of 2-year-old children as 8 days.

(4) A population of poor, urban children with pretreatment PbB concentrations greater than 50 µg/dl received chelation therapy and were than followed prospectively for the next 2 to 2 1/2 years (Chisolm et al., 1985). Following therapy, blood lead levels increased within one month to varying degrees, depending on the housing conditions the children returned to, and stabilized after three months. Individual records showed that PbB levels usually increased in 3 months by approximately 10 µg/dl in children who moved from lead-free or renovated housing to old housing with some lead-paint hazards and that PbB levels decreased in a similar fashion in those who moved in the opposite way. The authors conclude that such observations suggest that

PbB is "quite sensitive to changes in exposures to lead" (Chisolm et al., 1985).

(5) A more rapid equilibration rate for blood lead in children is indicated by regression analyses of NHANES II data in which individual children's PbB levels most closely correlated with the previous month's gasoline lead consumption compared to the current month and second previous month's gasoline lead use (the third previous month's gasoline lead coefficients were not significant) (Schwartz, 1985). A one month-lagged gasoline lead also best fit blood lead in regression analyses of New York and Chicago screening data (Schwartz, 1985) and of cord blood lead in Boston (Rabinowitz et al., 1984b). In addition, for the prevalence of children then reported (1976-1980) to have lead toxicity (PbB > 30 μg/dl) in CDC quarterly screening reports and in NHANES II, a greater portion of the variance was explained by one month-lagged gasoline lead, compared to concurrent or previous gasoline lead use (Schwartz 1985).

Based on the above data, it appears that increased lead exposure may produce increases in steady state PbB levels in children much sooner than the 60 days observed in adults, and that such changes may not reflect those occurring in the levels of toxicologically active, or mobile, lead throughout the body, particularly if exposure is in the form of intermittent pulses. Although it is difficult to specify a precise temporal pattern of lead exposure most critical in determining health risks, there is some cause for concern regarding the current 3-month averaging time. This concern is based on the following findings: 1) based on limited occupational and experimental studies, exposures < 2 weeks to high levels of lead result in significant changes in heme biosynthesis; effects on other physiological processes associated with similar short-term exposures, and effects of short-term exposures more typical of ambient conditions remain to be studied; 2) lead accumulates in the body and is only slowly removed, therefore repeated exposures to small amounts over many months may produce elevated PbB levels (CDC, 1985); 3) the

mean-life of lead in blood in adults is approximately 30 days and the toxicologically active fraction of blood lead appears to respond quickly to changes in exposure; 4) the rate of equilibration in children is expected to be much faster than in adults due to their overall higher metabolic rate. This would result in children being more responsive to short-term exposures; and 5) based on NHANES II and gasoline lead data, children's PbB, levels and the number of children with elevated lead levels, appear to respond to monthly variations in air lead emissions.

In summary, it appears that a monthly standard would be a more appropriate averaging time than the current quarterly standard, especially around point sources where emissions may vary significantly from day to day (see section II and section IV.B.). Not only would a monthly standard, when compared to a quarterly standard set at the same level, better capture significant excursions in lead exposure, it would also reduce average long-term air lead levels and deposition since controls would be necessary to meet the standard in months with increased emissions, and would thereby reduce the number of children with long-term elevated blood lead levels.

B. Form of the Standard and Sampling Frequency

1. Form of the Standard

Any ambient standard is defined not only by its averaging time and level, but by the characteristic way attainment of that standard is determined, i.e., its form. The method of judging attainment of the current lead NAAQS is deterministic--the maximum arithmetic mean average over a calendar quarter is not to exceed 1.5 $\mu g/m^3$. Although other NAAQS have adopted statistical forms to determine compliance, the staff recommends maintaining a deterministic form for the lead NAAQS due to the unique properties of lead contamination and exposure around point sources.

Several alternative forms of a revised NAAQS for lead have been examined, all of which emphasize peak monthly average

concentrations (Frank and Faoro, 1989). The analyses were conducted independent of a specific concentration level for the standard over a computed three calendar year attainment period. This procedure is consistent with the multi-year formats adopted for the ozone and particulate matter NAAQS. The forms considered are presented in Table 4.1. Associated with these forms are rules by which attainment is judged. For example, with the second highest monthly average form, at most one monthly value in a 3-year period would be permitted to exceed the stated level of the NAAQS.

In order to evaluate the statistical characteristics of each form, two types of analyses were conducted. First, a computer simulation was performed using generated daily lead concentrations over a three-year period. This permitted the examination of a wide range of possible data sets with identical, known characteristics. The second type of analysis involved the examination of actual lead data observed at point source-oriented sites. This provided additional perspective for currently monitored situations.

All of the comparisons were based on a design value, also referred to as the design concentration. This design value reflects the amount of air pollution control necessary to attain a standard. As used in this evaluation, as the design value increases, the stringency of the form being evaluated increases. The results were presented as relative values normalized to the expected maximum monthly average concentration (option 3). Using a reference indicator, the conclusions are independent of the concentration level selected for the standard.

Lead concentration distributions derived from actual point source-oriented monitoring sites were used as generating models for the simulation. Daily air quality data in the vicinity of an ASARCO refinery in Omaha and a lead oxide manufacturer in Philadelphia were used to estimate the underlying distributions.

TABLE 4-1. ALTERNATIVE STANDARD FORMS CONSIDERED AND THEIR RELATIVE STRINGENCY[a]

Alternative Forms	Computation Scheme	Average Design Value (ug/m^3)	Ratio to Reference
(1) Maximum monthly average	Choose maximum monthly average in a 3-year period	3.89	1.11
(2) Expected maximum calendar month	Compute average over 3 years for each calendar month (i.e., average all January's, all February's, etc.) to reflect the highest of these three averages	2.97	0.85
(3) Expected maximum month[b]	Choose maximum monthly average in each calendar year within the 3-year period; average these three values	3.51	1.0
(4) Expected highest 3 months	Compute average of the 3 highest monthly averages over 3 years	3.60	1.03
(5) 2nd highest monthly average	Choose the 2nd highest monthly average value from 3 years of data	3.54	1.01
(6) Maximum 2nd highest monthly average	Choose the 2nd highest monthly average per calendar year; choose the maximum of these three values. Note: standard could be violated each year of the 3-year period considered	3.09	0.88

[a]Based on multiple simulations of daily air quality over 3 years for a site near the Omaha lead refinery (see text).

[b]Reference Indicator

The simulation analyses based on 100 sets of 1080 values, each set representing 3 years of simulated lead data, were used to examine the relative stringency among the alternative forms and the potential effects of incomplete sampling (Frank & Faoro, 1989).

The first simulation analysis examined the relative stringency of each potential form of the standard in terms of average design values. The average design values produced for the alternative 3-year forms ranged from 2.97 to 3.89 $\mu g/m^3$, (see Table 4-1) with the maximum monthly average yielding the highest value (most stringent) and the expected maximum calendar month yielding the lowest value (least stringent). The maximum second highest monthly average per year produces a relatively low value of 3.09 $\mu g/m^3$. The other three alternatives yielded similar values which were each within 3% of the reference indicator. Among these three "middle" indicators, the simplest form is the second maximum month in three years. This standard allows a single exceedance of a monthly average lead level in a three year period.

In order to confirm the stringency findings from the first simulation analysis, actual lead data from point source monitoring sites which had violations of the present lead standard during the 1985-1987 time period were analyzed for comparisons among the six alternative forms of a revised lead NAAQS. Ten sites from 7 different states were used. These sites included the ASARCO refinery and the Philadelphia lead oxide manufacturer, along with other primary and secondary lead smelters. In order to compute the design value statistics from available data, two out of the three years had to be available. The empirical results from the 10 sites confirmed the relative stringency findings developed from the computer simulation. The average design values for these 10 lead sites ranged from 5.34 $\mu g/m^3$ for the maximum monthly average (Option 1) to 2.96 $\mu g/m^3$ for the expected maximum calendar month (Option 2). The

design value for the 2nd highest monthly average of 4.13 $\mu g/m^3$ (Option 5) was again only 1% greater than the expected maximum monthly average of 4.08 $\mu g/m^3$ (Option 3).

Among the alternative forms examined, the form based on the second highest monthly average in three years (Option 5) is recommended for a revised lead NAAQS. It is easy to comprehend, does not involve any complex statistical calculations, and produces design values comparable to the expected maximum monthly average. As stated previously, with the second highest monthly average form, at most one monthly value in a three year period would be permitted to exceed the stated level of the NAAQS. The exceedances could occur in adjacent months or in separate years. While this form is obviously less stringent than the form which does not permit any exceedances in a three year period (Option 1), it allows for explicit discounting of one "bad" month which may be caused, for example, by unusual meteorology. This approach is more stringent than the alternative maximum second highest month per year form (Option 6) in which one monthly exceedance is allowed each year. The staff therefore recommends that the standard be stated deterministically, in terms of a three-year period with no more than one monthly average exceedance.

2. Sampling Frequency and Monitoring Options

In reaching a decision on the standard, the averaging period, form, method of collection, and frequency with which ambient air lead samples are collected should be considered. Given the normal operation of the current one-in-six day lead sampling schedule, even with suggested 75% data capture, it is clear that 4-6 samples collected in the course of a month would not provide a statistically valid estimate of the actual air quality for the period (Thrall et al., 1984; Frank and Faoro, 1989). Consequently, in changing to a monthly average lead NAAQS, it would be necessary to increase the frequency of ambient air lead sampling, especially during periods and in areas of relatively high, variable air quality.

Because attainment is recommended to be based on peak monthly averages, (i.e., second highest monthly average in three years) the precision of the monthly average lead concentrations is critical. This is because, with imprecision, peak values selected from a set of data tend to be overestimated. One source of imprecision is measurement error. Another source is incomplete sampling. Although, averages of measurement concentrations have less measurement error than individual 24-hour samples, these errors still persist with small sample sizes. With one in six day (1/6) or even every other day (1/2) sampling (coupled with the inevitable missing samples), monthly averages would be based on few values. For example, there would be at most 5-6 values with 1/6 sampling. Consequently, such averages would be highly variable (imprecise), causing the potential for misleading monthly average concentrations. The peak values selected from these highly variable monthly averages could therefore yield overestimates of the true peak average concentrations.

Data from the ASARCO refinery based simulations, used to test the stringency of the alternative sample forms presented earlier, were also used to examine the effects of incomplete sampling on design values (Frank and Faoro, 1989). This analysis revealed a design value bias. Design values for each of the alternative forms considered increased with less than complete sampling. For example, evaluating option 1 (maximum monthly average), using every day sampling, produced a design concentration value of 3.89 $\mu g/m^3$. This same option evaluated with 1/2 and 1/6 sampling produced average design values of 4.64 $\mu g/m^3$ and 6.46 $\mu g/m^3$ respectively. This resultant bias could cause true attainment sites, which are close to the level of the standard and exhibit large variability in daily concentrations, to appear to be in nonattainment.

A striking example of the expression of this bias is seen in a simple evaluation of air lead data from the ASARCO refinery

presented in Table 4.2 below. The 1/6 day average for the month presented is 5.07 $\mu g/m^3$ a value based on 5 samples. However, the average of the 31 available daily values is 2.44 $\mu g/m^3$. Other months within this year demonstrated the same bias.

TABLE 4.2 DAILY AIR LEAD DATA FROM A LEAD REFINERY (MAY 1984)

DATE	AIR LEAD ($\mu g/m^3$)	DATE	AIR LEAD ($\mu g/m^3$)
1	1.22	21	6.45
2	0.21	22	0.46
3	0.19	23	5.82
4	1.03	24	8.44*
5	0.60	25	0.12
6	1.03*	26	0.58
7	0.24	27	0.07
8	0.21	28	0.05
9	0.70	29	0.24
10	1.25	30	8.24*
11	0.34	31	14.71
12	6.54*		
13	0.36		
14	0.35		
15	0.32		
16	6.99		
17	6.15		
18	1.11*		
19	0.58		
20	1.18		

*denotes the normal 1/6 day sample

Further simulation analyses using a variety of lead concentration distributions confirmed this bias and showed that large overestimates in design concentrations are possible with 1/6 sampling, and that moderate overestimates are still possible even with 1/2 sampling. It should be noted that this bias occurs in general, but not always.

Nevertheless, since attainment is judged on the highest monthly averages, it is imperative that these values be as precise as possible. Therefore, complete data sampling is

recommended in order to judge attainment/nonattainment for a revised monthly lead NAAQS when a site's maximum monthly readings approach the standard level. This is especially a concern around point sources which can have high daily variability in lead concentrations (see Figure 2-5). Analyses suggest that complete data sampling and highest data capture would only be needed when the design value is within a factor of 2 of the NAAQS level; this will maintain errors of attainment/nonattainment misclassification below 5 percent (Frank and Faoro, 1989). To maximize precision of the monthly average concentrations, general minimum data completeness criteria (e.g., 75 percent) would also be needed and should be explicitly stated in the NAAQS. Nevertheless, attainment or nonattainment could still be determined with less precise estimates for those cases in which the true peak averages were sufficiently far from the level of the NAAQS. At non-point source sites, such as roadside and non-industrial neighborhood sites where lead concentrations are below the current standard, incomplete sampling (i.e., 1/6) would be sufficient to show the long-term aggregate national trends.

The current reference method for the determination of lead in ambient air is based on the collection of suspended particulate matter on a glass fiber filter using a high-volume air sampler, and subsequent analysis of the collected sample for lead uses atomic absorption spectrometry. Samples are collected over 24-hour sample periods and analyzed, either individually or after compositing over a calendar month or quarter, to determine the average lead concentration for the calendar quarter. Several equivalent methods for lead have also been approved for use by state and local agencies under the provisions of FR Vol. 52 No. 126 July 1987; however, all use the high-volume sampler (hi-vol) for sample collection.

During the recent reviews of the air quality criteria for particulate matter and lead, attention was focused on the limitations of the high-volume sampler. Characterization of the

sampler by Wedding et al. (1977), McFarland and Rodes (1979) has demonstrated that the sampler flowrate and shelter geometry favor collection of particles up to 25-50 μm (aerodynamic diameter), depending on wind speed and direction. The sampling effectiveness for large particles is also substantially affected by wind speed and monitor inlet orientation.

The extent to which the hi-vol sampler will efficiently collect lead in ambient air may be estimated if the sampling characteristics of the sampling device and the size distribution of lead in the air are known. Available data characterizing the size distribution of lead in the atmosphere are somewhat limited and suspect due to inadequate sampling methodology. The large wind-generated lead particles, which are of most concern from a sampling viewpoint, and their contribution to the total size distribution of lead in the atmosphere have not been studied to any extent. Nevertheless, the hi-vol's ability to collect particles suspended in air can be reasonably estimated if some assumptions are made concerning the distribution of lead particles in the atmosphere.

Using the particle size distribution specified in the PM_{10} methodology requirements (FR Vol. 52 No. 126 July 1987), one can demonstrate that the hi-vol sampler should provide an "acceptable" measure of lead in ambient air. A hypothetical particle size distribution can be characterized by a fine mode mass median diameter of 0.5 μm, a coarse mode mass median diameter of 14 μm, fine and coarse mode geometric standard deviations of 2.0, a coarse to fine mass ratio of 3.0, and a total concentration of 300 $\mu g/m^3$. This distribution is believed to be an extreme case and somewhat representative of particle size distributions in the western states where frequent high winds and wind gusts are common. By assuming that lead is distributed everywhere in an identical fashion, the collection efficiency for lead can be estimated by integrating the product of the hi-vol's sampling effectiveness and the size distribution. In such an analysis (Purdue, 1988), of three wind speed scenarios, scenarios, the sampler was estimated to collect 85-90% of the total

mass of lead particles in the distribution. Even for a worst-case scenario, 80 percent collection was demonstrated.

The effectiveness of the hi-vol as compared with the PM_{10} sampler has been evaluated in the field. A study at the East Helena lead smelter used co-located PM_{10} and hi-vol samplers (Sternberg, 1988). Analysis of 22 sampling days showed the hi-vol captured, on average, twice as much lead (mass) than the PM_{10} sampler (Brion, 1988). The average percentage of lead of the total particulate weight for both samplers was comparable.

The reason for this observed phenomenon is clear. The PM_{10} sampler, by design, excludes particles larger than respirable size that the hi-vol collects. Given that exposure to lead occurs not only via direct inhalation, but via ingestion of deposited particles as well, especially among young children, the hi-vol provides a more complete measure of the total impact of ambient air lead.

Despite its shortcomings, the staff believes the high-volume sampler will provide a reasonable indicator for determination of compliance with a monthly lead standard. The measurement technology is in place, the monitor is relatively simple and inexpensive to operate, and it's continued use for compliance monitoring will result in historical continuity in the lead air quality data base.

C. Level of the Standard

This section presents a staff assessment of the degree of health protection that would be provided by alternative air lead scenarios and how this information may be used in decision-making on the level of the lead NAAQS. The presentation also outlines a qualitative assessment of the key factors that affect the margin of safety associated with alternative standards.

1. Evaluation of Alternative Lead NAAQS from Case-Study Results

a) Approach

As discussed earlier, blood lead (PbB) has been the common measure used in evaluating health risks associated with lead exposure. To assess the degree of protection provided by alternative lead NAAQS, the chosen approach is to predict distributions of PbB levels in sensitive populations living near lead point sources under different air lead scenarios. As discussed in Section III.E., it is difficult to specify a threshold PbB level below which there are no significant risks of any adverse effects; percentages of children with PbB levels above 10-15 µg/dl will be examined to evaluate alternative standards (see Section III.E).

Exposure results of 3 case-studies are presented below. Children with excessive exposures to paint lead hazards are excluded (see Section III.A). The methodologies used for the case-studies are fully described in the supplemental staff exposure report (EPA, 1989a).

For children, an uptake/biokinetic model is used; for adult men, a hybrid model of two other methodologies ("aggregate" and "disaggregate" models) that accounts for long-term resorption of bone lead is used. All of the exposure methodologies account for the fact that air lead contributes both directly (via inhalation) and indirectly (via ingestion of deposited particles onto soils, dusts, and crops) to total exposure, along with several other sources (e.g., solder in plumbing and food cans, historically-contaminated soils, old paint). Adjustment is made for recent and continuing downward trends in gasoline, canned foods, and drinking water. The aggregate and disaggregate models require an assumption that dust and soil lead concentrations are approximately in equilibrium with air lead levels, and that current air lead exposures reflect historical levels. These latter two approaches were also developed for young children.

risks. For example, approximately 60,000 children between the ages of 0 and 7 years live near major U.S. lead point sources. Therefore, even a 1% difference in the proportion of children above 10 μg/dl corresponds to about 600 children. Also, recognition of the limitations of any exposure modeling effort to fully and correctly simulate reality is important. The staff believes, however, that the uptake/biokinetic model does provide plausible and useful results for several reasons, including: a) The model's mathematical assumptions and numerical parameters combine plausible biological hypotheses with the full range of available and reliable animal experimental data, results of human experimental studies, and environmental lead data; b) Results of different validations of the model indicate good concordance between observed and predicted PbB levels in children living near lead point sources; and c) Of the 3 modeling approaches developed in EPA (1989a), it is not only the most flexible but the most conservative in terms of public health protection. To illustrate, using the midpoint estimates (for air and non-air exposures) of the 3 models, and a constant air lead exposure to 1.0 $\mu g/m^3$ results in a PbB level in a 2-year child in 1990 of: 10.9 μg/dl (uptake/biokinetic model); 8.7 μg/dl (aggregate model); 7.2 μg/dl (disaggregate model).

An effects threshold for increased blood pressure in men has not been defined; several studies have failed to find one while one longitudinal study suggests a threshold of 30 μg/dl (Section III.D.5). For analytical purposes of comparing alternative lead NAAQS, PbB levels of 10 and 12 μg/dl will be used to compare relative effects of alternative NAAQS on adult men. While the basis for a decision on the lead NAAQS should be on the most sensitive population (young children), the results in Table 4-4 indicate substantial reductions in PbB levels in men through attainment of the current NAAQS, and that the range of monthly lead NAAQS analyzed for children (0.5-1.5 $\mu g/m^3$) would be associated with corresponding improvements in adult men exposures compared to baseline conditions.

distributions are consistently lognormal and can be calculated using geometric standard deviations (GSDs) from point source and other population surveys. A range of GSD values (1.30-1.53) is derived from available data on children living near lead point sources (EPA 1989a); results calculated from the lower and upper bound GSD values are presented to reflect the uncertainty in this parameter. The midpoint value of 1.42 is considered to be a reasonable best estimate (EPA 1989a) and emphasis is placed on results using this GSD. A GSD value of 1.37 derived from the NHANES II survey is used for adults (EPA, 1989a).

As noted earlier, no attempt is made here to specifically assess exposures to lead in children with excessive "pica" behavior (i.e., abnormal tendency to repeatedly ingest non-food items) because of an absence of data that could quantify such highly variable intakes, or who are excessively exposed to lead in paint from deteriorating housing conditions. Such children cannot be effectively protected from the hazards of lead in their environment by a lead NAAQS (see Section III.A). Nevertheless, the data used for the exposure analyses implicitly include high exposure conditions.

The uptake/biokinetic model uses data on indoor and outdoor dust and soil lead concentrations measured in various locations where children were exposed. As best that can be determined from the studies, these data do not include measurements from in and around homes where peeling paint, holes in the walls, or other unsound conditions were reported. However, to the extent that the studies appeared to have sampled populations and dwellings representative of the study areas, a heterogeneous mix of homes including older homes with lead-based paint (but no overt hazards) are represented and appear suitable to represent average or "typical" lead exposures. [Data from homes with identified lead paint hazards are excluded from analysis; see Appendix A, EPA, 1989a]. In addition, where applicable, available data was used on the full range of "typical" rates of dirt ingestion

through inadvertent hand-to-mouth activity in children. Finally, the uptake/biokinetic model uses GSD values derived from blood lead distributions measured in a variety of childhood populations living near different lead point sources to capture the range of exposure variability to the fullest extent possible. Given these factors, the staff believes that the exposure analyses presented below reflect a wide range of biological, sociodemographic, and behavioral variability among children who live near point sources including, in part, those living in lead-painted homes (but without overt hazards such as chipping or flaking walls), and those who ingest higher than average amounts of soil and dust.

b) Case-Study Analyses

Populations living near a secondary smelter in Dallas, a secondary smelter and a battery recycling plant in Tampa, and a primary lead smelter in East Helena, Montana comprise the case-study groups. PbB levels in children living near the East Helena smelter were measured in 1983, along with lead in household dust, yard soil, drinking water, and ambient air. These data were used in a successful validation of the uptake/biokinetic model (Section VI, EPA, 1989a).

Air lead concentrations around the point sources were estimated by the Industrial Source Complex Model (ISC) that accounts for source sampling data on emissions, dry atmospheric deposition, background lead concentrations (i.e., mobile sources, re-entrained soil, local minor point sources), and site-specific meteorological data. Air lead levels generated by ISC were found to reliably predict average concentrations in the East Helena validation study. Modeled air quality was used to determine the geographic ranges for analysis; only those people living within an area that the source(s) impacted air lead by a concentration above 0.4 $\mu g/m^3$ were included (roughly 1-3 km radius depending on the source). Predicted air lead concentrations and populations were assigned by block group (or in the case of East Helena, enumeration district), as defined by census data. Soil and

household dust lead concentrations were estimated for the uptake/biokinetic model using relationships derived from available data collected near a wide range of point sources (Appendix B, EPA, 1989a). This approach allows estimation of effects, if any, of historical or possible future changes in air lead levels on soil and dust lead concentrations. Dietary lead intake estimates were derived from historical and current data and future projections of the Multiple Source Food Model, originally developed in the 1986 CD, and updated to include more recent information (Appendix A, EPA, 1989a).

Additional considerations related to the uptake/biokinetic modeling results presented in this section are:

(1) Several parameters in the model were assigned lower and upper bound values defined by the ranges of available data of comparable reliability and relevance. These parameters include time spent outdoors, volume of air respired, absorption efficiency of dietary lead in the gastrointestinal tract, soil and dust lead levels associated with different air lead concentrations, and the amount of dirt typically ingested by children (Appendix A; EPA, 1989a). Midpoint estimates of these parameters are considered best estimates and are incorporated into analyses presented here. Results using the full range of values are presented in Appendix B.

(2) As noted above, the midpoint GSD value of 1.42 is considered a best estimate for point source PbB distributions. Results based on lower and upper bound GSD values of 1.30 and 1.53 are also presented.

(3) Two alternative assumptions were made regarding the response of soil lead levels to future changes in air lead standards: a) that soil lead levels equilibrate to changing air lead levels within a few years. Under this assumption, a different soil lead level would exist for each air lead

concentration in the model between 1990 and 1996. Each soil lead level could be specified by the equilibrated air lead:soil lead relationships derived from mainly cross-sectional data summarized in Appendix B of the staff exposure report (EPA, 1989a) or; b) baseline soil lead levels in 1990, which are the result of long-term deposition, will remain constant for at least six years after a new standard is implemented. The staff, with concurrence from the CASAC Subcommittee that reviewed the lead NAAQS exposure analysis, believes that the latter assumption is more realistic and results presented here reflect a "fixed soil lead" scenario (with varying house dust lead levels). For a given standard, PbB levels are predicted higher under this scenario than under a variable soil lead scenario, although relative differences between standard alternatives are less using this approach.

Blood lead distributions are predicted for non-occupationally exposed middle-aged men assuming a blood lead:inhaled air lead slope of 1.8 $\mu g/dl$ per $\mu g/m^3$ (the weighted average derived from various clinical and epidemiology studies, incorporating a long-term bone resorption factor of 30%; EPA, 1989a, Section V.A), and an average background PbB contribution from non-air sources of 4.4 $\mu g/dl$ (for white men) and 5.3 $\mu g/m^3$ (for black men) (see EPA, 1989a, Appendix C).

c) Case-Study Results

Table 4-3 summarizes case-study results for children, born in 1990 and modeled up to their 7th birthdays, living within areas of significant impact (air lead >0.4 $\mu g/m^3$) near point sources in East Helena, Dallas, and Tampa under alternative lead NAAQS. Percentages above selected PbB levels within the estimated distributions are presented. Other points of the distribution can be calculated; for example, percentages of children above 25 $\mu g/dl$, the CDC definition of undue lead absorption for medical intervention. Because children with pica and with exposures to lead paint hazards are excluded from the

TABLE 4-3. ESTIMATED CHILDREN'S (0-6 YRS.) PbB LEVELS UNDER ALTERNATIVE LEAD NAAQS IN 3 CASE STUDY ANALYSES: 1990-1996*

Case Study (# Children) / PbB Level[a]	Baseline[b]	Lead NAAQS Level (µg/m³) 1.5 Quarterly[c]	Monthly[d] 1.5	1.25	1.0	0.75	0.5
Dallas (241)							
Mean PbB (µg/dl)	6.9	4.9	4.8	4.8	4.7	4.6	4.5
% > 10 µg/dl	14.2	2.2	1.9	1.7	1.5	1.4	1.2
% > 15 µg/dl	1.3	0.08	0.06	0.05	0.04	0.04	0.03
East Helena (217)							
Mean PbB (µg/dl)	6.2	5.2	5.1	4.9	4.8	4.6	4.4
% > 10 µg/dl	8.3	2.9	2.6	2.1	1.7	1.4	1.0
% > 15 µg/dl	0.6	0.1	0.1	0.07	0.05	0.04	0.02
Tampa (10)							
Mean PbB (µg/dl)	10.1	8.3	7.8	7.4	7.0	6.6	6.3
% > 10 µg/dl	50.9	29.7	23.4	19.4	15.6	12.1	9.2
% > 15 µg/dl	12.9	4.6	3.0	2.2	1.5	1.0	0.6

* Assumes soil Pb remains at baseline levels (see text)
[a] PbB distributions calculated assuming GSD = 1.42
[b] Baseline scenario represents current conditions for air quality, as well as soil and dust Pb. Dietary intake assumed to be at 1990-1996 levels
[c] Current NAAQS level and averaging time (calendar quarter)
[d] Alternative NAAQS levels with monthly averaging time

analysis, very few, and in most cases no children, were estimated to have such high levels.

The results for Tampa should not be extrapolated since the secondary smelter and battery plant modeled there were surrounded by mainly non-residential areas. According to the overlay of air dispersion estimates onto block group census data, only 10 children and 20 men live close enough to those point sources to be significantly affected by changes in emissions. Further analyses are necessary to determine whether these results for Tampa are applicable to other point source areas with small populations living nearby.

The results indicate that significant reductions in exposure in all 3 case-study areas could be achieved through attainment of the current NAAQS. Progressive but smaller improvements are indicated for alternative monthly standards, beginning with the current level down to 0.5 $\mu g/m^3$.

The level of protection that should be provided by a lead NAAQS is difficult to specify. The current standard was set in 1978 so that 99.5% of all children (including those with pica) would have PbB levels below 30 µg/dl, which at that time was CDC's definition of lead toxicity for screening programs, and which was considered to provide an adequate margin of safety from clearly adverse effects (e.g., anemia). Since then, a PbB of 15 µg/dl has been associated with risks of several health effects in children, including newborns (see Section III.D), and may provide a small margin of safety from adverse effects. According to the analyses using the best estimate GSD value, a monthly NAAQS between 0.5 and 1.5 $\mu g/m^3$ would keep more than 99.9% of the non-pica children, living without lead-paint hazards near the Dallas and E. Helena smelters, below a PbB of 15 µg/dl.

A NAAQS at 0.5 $\mu g/m^3$, according to the best estimate Dallas and E. Helena case-studies, would protect 99.97% of affected

children from 15 μg/dl PbB and keep 98.8 - 99.0% below 10 μg/dl PbB. A PbB of 10 μg/dl obviously provides a relatively greater margin of safety than 15 μg/dl, although it cannot be considered devoid of any risks of some health effect, however uncertain in terms of functional or "clinical" significance (see Section III.D). No NAAQS can adequately protect all children, even non-pica children living without lead paint hazards, from PbB levels above 10 μg/dl. EPA's exposure analysis estimated that by 1990, non-air contributions to children's total lead exposure (excluding excessive paint lead) would result in a range of PbBs from 4.2 to 5.2. The lower bound was used in their analyses (EPA, 1990). Assuming a GSD of 1.42, this mean increment attributable to non-air lead sources alone would be associated with 0.7% of children above 10 μg/dl, (and 0.02% above 15 μg/dl). Reducing the NAAQS would reduce the estimated proportion of children with PbB levels above 10 μg/dl. For the East Helena and Dallas case studies, an estimated 8.3-14.2% of children currently exceed 10 μg/dl, whereas a monthly NAAQS of 1.5 $\mu g/m^3$ would reduce this fraction to 1.9-2.6%, and a monthly NAAQS of 0.5 $\mu g/m^3$ would reduce it to 1.0-1.2%. Given that a lead NAAQS of 0.5 $\mu g/m^3$ would appear to minimize the number of additional children with PbB levels over 10 μg/dl compared to a "zero air lead" scenario (an additional 0.3-0.5%), and would keep more than 99.97% below 15 μg/dl, it can be considered as a reasonable lower bound for a revised lead NAAQS.

According to the best estimate analyses using a GSD of 1.42, intermediate NAAQS levels (0.75, 1.0, 1.25 $\mu g/m^3$) would be associated with an additional 0.7-1.4% of children above 10 μg/dl over what would be expected with zero air lead emissions, and a total of 99.95-99.96% below 15 μg/dl (0.063-0.066% increase over "zero air lead" scenario).

Interpretation of the above results must consider that although the differences among standard alternatives appear small, they are in fact, significant in terms of population

risks. For example, approximately 60,000 children between the ages of 0 and 7 years live near major U.S. lead point sources. Therefore, even a 1% difference in the proportion of children above 10 μg/dl corresponds to about 600 children. Also, recognition of the limitations of any exposure modeling effort to fully and correctly simulate reality is important. The staff believes, however, that the uptake/biokinetic model does provide plausible and useful results for several reasons, including: a) The model's mathematical assumptions and numerical parameters combine plausible biological hypotheses with the full range of available and reliable animal experimental data, results of human experimental studies, and environmental lead data; b) Results of different validations of the model indicate good concordance between observed and predicted PbB levels in children living near lead point sources; and c) Of the 3 modeling approaches developed in EPA (1989a), it is not only the most flexible but the most conservative in terms of public health protection. To illustrate, using the midpoint estimates (for air and non-air exposures) of the 3 models, and a constant air lead exposure to 1.0 $\mu g/m^3$ results in a PbB level in a 2-year child in 1990 of: 10.9 μg/dl (uptake/biokinetic model); 8.7 μg/dl (aggregate model); 7.2 μg/dl (disaggregate model).

An effects threshold for increased blood pressure in men has not been defined; several studies have failed to find one while one longitudinal study suggests a threshold of 30 μg/dl (Section III.D.5). For analytical purposes of comparing alternative lead NAAQS, PbB levels of 10 and 12 μg/dl will be used to compare relative effects of alternative NAAQS on adult men. While the basis for a decision on the lead NAAQS should be on the most sensitive population (young children), the results in Table 4-4 indicate substantial reductions in PbB levels in men through attainment of the current NAAQS, and that the range of monthly lead NAAQS analyzed for children (0.5-1.5 $\mu g/m^3$) would be associated with corresponding improvements in adult men exposures compared to baseline conditions.

TABLE 4-4. ESTIMATED MEN'S (40-59 YRS.) PbB LEVELS UNDER ALTERNATIVE LEAD NAAQS IN 3 CASE STUDY ANALYSES*

Case Study (# Men) / PbB Level[a]	Lead NAAQS Level (µg/m³)						
	Baseline[b]	1.5 Quarterly[c]	Monthly[d] 1.5	1.25	1.0	0.75	0.5
Dallas (131)							
Mean PbB (µg/dl)	6.3	5.5	5.4	5.3	5.2	5.1	5.0
% > 10 µg/dl	7.2	2.8	2.5	2.1	1.9	1.5	1.4
% > 12 µg/dl	2.1	0.7	0.5	0.4	0.4	0.3	0.3
East Helena (173)							
Mean PbB (µg/dl)	6.9	5.8	5.7	5.6	5.5	5.4	5.3
% > 10 µg/dl	12.1	4.2	3.5	3.3	2.8	2.5	2.1
% > 12 µg/dl	4.0	1.0	0.9	0.7	0.7	0.5	0.4
Tampa (17)							
Mean PbB (µg/dl)	6.6	5.8	5.6	5.4	5.2	5.1	4.8
% > 10 µg/dl	9.2	4.2	3.3	2.3	1.9	1.5	1.0
% > 12 µg/dl	2.8	1.0	0.7	0.5	0.4	0.3	0.2

* Weighted averages of white and non-white men.
[a] PbB distributions calculated by assuming GSD = 1.37
[b] Baseline scenario represents current air quality; non-air contributions assumed to be at 1996 levels
[c] Current NAAQS level and averaging time (calendar quarter)
[d] Alternative NAAQS levels with monthly averaging time

According to the case-study analyses, a monthly NAAQS between 0.5 and 1.5 $\mu g/m^3$ would result in between 1.4 - 3.5% of non-occupationally exposed middle-aged men with PbB levels above 10 $\mu g/dl$ (compared to 7.2 - 12.1% at current baseline air and 1990 non-air exposures); percentages above 12 $\mu g/dl$ would be 0.3-0.9%.

As seen for children, even with zero air lead emissions, average PbB in adult men is expected to be about 4.5 $\mu g/dl$ in 1990; with 0.6% above 10 $\mu g/dl$ and 0.1% above 12 $\mu g/dl$. In other words, a NAAQS of 0.5 $\mu g/m^3$ would increase the number of men in these analyses above 10 $\mu g/dl$ by only 0.4-0.5%; a 1.5 $\mu g/m^3$ NAAQS would increase this fraction by 1.9-2.9%.

No estimates are derived for pregnant women. Although the fetus is highly sensitive to lead, direct and indirect contributions from atmospheric lead via the mother is limited compared to young children. The staff recommends that the analytic focus remain on young children as the most "sensitive" in terms of the present standard review. As discussed in the staff exposure report, approximately 95% of adult body lead burden is sequestered in bone. Fetal exposures in most cases can therefore be expected to be dominated by maternal bone lead stores from past, higher-level exposures compared to current ones (EPA, 1989a). Given this and the fact that children are exposed to, absorb, and retain proportionally more lead from the environment than women, it can be concluded that a lead NAAQS will influence children's exposures more than fetal exposures.

As discussed earlier, the effects of mobilization of skeletal lead sequestered from past exposures, during pregnancy, on transplacental transfer of lead to the fetus cannot be quantified at this time. It is possible, however, to gain some insight into what might be expected in the future under alternative standards. The available data indicate that any PbB: air slope used for adult women would be similar to that used for

adult men. Furthermore, the non-air background contributions to PbB are estimated to be lower in adult women compared to men (EPA, 1989a; Section V.A. and Appendix C).

Given this, the case study results for adult men would be expected to be reasonable upper bound surrogates for those that would be derived for adult women. This suggests that the small improvements in PbB levels between future lead NAAQS in the range of 0.5-1.5 $\mu g/m^3$ estimated for adult men could also be expected for adult women. Thus, it can be anticipated that in the future, changes in atmospheric lead will have a relatively small impact on maternal bone lead stores, and consequently on fetal exposures. In contrast, young children are much more responsive, indirectly and directly, to changes in atmospheric lead emissions and provide the most sensitive indications of the relative protection afforded by alternative NAAQS.

While the fetus may not be the most responsive or "sensitive" subgroup of the population in assessing the future impacts of alternative lead NAAQS, the fact remains that there are now approximately 140,000 women of childbearing age living near major lead point sources whose offspring may be at risk from past lead exposures. A conservative approach to the decision on the lead NAAQS would benefit the future generation born to women who are children today.

2. Factors to Consider in Evaluating Margin of Safety for the Lead NAAQS

a) The Significance and Persistence of Observed or Anticipated Health Effects

Little controversy exists that high-level lead exposures are associated with adverse health effects. There is substantial concern regarding several health effects associated with low-level lead exposure as well:

(1) The significance of alterations in the heme synthetic pathway may be questioned given the physiological reserve capacity of ALA-D activity, for example, and that effects on EP elevation are reversible. Given that disturbances in heme formation can extend throughout multiple organ systems and physiological functions (e.g., neurotransmission, vitamin D metabolism), however, even low-level disturbances have potentially long-term effects;

(2) The relatively small effect on children's IQ attributable to lead at low-moderate exposures, compared to other socio-hereditary influences, (≈ 4 IQ point deficit at 30-50 μg/dl; 1-2 points at 15-30 μg/dl) indicates nevertheless, potentially large population impacts. For example, Needleman et al. (1982) calculated that a 4 point decrement in the mean IQ of a normal population distribution would be associated with a three-fold increase in the number of children with severe deficits (IQ < 80), along with a 5% reduction in the number of children who attain superior function (IQ > 125). Although there is some evidence that low-level lead (<30 μg/dl) effects on IQ may be reversible (Hawk et al., 1986), follow-up investigation of a subset of the children initially evaluated by Needleman et al. indicated that grade retention was significantly associated with past lead exposure (Bellinger et al., 1984);

(3) The small but significant impacts of lead on auditory function may have long-lasting consequences in some children by interacting with lead-induced effects on, or resulting in, delays or deficits in language acquisition and processing, attention, and learning;

(4) Definitive conclusions about the persistence and ultimate impact of low-level effects on infant mental and physical development, due to prenatal and neonatal exposures, must await further results of ongoing longitudinal studies. Some data suggest that children with early neurobehavioral deficits

are able to catch up later on in childhood (Dietrich et al., 1989b), and that natural over-production of neural cells pre-and post-natally may compensate for structural perturbations. However, as stated in the ATSDR (1988; page IV-23) report, "research in developmental and physiological psychology has shown that the actualization of behavioral capabilities requires appropriate periods of functional neural activity for proper development. Thus, even transient, or in themselves, reversible deficits during early development may have potentially serious and long-lasting sequelae. Given the complex interactions that figure into the psychosocial development of children, attempts to compensate for lead-induced deficits in one area of a child's development may affect other areas of development";

(5) Linkages have been drawn from animal experiments between the persistence of lead-induced effects on neurobehavior and neurological biochemistry and morphology, and the accumulation and retention of lead in the brain. This illustrates that, even if effects appear to be reversible, as long as absorbed lead remains in soft tissues or is available from long-term storage, continuing risk of lead toxicity remains.

b) Persistence of Lead in the Environment

Atmospheric lead deposits on soils, crops, and street and playground surfaces. Soil lead, which serves as a continuous source of outdoor and indoor (household) dusts as well as a direct exposure route for young children, is relatively insoluble and immobile and can continue to accumulate indefinitely. The persistence of lead in soil, and its movement into accessible dusts has been taken into account in the uptake/biokinetic model. Nevertheless, the long-term presence of atmospheric lead in the environment, once deposited, beyond the time-frame addressed in the exposure analyses, should be considered in evaluating the margin of safety of alternative NAAQS.

c) Sensitivity of Exposure Results

The full range of available and reliable data were used to estimate PbB distributions of populations exposed under alternative lead NAAQS. Wherever possible, best estimates were derived from the data to use for various input parameters. Where lower and upper bound parameter values could not be distinguished in terms of reliability or relevance, midpoint estimates were chosen. As with any modeling exercise, the results are sensitive to the required assumptions. Appendix B presents results of the analyses on children with either all upper bound assumptions or all lower bound assumptions. The upper bound results indicate much higher percentages of children above PbB cutoffs (e.g., 10 and 15 μg/dl) for a given standard. While the case-study results presented in this section should not be considered as precise and absolute predictions, the staff believes they adequately represent the relative impacts associated with alternative lead NAAQS. Further refinements can be made as additional data become available.

d) Groups Not Evaluated

Young children have the highest rates of lead exposure and absorption and any lead standard derived to protect them should also protect other sensitive groups evaluated quantitatively (adult men) or qualitatively (pregnant women/fetus). The analyses summarized in this section omit young children who cannot be substantially affected by any changes in atmospheric lead emissions under different standards. These children (e.g., those with pica and/or living in deteriorated lead-paint homes) total several million and require direct parental and public health intervention to reduce their high-level exposures (see Section III.A). Nevertheless, any reduction in air lead levels can be expected to have at least a small beneficial effect on these children and should be considered in establishing the lead NAAQS. Similarly, adult women whose blood pressure is affected by ongoing lead exposure, and women experiencing bone

demineralization during osteoporosis (as well as during pregnancy) and increased lead mobilization, will also benefit, however slightly, from any reduction in ambient air lead levels.

D. Summary of Staff Conclusions and Recommendations

The major staff conclusions and recommendations made in Sections IV.A-C are briefly summarized below:

1) A monthly averaging period would better capture short-term increases in lead exposure and would more fully protect children's health than the current quarterly average.

2) The most appropriate form of the standard appears to be based on the second highest monthly average. This form would be nearly as stringent as a form that does not permit any exceedances and allows for discounting of one "bad" month in 3 years which may be caused, for example, by unusual meteorology.

3) With a revision to a monthly averaging time, complete data is needed, except in areas, like roadways remote from lead point sources, where the standard is not expected to be violated. In those situations, the current 1-in-6 day sampling schedule would sufficiently reflect air quality and trends.

4) Because exposure to atmospheric lead particles occurs not only via direct inhalation, but ingestion of deposited particles as well, especially among young children, the hi-volume sampler provides a reasonable indicator for determination of compliance with a monthly lead standard and should be retained as the instrument to monitor compliance with the lead NAAQS.

5) Because young children are exposed to, absorb, and retain proportionally more environmental lead than other populations, they are most responsive to changes in atmospheric lead emissions and provide the most sensitive indications of relative protection afforded by alternative NAAQS. Case-study analyses of children populations living near Dallas and East Helena smelters indicate that substantial reductions in lead exposure could be achieved through attainment of the current lead NAAQS. Progressively smaller improvements are estimated for the alternative monthly lead NAAQS levels evaluated, ranging from 1.5 $\mu g/m^3$ to 0.5 $\mu g/m^3$.

A PbB concentration in the range of 10-15 µg/dl is considered the level of concern for infants and children, and is used to compare the relative protection provided by alternative standards. According to the best estimate analyses, over 99.9% of children living in areas significantly affected by the smelters would have PbB levels below 15 µg/dl. The staff believes that evaluation of alternative standards based on children's PbB levels above 10 µg/dl is more appropriate given the health risks associated with lead. Reducing the NAAQS levels would reduce the estimated proportion of children with PbB levels above 10 µg/dl. For the Dallas and East Helena case studies, an estimated 8.3-14.2% of children currently exceed 10 µg/dl, whereas a monthly lead NAAQS of 1.5 $\mu g/m^3$ would reduce this fraction to 1.9-2.6%, and a monthly NAAQS of 0.5 $\mu g/m^3$ would reduce it to 1.0-1.2%. Because of unavoidable background exposures to lead in the diet, historically-contaminated soils and dusts, and maternal bone lead stores <u>in utero</u>, no standard can keep all children below a PbB of 10 µg/dl. It is estimated that even at zero air lead emissions, 0.7% of children would have PbB levels above 10 µg/dl. For example, Dallas and East Helena results indicate that a monthly lead NAAQS of 1.5 $\mu g/m^3$ would result in an additional 1.2-1.9% of children with PbB levels above 10 µg/dl over what would be expected with zero air lead emissions. A NAAQS of 0.5 $\mu g/m^3$ would appear to minimize the

number of additional children with PbB levels above 10 μg/dl compared to a zero air lead scenario and appears to be a reasonable lower bound for consideration of a revised lead standard. Intermediate increments are indicated for lead NAAQS levels of 0.75, 1.0 and 1.25 $\mu g/m^3$.

6) While the basis for a decision on the lead standard should be the most sensitive population, i.e., young children, the case-study results on adult men indicated small PbB reductions with progressively lower monthly lead NAAQS levels evaluated, beginning with 1.5 $\mu g/m^3$ down to 0.5 $\mu g/m^3$. A PbB threshold for blood pressure effects in men has not been defined. Two PbB levels, 10 and 12 μg/dl, are selected to compare the relative protectiveness of alternative lead NAAQS. The results indicate that a monthly NAAQS between 0.5 and 1.5 $\mu g/m^3$ would result in between 1.0 - 3.5% of non-occupationally exposed men with PbB levels above 10 μg/dl, compared to 7.2-12.1% at current baseline exposures and 0.6% above 10 μg/dl simply because of non-air background exposure. The percentages above 12 μg/dl for this range of standards are estimated to be 0.3-0.9%, compared to 0.1% due to background exposures.

7) Fetal exposures are not evaluated quantitatively in the case-study exposure analyses. While young children are the most responsive population in terms of the lead NAAQS, and represent the appropriate group to focus on in the exposure analyses, the sensitivity of the developing nervous system in the fetus, and uncertainties regarding other possible fetal effects, require consideration in determining the appropriate margin of safety that should be provided by a lead NAAQS.

8) Other factors that should be considered in evaluating the margin of safety are the significance and persistence of observed or potential health effects, the persistence of lead in the body and in accessible environmental reservoirs (i.e., soil),

the sensitivity of the exposure analyses to alternative assumptions, the potential carcinogenicity of lead, and groups beside the fetus that have not been evaluated quantitatively because any lead NAAQS, no matter how stringent, could not remedy their excessive background exposures (e.g., children with pica or living with lead-paint hazards), or because there are insufficient data to quantify their risks at this time (e.g., post-menopausal women).

V. CRITICAL ELEMENTS IN THE REVIEW OF THE SECONDARY STANDARD

This section includes a discussion of information drawn from the criteria document that appears most relevant to the review and possible revision of the current secondary NAAQS for lead. It focuses on field and laboratory studies that have identified potential effects of lead in terrestrial and aquatic ecosystems.

A. Effects in Terrestrial Ecosystems

Anthropogenic emissions of lead deposit on terrestrial ecosystems via wet and dry deposition. After initial deposition on vegetation and other surfaces, the migration and distribution of lead in the soil reservoir depends on a number of environmental factors including precipitation, surface adsorption, and ion exchange reactions (Zimdahl and Skogerboe, 1977; Miller & McFee, 1983; Camerlynck & Kiekens, 1982). Once in the soil reservoir, lead is relatively insoluble and immobile (NAS, 1980; Nriagu, 1978) and is not readily removed by such mechanisms as leaching and stream run-off (EPA 1986a, pp. 6-29, 8-8). As a result, lead accumulates in the soil reservoir even when the deposition rate is relatively low.

When examining the potential impact of lead on terrestrial ecosystems, a distinction must be made between total soil lead content and the available or potentially available fractions. The fraction of soil lead that may be biologically available includes the potentially available lead (exchangeable forms determined by chemical extraction) and the actually available water soluble forms (lead in soil moisture) (EPA, 1986a, p. 6-29). The generally low solubility of lead and the apparently small percentage (1-12%) of total soil lead that is exchangeable (Camerlynck and Kiekens, 1982; Miller and McFee, 1983; Hughes, 1981; Atkins et al., 1982) suggest that the bioavailability of lead for plants is quite limited. The potential effect of acid precipitation to increase the relative mobility of lead in soil

(Tyler, 1978; Hutchinson, 1980) is of clear concern as a mechanism that may increase the bioavailability of this heavy metal.

Given the varying capacity of different soil types to immobilize lead under different environmental conditions (Zimdahl and Skogerboe, 1977), and the limited usefulness of chemical extraction studies to provide reliable estimates of exchangeable soil lead fractions, it is difficult to determine the percentage of total soil lead that is biologically available (actual or potential).

The major concern regarding deposition of atmospheric lead onto plant surfaces is its eventual entry into the human food chain. Effects on plants may also occur directly through foliar uptake or indirectly via root uptake from the nutrient medium (soil moisture) (Facchetti and Geiss, 1982; Lindberg and Harriss, 1981). Although 90% or more of lead taken up via the roots may remain tightly bound in the roots (Koeppe, 1981), field and laboratory studies provide evidence that some lead is translocated to physiologically active tissues in vascular plants (CD, pp. 8-18 to 8-19). While the relative significance of foliar uptake has not been clearly determined, it is potentially high since surface deposition of lead is estimated to account for 90% of total plant lead (CD, p. 8-42). Elevated lead burdens in plants near smelters and along roadsides, for example, have been attributed primarily to surface deposition (Getz et al., 1977; Nriagu, 1978; Smith, 1976).

Experimental data on lead-induced effects in plants indicate that: (1) at relatively low concentrations, ranging from 2-10 μg Pb/g hydroponic solution, inhibition of photosynthesis, alteration in enzyme activity, and reduction in growth can occur. Factors such as length of treatment (exposure), chemical form of lead, level of nutrients in solution, and age and species of plant can influence the experimental results (Koeppe, 1981;

Paivoke, 1979); (2) high concentrations of total soil lead are necessary before physiological effects in plants are observed. For example, Khan and Frankland (1983) report significant growth reduction in radish plants with exposure to 1000 µg Pb/g soil and complete growth inhibition at 5000 µg Pb/g soil; and (3) lead tolerant plant communities appear near roadsides and stationary source emissions (Antonovics et al., 1971; Atkins et al., 1982). Potential changes in species composition in these areas have implications for the long-term effect of lead on ecosystem function and stability. Atkins et al. (1982) suggest that selection pressure due to even low total soil lead concentrations (112 µg Pb/g soil), resulted in the evolution of lead tolerance in a roadside grass.

Available data suggest that the impact of lead in terrestrial ecosystems may be evident first in the components of the soil and litter microcosm (e.g., fungi and bacteria) that play a critical role in the decomposition of organic matter and in nutrient cycling (Tyler, 1972; Doelman and Haanstra, 1979a; Babich and Stotgky, 1979). In the presence of lead (1500 µg Pb/g soil), the composition of microbe communities may shift to more lead-tolerant populations (Doelman and Haanstra, 1979b) and, at soil lead concentrations found near roadways and stationary sources (750-2000 µg Pb/g soil), soil microbial activity may be sufficiently reduced to inhibit the decomposition and nitrification processes (Smith, 1981; Doelman and Haanstra, 1979a; Liang and Tabatabai, 1978). However, Crist et al. (1985) reported no inhibition during the early stages of leaf-litter decomposition for the range of lead concentrations evaluated, i.e., 0 to 1000 µg Pb/g leaf added as lead sulfate. Subtle changes in ecosystem structure and function have been attributed to lead contamination. Friedland et al. (1984) suggest that the increase in percent organic matter in a New England forest may have resulted from the accumulation of lead and other trace metals that inhibited decomposition. In other more heavily contaminated areas, reduced abundance and altered composition of

microflora populations have been observed accompanied by accumulation of litter and alterations in soil parameters (Jackson and Watson, 1977; Bisessar, 1982; Williams et al., 1977c).

Although these field observations suggest inhibitory effects of lead on microbial activity in certain heavily contaminated areas, quantitative assessment is limited by the lack of adequate controls for confounding effects of other stationary source emissions (including other metals) and of environmental influences (e.g., temperature, moisture). Further, the long-term significance of lead-induced changes in soil microbial populations is unclear and depends on whether the ecosystem has the ability to compensate for such perturbations. Nevertheless, the critical role of soil microbes in terrestrial ecosystem processes (decomposition and nutrient cycling) indicates the need for additional research to more clearly define the potentially serious effects of lead on microbial activity.

Decreased soil invertebrate abundance has also been observed in lead-contaminated soils (Watson et al., 1976; Williams et al., 1977c; Bisessar, 1982).

Very few field studies reporting lead exposures, body burdens and associated effects in wildlife are available. With the exception of cattle and waterfowl, incidence rates of lead poisoning in terrestrial fauna are generally unavailable (Forbes and Sanderson, 1978; Botts, 1977) and difficult to verify. Sources of these exposures have typically included lead wastes, paint and spent lead shot (unrelated to airborne lead emissions), and contaminated forage near lead smelters (NAS, 1980; Forbes and Sanderson, 1978).

Lead burdens in animals are elevated relative to natural background levels (EPA, 1986a, pp. 8-33, 8-34), and have been correlated with proximity to roadways and lead point sources

(e.g., mining sites, smelters) (Williamson and Evans, 1972; Quarles et al., 1974; NAS, 1980; Clark, 1979; Beresford et al., 1981; Kisseberth et al., 1984).

When assessing the effects of lead on domestic animals and wildlife, it is important to consider the more subtle effects that are not readily discernible in field observational studies, but found on laboratory experiments such as alterations in neurobehavior and reproduction and development. Because of species differences in susceptibility (Forbes and Sanderson, 1978) and a lack of sufficient quantitative exposure/uptake/response data in natural habitats, results from controlled animal studies have not been extrapolated to animals in natural environments. Nevertheless, the available data indicate that domestic animals and wildlife are at least as sensitive to lead as those studied in laboratories.

B. Effects in Aquatic Ecosystems

Although lead is readily complexed in natural water systems (EPA, 1986a, p. 6-34), concentrations exceeding 100 µg Pb/l (lead in solution) have been reported for surface waters receiving urban runoff and sewage and industrial effluents (NAS, 1980). Freshwater ecosystems function as potential sinks for lead loading (McNurney et al., 1977; Getz et al., 1977), with the sediment as the primary collection site (Rickard and Nriagu, 1978). As a result, the soluble fraction comprises only a small percentage of the total lead burden (Rickard and Nriagu, 1978; Wershaw, 1976). The solubility and sedimentation of lead depends on a number of physical, chemical and biological factors (EPA, 1986a, p. 8-14), and the retention of lead within the sediment is influenced by the substrate type (McNurney et al., 1977; Wershaw, 1976; Newman and McIntosh, 1982). Over the past century, a trend of increasing deposition of lead in the sediments of freshwater systems has been observed (EPA, 1986a, p. 5-1, Figure 5-1), with elevated lead concentrations observed in sediments draining urban areas relative to rural areas (McNurney et al., 1977; Getz et al.,

1977). Some reversal of this trend has been observed in river and ocean sediments in and around the U.S., likely a result of recent, significant reductions in atmospheric lead emissions (Alexander and Smith, 1988; Rabinowitz, 1989). For example, Trefry et al. (1985) reported a 40% decrease in lead transport by the Mississippi River in the decade since the regulation of lead additives in gasoline.

Lead in the sediment can become a source of soluble lead even after the discontinuation of lead inputs (Wershaw, 1976). Increased availability of waterborne lead to aquatic biota is most pronounced in water bodies in which complexed lead in the sediment remains at the water-sediment interface (Getz et al., 1977).

Water lead concentrations as low as 19-30 µg/L have been associated with increased mortality and impaired reproduction) in aquatic invertebrates (Borgmann et al., 1978; Biesinger and Christensen, 1972). Vertebrates (fish) appear even more sensitive. Hematological and neurological changes have been observed in fish exposed under laboratory conditions to concentrations between 8-12 µg Pb/l. The neurological effects include black tails, an early indicator of spinal deformity, and spinal curvature, which increases mortality and prevents successful reproduction (Hodson et al., 1978a,b). Effects observed at these lower levels may have been enhanced by the relatively soft water conditions used in the experiments (Hodson, 1979). In 1985, the U.S. EPA Office of Water Regulations and Standards published new ambient water quality criteria for lead to protect aquatic life. These criteria concentrations are expressed as a function of water hardness and indicate the need to consider the influence of this chemical water quality parameter on the bioavailability and toxicity of lead. For example, at hardnesses of 50, 100, and 200 mg/l as $CaCO_3$ the 4-day average criteria concentrations of lead for freshwater systems are 1.3, 3.2, and 7.7 µg/l, respectively, and the one-

hour average concentrations are 34, 83, and 200 µg/l (50 FR 30791).

C. Staff Conclusions and Recommendations

The available laboratory and field data indicate that at high concentrations, lead can: 1) affect certain plants (e.g., inhibition of photosynthesis, reduced growth, changes in species composition), and fish (e.g., neurological changes); and 2) alter the composition of soil microbial communities and inhibit invertebrate activity resulting in delayed decomposition, reduced nutrient supply, and altered soil properties (e.g., lower organic content). A qualitative assessment of the available field studies and animal toxicological data suggests that domestic animals and wildlife are as susceptible to the effects of lead as laboratory animals used to investigate human lead toxicity risks.

The available data also raise concerns about the continued accumulation of lead in soil and sediment reservoirs. Due to the persistence of lead in the environment, such accumulations are expected to continue as long as inputs exceed outputs. Thus, even at relatively low deposition rates, lead could affect the ecosystem over time. This concern is primarily directed to urban and stationary source areas that may already be approaching or have exceeded their soil capacity to bind lead.

In summary, while the available data are limited and do not provide clear quantitative relationships, they generally support the need for limiting lead emissions to protect against potential ecosystem effects. Indications are that the emission reductions achieved since promulgation of the current standards in 1978, particularly when coupled with reductions achieved by the phasedown of lead in gasoline (gasoline combustion in the early 1980's accounted for 85-90% of total airborne lead emissions), may have mitigated or delayed the potential risk of lead-induced ecosystem effects occurring in many areas of the country. In urban centers, along roadsides, and in the immediate vicinity of

major stationary sources that have experienced a long-term, historical accumulation of lead, and where the natural soil sinks for lead may be approaching or have exceeded their capacity to bind lead, the more sensitive components of the ecosystem (e.g., soil microbes) may remain at some risk that is difficult to quantify at present.

Until a stronger data base is developed that more accurately quantifies ecological effects of different lead concentrations, the staff recommends that consideration be given to retaining a secondary standard at or below the level of the current secondary standard of 1.5 $\mu g/m^3$. If the level, averaging time, or form is changed for the primary standard, consideration should be given to making a similar change for the secondary standard to facilitate implementation.

APPENDIX A. SUMMARY OF PROBABILITY ENCODING ON LEAD-INDUCED HEALTH EFFECTS

The scientific information describing dose-response relationships for lead, as with most environmental pollutants, is generally limited and incomplete. There is a large variation in people's susceptibility to air pollution-induced health effects, and scientific evidence is rarely conclusive in establishing a causal relationship for health effects resulting from pollutant exposure, especially if these effects involve a latency period or other contributing factors. Given the precautionary nature of the Clean Air Act and the need to protect public health with an adequate margin of safety, it is important to characterize, as explicitly as possible, the range and implications of uncertainties in the data base as part of the ambient standard review. One way to address uncertainties in the scientific knowledge about a particular health effect is to obtain probability distributions based on expert judgments. Obtaining, or encoding these judgments involves interviewing experts to assess their judgments concerning the probability that a certain fraction of the sensitive population would suffer a particular adverse health effect at a given exposure level. Probability judgments can be used to describe an individual's assessment of the likelihood of an event based on the current state of information, which includes both his or her judgments or interpretations of existing studies and theories and the quantitative data available. Because different experts will have different judgments, it is also important not to merge these judgments into a single average, but rather to present to the decision makers the range of risks based on the range of judgments, and thereby also identify the range and form of disagreement among experts.

In 1984-1985, probability distributions representing the judgments of experts on two health effects were formally and directly assessed using the technique of probability encoding.

Detailed results of the encoded judgments and their application to compute health risks in children living near representative lead point sources are provided in Wallsten and Whitfield (1986). The report also describes the methods used to elicit the judgments. These methods were reviewed in 1985 by CASAC who found them to be sound.

Of the numerous health effects of lead, reductions in hemoglobin levels and IQ decrements were chosen for probability encoding. It must be emphasized that although there is considerable uncertainty regarding the dose-response functions for these two effects, particularly at low lead levels, these endpoints are not the most sensitive indicators of lead toxicity, nor are they necessarily the most critical in terms of public health. Because this exercise was EPA's first application of formal risk assessment procedures in reviewing a NAAQS, it was important to select health endpoints: a) that could be readily quantifiable in common measurement units (in contrast to classroom behavior, for example); b) that could be readily understood in terms of their medical significance (in contrast to changes in ALA or nerve conduction velocity, for example); and c) for which exist a sufficient number of qualified experts who span the range of respected opinion and interpretation (unlike for example,lead-induced changes in vitamin D metabolism for which few experts can be identified).

Since only a finite number of PbB levels can be presented for encoding,it is necessary to interpolate between levels in order to use the judgments in risk assessments. Such interpolations were made by fitting suitable probability distributions to the encoded values for both hemoglobin and IQ effects (see Wallsten and Whitfield, 1986, for a detailed description). The present discussion utilizes the functions fit to each individual's probabilistic judgments to present a summary of the quantitative results for both hemoglobin and IQ. The functions provide an accurate representation of the underlying encoded values, both because goodness of fit was excellent and

because each expert endorsed the output of the respective functions as representing his or her judgments.

A. Encoding Judgments on Lead-Induced Hemoglobin Decrements

Of five experts selected, probability judgments of four were encoded with respect to the frequency of lead-induced hemoglobin levels below either 9.5 or 11.0 grams per deciliter (g/dl) in homogeneously exposed populations of young children. The fifth expert (Expert B) felt uncomfortable with the notion of judgmental probability encoding and declined to have his judgments encoded. The experts were given the option of considering separately the population of children in the age groups 0-3 and 4-6 years, because of the age-related differences in iron deficiency.

It is generally agreed that for children a hemoglobin level of about 12 g/dl is normal and about 9 g/dl is anemic. Thus, of the two levels specified, a hemoglobin concentration of 9.5 g/dl would be much more likely to be considered as an adverse health effect. Although both hemoglobin levels are sufficiently low to warrant concern, there would likely be extensive debate over whether a hemoglobin level of 11 g/dl would necessitate preventative measures in terms of a lead air quality standard. In the interests of brevity and of focusing in on the more critical effects, results are summarized here only for the judgments regarding 0-3 year olds (the more sensitive age group), and for the dose-response function for hemoglobin levels less than or equal to 9.5 g/dl (See Figure A-1). [Expert C, believes that a single dose-response function applies to children in the 0-6 year age range; with his concurrence, his judgments were reproduced in both the 0-3 and 4-6 year age groups.]

The following discussion regarding Figures A-1 and A-2 is extracted directly from Wallsten and Whitfield (1986):

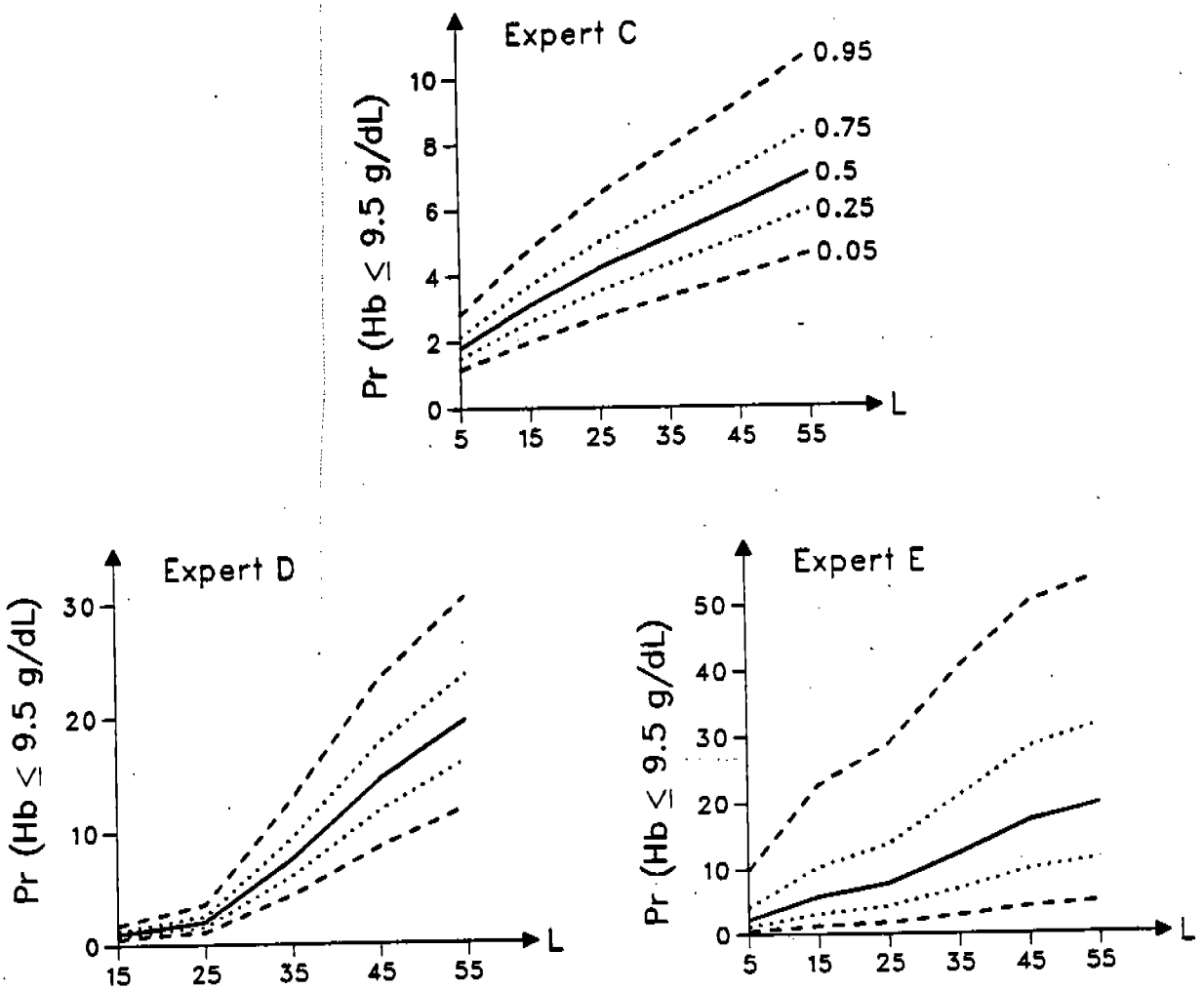

Figure A-1. Probabilistic Judgments of Experts Regarding Lead-Induced Hemoglobin Levels $\leq$ 9.5 g/dl in children aged 0-3 years. Blood lead (L) is on abscissa (in ug/dl) (from Wallsten and Whitfield, 1986).

The graphs are analogous to the usual dose-response functions found in the literature, except, of course, they are based on probabilistic judgments rather than on direct data. The dark, central curve in each panel shows the median judged dose-response curve for each expert. In other words, for a given panel, according to that expert, at each blood lead level there is a 0.50 probability that the true response rate is above the indicated value and a 0.50 probability that the true response rate is below it.

The two lighter lines on either side of the median curve contain the central 50% credible interval. Thus, according to the expert in a particular panel, at each blood lead level there is a 0.25 probability that the true response rate is below the lower light curve, a 0.50 probability that it is between the two light curves, and a 0.25 probability that it is above the upper one. In a similar manner, the dashed curve contains the 90% credible interval.

The more tightly packed are a family of functions in a panel, the less uncertainty does an expert indicate in his judgments. Thus, Figure A-1 gives a rather complete representation of each expert's probabilistic judgments.

Figure A-2 is less complete, but provides a convenient means of comparing judgments across experts. The axes are the same as in Figure A-1. The vertical bars at each lead level represent each expert's central 90% credible interval for response rate, and the symbol within each bar indicates the median judgment at that lead level.

It must be borne in mind that these judgments are with respect to lead-induced response rates over and above any base response rate due to iron deficiency and other factors. Thus, levels of uncertainty, as well as differences or similarities of opinion reflected here, are focused solely on the effects of lead on hemoglobin.

Note first that expert A did not feel that there was a measurable lead-induced hemoglobin effect at PbB levels below 45-55 µg/dl, and therefore judgments at 9.5 g/dl are not shown for him; indeed, his median judgment for the percentage of children

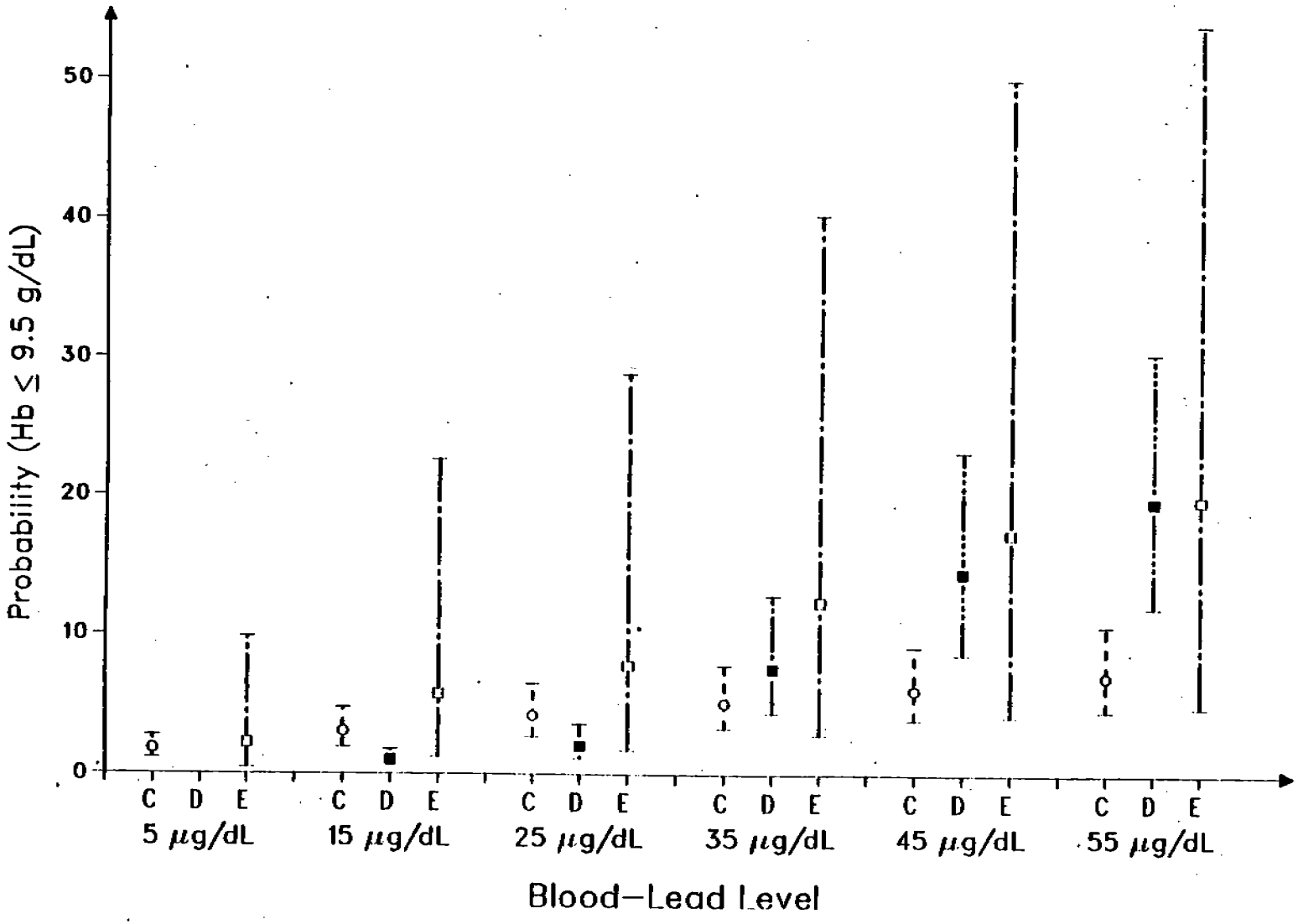

Figure A-2. Comparison of judgments of Experts C, D, and E regarding the probability of hemoglobin levels ≤ 9.5 g/dl, in children ages 0-3 years at different blood-lead levels. The vertical bars at each blood-lead level represent each expert's 90% credible interval for response rate and the symbols indicate the median judgment at that blood-lead level (from Wallsten and Whitfield).

age 0-3 years with hemoglobin levels below 11 g/dl at PbB = 45 µg/dl is 3%, and this rises to a most likely rate of 17% at PbB = 75 µg/dl.

There is overlap in the judgments of experts C, D, and E, although not to the degree as for their judgments regarding hemoglobin levels below 11.0 g/dl which are not displayed here. For example, these experts judged with a probability of 0.9 that the following fraction of children 0-3 years old which would have hemoglobin levels below 9.5 g/dl with PbB of 35 µg/dl were within the following ranges: 3-8% (Expert C); 4-13% (Expert D); 3-41% (Expert E). At a PbB of 25 µg/dl, the corresponding range of the fraction of children affected with a probability of 0.9 are:3-6% (Expert C); 1-4% (Expert D); 2-29% (Expert E). For a PbB of 15 µg/dl, these 0.9 credible intervals are: 2-5% (Expert C); 1-2% (Expert D);1-23% (Expert E). For a PbB of 5 µg/dl, the following range of fractions of children 0-3 years would have hemoglobin levels below 9.5 g/dl with 0.9 probability: 1-3% (Expert C); 0 (Expert D); 0-10% (Expert E).

Considering the median judgments (i.e., the response rate for which there is a 0.5 probability that the actual rate is either above or below the indicated value), C and E agree in estimating the most likely response rate at 5 µg/dl to be 2%, while D is most certain that the response rate is 0. Expert C's median response rate judgment increases relatively slowly with increased PbB, while that of expert D increases relatively quickly. As a result, at PbB = 55 µg/dl, D and E agree that the most likely response rate is 20%, while C considers it to be 7%.

Of these 3 experts, expert E expresses considerable uncertainty in his judgment about the dose-response function, while experts C and D express much less. Note also that the judgment of expert D suggests a slight threshold between PbB levels 25 and 35 µg/dl, but that the judgments of the other two

do not suggest a threshold for hemoglobin levels below 9.5 g/dl in 0-3 year olds.

The corresponding judgments for lead-induced hemoglobin levels at or below 11.0 g/dl, and for children 4-6 years old, are not displayed here. Expert A judged that blood lead below 45 μg/dl would not cause hemoglobin levels to drop as low as 11.0 g/dl. As with 9.5 g/dl, the judgments of experts C, D, and E for 11.0 g/dl tend to overlap, but the degree of similarity displayed is greater than at the low hemoglobin level.

None of these 3 experts' judgments suggest a threshold above which blood lead would result in a hemoglobin level below 11.0 g/dl. According to their median judgments, the best estimate of response rate for 0-3 year olds, hemoglobin $\leq$ 11.0 g/dl, is between 2% and 7% at PbB = 5 μg/dl, rising to between 14% and 26% at PbB = 55 μg/dl. The judgments for children 4-6 years of age followed the same patterns as for children 0-3 years, with all the experts judging smaller probabilities of effects in the older group. Detailed results can be found in Wallsten and Whitfield (1986).

B. Encoding Judgments on Lead-Induced IQ Decrements

It should be noted again that IQ was chosen not because it is the only,nor necessarily the best, measure of cognitive ability, nor is it being considered as a surrogate for other suspected lead-related central nervous system and behavioral effects that have been explored (e.g., brain wave activity, sensory motor, perceptual and attentional deficits, negative classroom behaviors). Rather, IQ decrement emerged as most appropriate to consider because of its acknowledged functional significance, its easy specification, and the amount of data on its relationship to lead exposure.

It must also be emphasized that the encodings were conducted prior to publication of several important studies or IQ effects in children (e.g., Schroeder et al., 1985; Hawk et al., 1986; Fulton et al., 1987; see section III.D.2.c). Although these recent studies tend to support earlier data, interpretation of the encoded judgments here must recognize their time context.

The probability judgments of six experts were encoded with respect to the outcomes of a hypothetical, ideal experiment in which a very large number of subjects were randomly assigned at conception to various exposure groups and were exposed to (or sheltered from) lead until their seventh birthdays. Although each child's lead uptake would not be constant due to changes with age, physiology and behavior, the hypothetical experimental conditions were specified such that at their third birthdays, all children in each group have the same measured PbB level. Environmental lead levels necessary to yield a given PbB level at age 3 in a particular child were specified as remaining constant through the seventh birthday, at which time the WISC-R IQ test was administered. The very large numbers of subjects per group eliminated any concern about sampling error, and the random assignment of subjects to conditions eliminated any concern about complex analyses of covariance. Each group was assumed to differ only in terms of exposure to lead.

Probabilistic judgments were encoded regarding: (a) the mean IQ decrement for each exposure group (5, 15, 25, 35, 45, and 55 µg/dl on their 3rd birthday) relative to a lead-free control group; (b) the mean IQ of the control group; and (c) the within-group IQ standard deviation. Judgments about control group mean IQ values and within-group standard deviations were necessary to derive probabilistic estimates about the lead-induced increase in percent of children at each lead level whose IQ scores are below a specified IQ value of interest. Detailed results, including the encoded judgments, mathematical functions fit to those judgments, goodness of fit measures, and derived subjective

probabilities about dose-response functions, are given in Wallsten and Whitfield (1986). For brevity, summaries of results for IQ decrements only are presented here.

The experts were given the option of considering possible interactive effects of socio-economic status and lead on IQ (based on findings from several studies discussed in the CD and this staff paper) by considering low SES children living in households with incomes in the lowest 15th percentile separate from the remainder of the population. All the experts, except F, believe that at the doses under consideration, lead interacts with variables that contribute to SES level. Therefore, all except Expert F provided separate judgments for the two SES levels.

Figure A-3 summarizes the judgments of all six experts regarding mean IQ decrements for the low SES group. The following discussion regarding the figure is extracted directly from Wallsten and Whitfield (1986).

> Each person's judgments are shown in a separate panel. Blood lead is on the abscissa and mean IQ decrement (mean control group IQ minus mean exposed group IQ) is on the ordinate.
>
> The dark, central curve in each panel shows the median judged IQ decrement for each lead level. In other words, for a given panel, according to that expert there is a 0.50 probability that the actual mean IQ decrement would be greater than the indicated value, and a 0.50 probability that it would be less. The successively lighter pairs of curves that bracket the median curve represent central 50%, 90%, and 95% credible intervals.
>
> Figure A-4 allows a comparison of judgments across the experts. The axes are the same as in Figure A-3. The vertical bars at each lead level represent each expert's central 90% credible interval, and the symbols are his or her median judgments.
>
> Expert F consistently judged the IQ effects of lead to be less than did the other experts, and evidenced considerably less uncertainty about the magnitude of

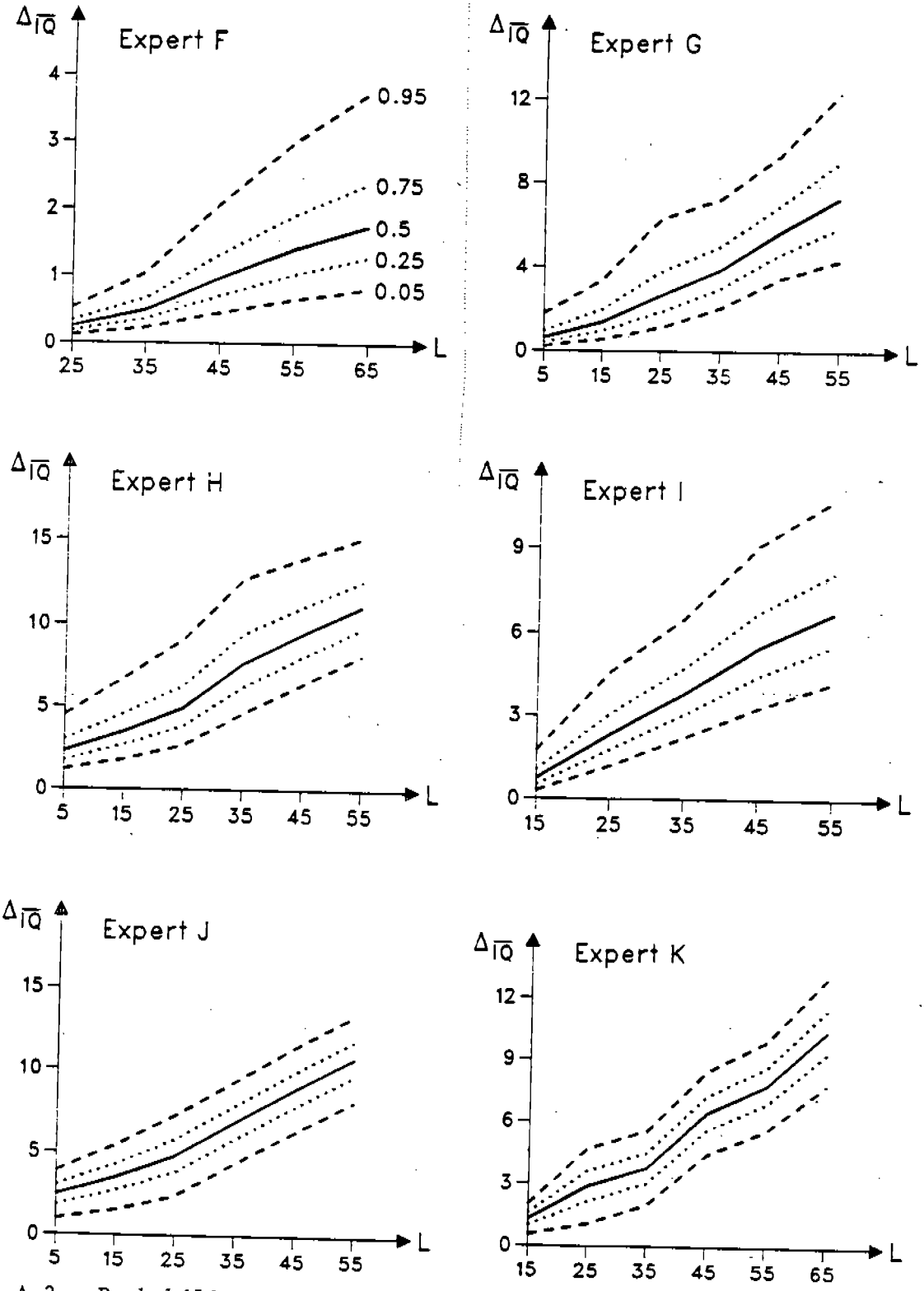

Figure A-3. Probabilistic Judgments of Experts Regarding Mean, Lead-Induced IQ Decrements for Low SES Group. Blood lead (L) is on abscissa (in ug/dl) and mean IQ decrement (mean control group IQ minus exposed group IQ) is on the ordinate of each panel (from Wallsten and Whitfield, 1986).

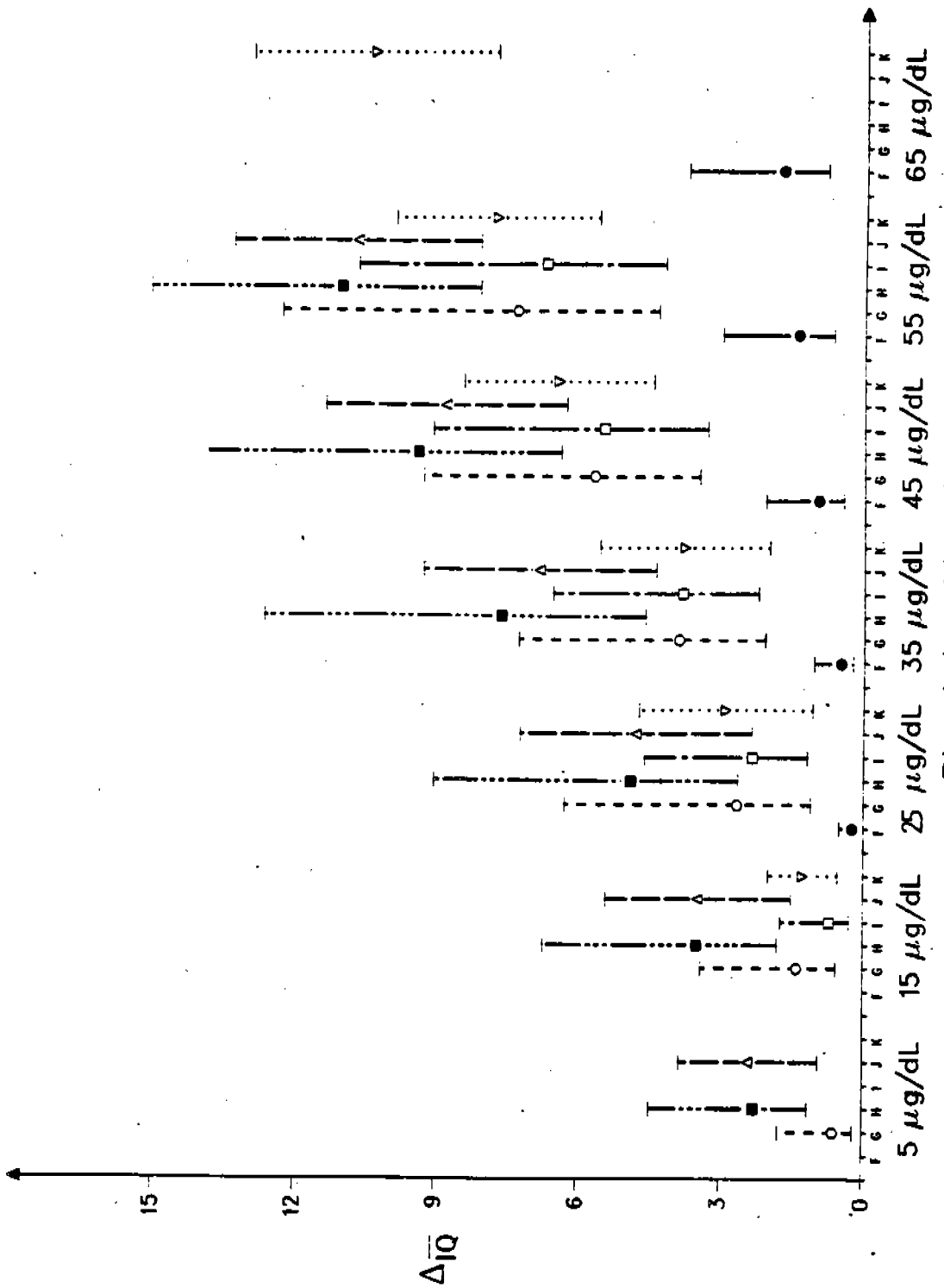

Figure A-4. Comparison of judgments across experts regarding mean IQ decrements for low SES group. The vertical bar at each, blood-lead level represents each expert's central 90% credible interval, and the symbols indicate the median judgment at that blood-lead level (from Wallsten and Whitfield, 1986).

these effects than did the others. F was certain that there is no IQ effect of lead up to at least 15 µg/dl. At 25 µg/dl, the median judged IQ decrement is about a 0.25 point, and this increases to a median judged IQ decrement of just under 2 points at 65 µg/dl. According to F, at 25 µg/dl, the IQ decrement exceeds approximately 0.5 point with probability 0.05, while at 65 µg/dl, it exceeds 3.7 points with the same probability.

There are overriding similarities in the judgments of the other experts, although there are also small, consistent differences among them. Thus, only G, H, and J give any credibility to there being IQ effects as low as 5 µg/dl, while I does so at 15 µg/dl, and K does at 25 µg/dl. The judgments of H and J are consistently very close, as are those of G, I, and K, which as a group are somewhat lower than those of and H and J. Considering the five sets of judgments, the median judged IQ decrement at 5 µg/dl ranges from 0 to 2.4 points. The median judged IQ decrement at 55 µg/dl is from about 7 to 11 points. According to the judgments of G, H, and J, with probability 0.05, the IQ decrement exceeds 1.8 to 4.5 points at 5 µg/dl, while according to all 5 experts, it exceeds 9.9 to 15.1 points at 55 µg/dl with the same probability.

Considering intermediate PbB levels, Expert F judged a probability of 0.5 that the mean IQ decrement at a PbB level of 35 µg/dl in low SES children would be 0.5 points. Corresponding median judged IQ decrements at 35 µg/dl for the other experts are: 1.5 (Expert G); 8.4 (Expert H); 3.6 (Expert I); 7.0 (Expert J); 4.0 (Expert K). The median judged IQ decrements at 25 µg/dl for low SES children are: 0.25 (Expert F); 2.7 (Expert G); 4.9 (Expert H); 2.3 (Expert I); 4.8 (Expert J); 2.9(Expert K). At a PbB level of 15 µg/dl, the median judged IQ decrements for low SES children are according to these experts: 0 (Expert F); 1.4 (Expert G); 3.5 (Expert H); 0.7 (Expert I); 3.5 (Expert J); 1.3 (Expert K).

As with hemoglobin, credible intervals were calculated for each expert's judgments. For example, the 0.9 credible interval is a set of mean IQ decrement values such that there is a 0.9 probability of the true value falling within it. The 0.9

credible intervals concerning mean IQ decrements for the low SES children for different PbB levels are as follows:

45 µg/dl: 0.45-2.07 (Expert F); 3.5-9.3 (Expert G); 6.4-13.9 (Expert H);3.3-9.1 (Expert I); 6.3-11.4 (Expert J); 4.4-8.4 (Expert K).

35 µg/dl: 0.23-1.05 (Expert F); 2.1-7.3 (Expert G); 4.6-12.7 (Expert H);2.2-6.5 (Expert I); 4.4-9.3 (Expert J); 2.0-5.5 (Expert K).

25 µg/dl: 0.11-0.52 (Expert F); 1.1-6.3 (Expert G); 2.6-9.0 (Expert H);1.2-4.6 (Expert I); 2.3-7.2 (Expert J); 1.1-4.7 (Expert K).

15 µg/dl: 0 (Expert F); 0.6-3.5 (Expert G); 1.8-6.7 (Expert H);0.3-1.7 (Expert I); 1.5-5.4 (Expert J); 0.5-1.8 (Expert K).

5 µg/dl: 0 (Expert F); 0.2-1.8 (Expert G); 1.2-4.5 (Expert H); 0 (Expert I); 0.9-3.9 (Expert J); 0 (Expert K).

Judgments about mean IQ decrement for the high SES group are not displayed here, although all the experts, except F, felt that the risks of lead effects on IQ would be smaller in the high SES children. Also, as with the low SES population, F consistently judged the IQ effect to be less than did the other experts. From 25 µg/dl on, the judgments of the others overlap, with, as before, those of H and J being very similar and somewhat greater than those of G, K, and I, which themselves are similar. Only H gave any credibility to the existence of an IQ effect at 5 µg/dl, G, I,and J did so at 15 µg/dl, and F and K concur at 25 µg/dl (Wallsten and Whitfield, 1986).

Considering all the experts simultaneously, the median judged IQ decrement at 15 µg/dl in the high SES group ranges from 0 to 2.4 points;at 55 µg/dl, it ranges from 1.4 to 7.9 points.

According to G, H, I, and J, with probability 0.05 it exceeds 1 to 7 points at 15 µg/dl, while according to all the experts it exceeds 4 to 11.5 points at 55 µg/dl with probability 0.05.

C. DISCUSSION

Considering the scientific debate that has prevailed about the IQ effects of lead, the degree of consensus reflected in the results is notable. This is particularly so, since the experts were selected so as to span the credible range of opinion. For both health endpoints, encoding subjective probabilities from the scientific experts about specific, well-defined scientific outcomes eliminated or minimized disagreements about definitions, policy, and other matters. The remaining differences, evidenced in the preceding results, are mainly due to differing interpretations of, and extrapolations from, the scientific evidence.

As discussed previously, the health endpoints that were assessed using probability encoding should not be considered the individual effects most crucial to a determination of the appropriate maximum acceptable PbB level. Further, the encodings were conducted in 1985-86 prior to publication of several important studies on IQ effects in children; these studies tend to support earlier data. Several of the experts assigned fairly high probabilities that potentially important hemoglobin and IQ decrements could occur in children with PbB levels starting at 25 µg/dl. Judgments of some of the experts suggest that effects on IQ and hemoglobin could occur at and below 15 µg/dl. In general the judgments tend to support that the range of 10-15 µg/dl is appropriate for evaluating in Section IV.C the health protection provided by alternative lead NAAQS.

APPENDIX B. EXPOSURE CASE STUDIES: SENSITIVITY ANALYSES

This appendix presents results of sensitivity analyses of the three case studies on children described in Section IV.D.2. Populations of children living near a Dallas secondary smelter, the East Helena primary smelter, and a secondary smelter and battery plant in Tampa were modeled from birth up to their seventh birthdays, 1990-1996. Blood lead distributions under alternative lead NAAQS are estimated using the uptake/biokinetic model which accounts for age-specific differences in exposure, absorption, and physiological distribution of lead from food, water, soil and housedusts, as well as air; behavioral and biological variability not captured by the model parameters is accounted for through use of empirically-derived measures of blood lead variance (GSDs). Several parameters were assigned lower and upper bound values that span the range of credible estimates derived from available data. These include time spent outdoors per day, volume of air respired per day, percent absorption in the gastrointestinal tract of ingested lead in diet, concentrations of lead in soil and housedust associated with different air lead concentrations, the amount of dirt typically ingested by children daily, and the GSD value that best represents variability in childhood lead exposure around lead point sources.

The results presented for children in Section IV.D.2 incorporate midpoint estimates of those parameter values with lower and upper bounds. Tables B.1 and B.2 summarize blood lead distributions estimated by the uptake/biokinetic model using either all lower bound values or all upper bound values. While the staff believes that the results in Section IV.D.2 are better representations of future scenarios, the results shown here illustrate the extremes in possibilities. Sensitivity analyses that focus on altering only one or two parameters at a time are possible but are not shown here in the interest of space. Results of any such analysis, using the same range of estimates, would be intermediate to the results in the following two tables.

TABLE B-1. LOWER BOUND SENSITIVITY ANALYSIS: CHILDREN'S PbB LEVELS IN 3 CASE STUDIES*

Case Study (# Children) / PbB Level[a]	Lead NAAQS Level (µg/m³) Baseline[b]	1.5 Quarterly[c]	Monthly[d] 1.5	1.25	1.0	0.75	0.5
Dallas (241)							
Mean PbB (µg/dl)	4.9	3.8	3.8	3.7	3.7	3.6	3.6
% > 10 µg/dl	0.3	0.01	0.01	0.01	0.01	0.005	0.004
% > 15 µg/dl	0.001	0	0	0	0	0	0
East Helena (217)							
Mean PbB (µg/dl)	4.0	3.6	3.5	3.4	3.4	3.3	3.2
% > 10 µg/dl	0.03	0.004	0.003	0.002	0.002	0.001	0.001
% > 15 µg/dl	0	0	0	0	0	0	0
Tampa (10)							
Mean PbB (µg/dl)	6.5	5.6	5.4	5.2	5.0	4.8	4.7
% > 10 µg/dl	5.3	1.4	0.9	0.6	0.4	0.3	0.2
% > 15 µg/dl	0.08	0.009	0.005	0.003	0.001	0.001	0

* Assumes lower bound values for parameters specified in text.
[a] PbB distributions calculated by assuming GSD = 1.30.
[b] Baseline scenario represents current conditions for air quality, as well as soil and dust. Dietary intake assumed to be at 1990-1996 levels.
[c] Current NAAQS and averaging time (calendar quarter).
[d] Alternative NAAQS levels with monthly averaging time.

TABLE B-2. UPPER BOUND SENSITIVITY ANALYSIS: CHILDREN'S PbB LEVELS IN 3 CASE STUDIES*

Case Study (# Children) / PbB Level[a]	Lead NAAQS Level (µg/m³) Baseline[b]	1.5 Quarterly[c]	1.5 Monthly[d]	1.25 Monthly[d]	1.0 Monthly[d]	0.75 Monthly[d]	0.5 Monthly[d]
Dallas (241)							
Mean PbB (µg/dl)	8.9	6.1	5.9	5.8	5.7	5.6	5.5
% > 10 µg/dl	38.8	12.0	10.8	10.1	9.3	8.6	7.9
% > 15 µg/dl	10.8	1.7	1.4	1.3	1.1	1.0	0.9
East Helena (217)							
Mean PbB (µg/dl)	8.3	6.7	6.6	6.4	6.1	5.9	5.6
% > 10 µg/dl	32.7	17.7	16.6	14.5	12.6	10.9	8.6
% > 15 µg/dl	8.1	3.0	2.7	2.2	1.8	1.4	1.0
Tampa (10)							
Mean PbB (µg/dl)	13.6	11.0	10.1	9.6	9.0	8.4	7.9
% > 10 µg/dl	76.6	58.7	51.3	46.1	40.3	34.4	28.7
% > 15 µg/dl	41.0	23.1	17.9	14.7	11.6	8.8	6.5

* Assumes upper bound values for parameters specified in text.
[a] PbB distributions calculated by assuming GSD = 1.53.
[b] Baseline scenario represents current conditions for air quality, as well as soil and dust. Dietary intake assumed to be at 1990-1996 levels.
[c] Current NAAQS and averaging time (calendar quarter).
[d] Alternative NAAQS levels with monthly averaging time.

APPENDIX C: CASAC CLOSURE REPORT

EPA U.S. Environmental Protection Agency Washington, DC
EPA-SAB-CASAC-90-002

Report of the Clean Air Scientific Advisory Committee (CASAC)

Review of the OAQPS Lead Staff Paper and the ECAO Air Quality Criteria Document Supplement

A SCIENCE ADVISORY BOARD REPORT JANUARY 1990

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
THE ADMINISTRATOR

January 3, 1990

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

RE: National Ambient Air Quality Standards for Lead

Dear Mr. Reilly:

I am pleased to transmit the advice of the Clean Air Scientific Advisory Committee (CASAC) concerning the National Ambient Air Quality Standards (NAAQS) for Lead. The CASAC has reviewed and offered comments directly to EPA Staff on the EPA Air Criteria Document update, "Supplement to the 1986 EPA Air Quality Criteria for Lead - Volume I Addendum (Pages A1 - A67)", and the Office of Air Quality Planning and Standards (OAQPS) staff position paper "Review of the National Ambient Air Quality Standards for Lead: Assessment of Scientific and Technical Information", both dated March 1989.

The Committee previously reached closure on the 1986 Air Quality Criteria Document and Criteria Document Supplement. At a meeting held on April 27, 1989, CASAC reviewed and was prepared to close on the 1989 Criteria Document Addendum and the 1989 Staff Position Paper, but withheld closure pending receipt and consideration of additional public comments. The public comment period, scheduled to close 30 days following the CASAC meeting, was extended through June 12, 1989, providing the interested public further time to prepare comments. The additional comments received as a result of the extended comment period were provided to the Committee and taken into consideration before reaching closure. The Committee concludes that these EPA documents, along with the 1986 documents previously closed upon, provide a scientifically balanced and defensible summary of our current knowledge of the

effects of this pollutant, providing an adequate scientific basis for EPA to retain or revise primary and secondary NAAQS for airborne lead.

As part of this review process, the Committee considered and approved the CASAC Exposure Subcommittee review of the August 1988 EPA document "Review of the National Ambient Air Quality Standards for Lead: Exposure Analysis Methodology and Validation". That approval is formally contained in the CASAC report transmitted to you in April 1989 (EPA-SAB-CASAC-89-018, April 1989).

In November 1988, the CASAC formed an ad hoc Joint Study Group with the Science Advisory Board (SAB). The broad charge to this Study Group included assessment of the weight of evidence classification of lead and lead compounds as carcinogens; review of lead-related health effects and exposure issues which cut across EPA organizational lines; and an assessment of how the scientific information concerning lead is applied to standard setting and other regulatory decisions in the Agency. The report of that Joint Study Group, based on their March 30, 1989 and April 28, 1989 meetings, is contained in their report (EPA-SAB-EC-90-001, December 1989), transmitted to you separately.

A key point of the Joint Study Group Report is the contrasting nature of the data base for central nervous system versus carcinogenic effects. The carcinogenic risk assessment is based primarily on induction of kidney tumors in rodents administered large quantities of lead. Use of these data for human risk assessment involves two extrapolations: from rodents to people, and from high doses to the low doses encountered in ambient exposures of lead. In contrast, central nervous system effects are observed directly in people and at exposures at or near the levels of exposure relevant to setting the standard. Thus, and unless, more quantifiable and relevant scientific evidence is available on the carcinogenicity of lead, the Committee feels it appropriate to give primary consideration to nervous system effects in setting the national ambient air quality standard for lead.

During the course of the CASAC meeting several recommendations were made to the EPA Staff as to actions that can be taken that will provide an improved basis for setting the NAAQS for lead. These include calculation of the distribution of blood lead levels estimated to result from achieving an air lead concentration of

0.25 ug/m^3. In addition, it was suggested that it would be appropriate to evaluate the estimated distribution of effects on childrens intelligence at a given level of lead exposure.

While the Committee is willing to further advise you on the lead standard, we see no need, in view of the extensive comments provided, to review any proposed changes prior to their publication in the Federal Register. The public comment period following publication will provide sufficient opportunity for the Committee to provide any additional comment or review, if needed.

The attached report contains the detailed analysis and recommendations of the CASAC concerning its closure on the Criteria Document Addendum and the EPA Staff Position Paper for airborne lead. In considering the CASAC's recommendations for the lead NAAQS it is important to recognize that air is just one source of exposure to lead; reducing the total population risk from lead will require a concerted effort to reduce lead intake from all sources.

We appreciate the opportunity to provide advice on this important issue and look forward to your response to our recommendations.

Sincerely,

Roger O. McClellan

Roger O. McClellan, D.V.M.
Chairman, Clean Air Scientific
Advisory Committee

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16. ABSTRACT

This paper evaluates and interprets the updated scientific and technical information that EPA staff believes is most relevant to the review of the primary (health) and secondary (welfare) national ambient air quality standards for lead. This assessment is intended to bridge the gap between the scientific review in the EPA criteria document and the judgements required of the Administrator in setting the ambient air quality standards for lead.

The major recommendations of the staff paper are: (1) the range of standards under consideration should be from 0.5 to 1.5 ug/m^3; (2) a monthly averaging period would better reflect children's responsiveness to lead exposures than a quarterly averaging period; (3) the most appropriate form of the standard is the second highest monthly average in a 3 year span; (4) with a monthly averaging period, more frequent sampling is needed in areas with point sources; and (5) the hi-volume sampler should be retained to monitor compliance with the lead NAAQS.

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