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Estimating the global burden of disease of mild mental retardation and cardiovascular diseases from environmental lead exposure ☆

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Abstract

The disease burden from exposure to lead resulting in mild mental retardation (due to IQ point decreases) and cardiovascular outcomes (due to increases in blood pressure) was estimated at a global level. Blood lead levels were compiled from the literature for 14 geographical regions defined by the World Health Organization according to location and adult and child mortality rates. Adjustments were applied to these levels, where appropriate, to account for recent changes relating to the implementation of lead-reduction programs and the lower levels seen in rural populations. It is estimated that mild mental retardation and cardiovascular outcomes resulting from exposure to lead amount to almost 1% of the global burden of disease, with the highest burden in developing regions. This estimate can be used to assess the magnitude of the benefits that could be accrued by increasing the global coverage of lead-reduction programs.

Keywords: Blood pressure; Burden of disease; Environmental exposure; Mental retardation; Lead

1. Introduction

Exposure to lead has long been recognized as resulting in significant health impacts, and consequent policy action has led to a dramatic decrease in population exposures in developed countries. However, removal of lead in gasoline has not been tackled in numerous countries, despite it being an extremely effective mechanism for reducing blood lead in children (Landrigan et al., 2000), and, as a result, these countries have been falling behind in terms of population protection. Thus, exposures are still considerable in many parts of the world.

During the last decade, increasing evidence has become available for some milder disease outcomes and physiological changes, such as loss of IQ points and blood pressure increases. Although these conditions may be considered "mild" at the individual level, in population terms their impact may be very significant. Additionally, recent research has shown that some of the health effects occur at levels of exposure that were considered safe previously.

Burden of disease estimates are a tool for expressing various health impacts in a comparable way. Such estimates provide rational information that can be used to prioritize action aimed at health improvement, in addition to information on resource availability, cost-effectiveness, policy, environment, and technology (Murray and Lopez, 1996), although they are not universally accepted (Williams, 1999). Estimating the disease burden provides policy makers with information that may enable them to directly modify the specific risk factor (Prüss et al., 2001). Estimates are generally

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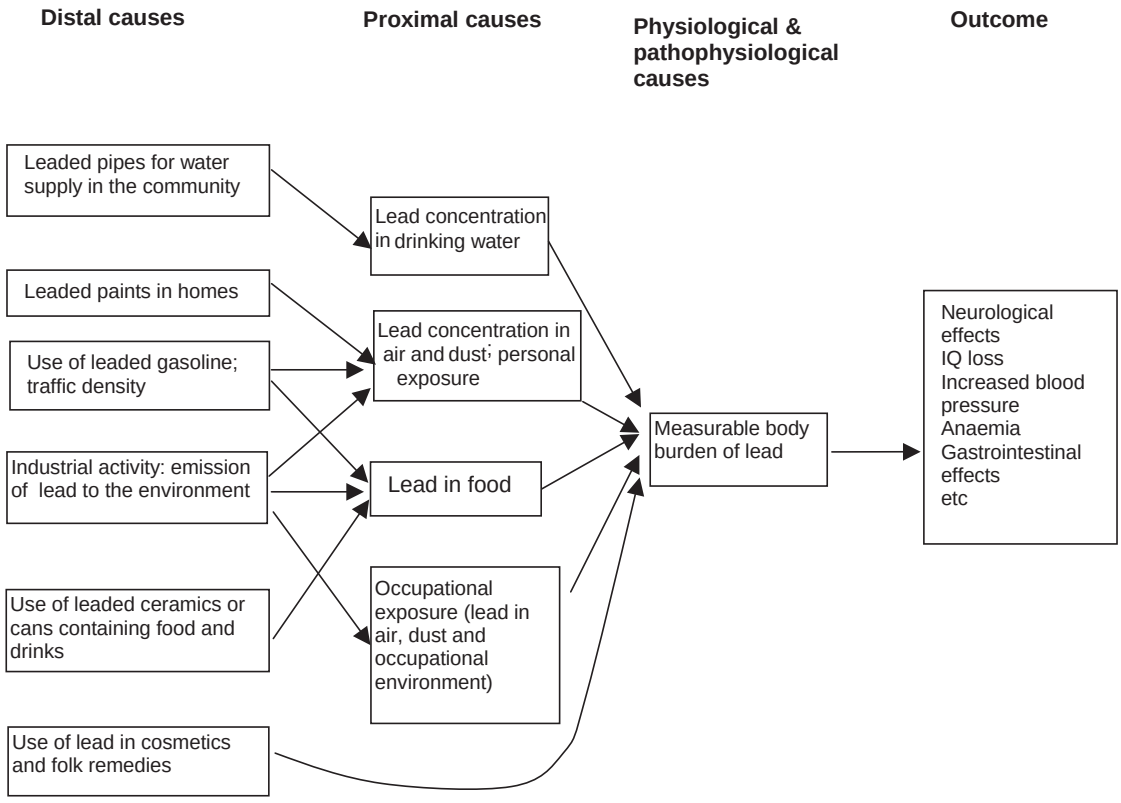


Fig. 1. Framework for exposure to lead.

reported as summary measures of population health, such as the disability-adjusted life year or DALY (Murray and Lopez, 1996), which combines morbidity and mortality. The DALY is the sum of years of life lost due to death and years of life with disability, where each condition is attributed a defined severity weight.

The World Health Organization has recently assessed the disease burden from a number of "risk factors" at a global level (WHO, 2002), one of which is the environmental exposure to lead described here. In addition, further methods for assessment of disease burden from environmental risk factors at the national level are being developed (McMichael et al., 2001; WHO, 2001a).

A large number of sources may contribute to lead exposure. Some of these exposures involve large parts of the world's population, whereas others are more locally or culturally specific. Fig. 1 outlines these sources and structures them in a logical framework according to their "distance" from the health outcome (Murray and Lopez, 1999).

2. Methods

Disease burden was evaluated by estimating the population exposure distributions (based on blood lead) at a regional level in combination with estimates of disease rates for various health outcomes (the so-called "exposure-based approach") (WHO/ILO, 1998).

2.1. Exposure estimate

Blood lead level was chosen to describe population exposure for the following reasons:

- It is a commonly measured parameter, with measurements available from many parts of the world.
- It is an objective physiological measure indicating lead exposure, which can be measured accurately.
- It is strongly related to outcome and can be expected to reflect exposure more closely than estimates derived from the measurement of lead levels in the air, soil, dust, or food.

Population exposure data were obtained principally through a MEDLINE search, using a wide range of keywords. Initial queries were refined using the "Related Articles" facility of MEDLINE and additional author searches. The reference list of any relevant article was also examined. This initial database, of more than 700 articles, was compiled by the Centers for Disease Control. Additionally, the databases LILACS (*Latin American and Caribbean Information System of Health Sciences*), IMEMR (*Index Medicus of WHO's Eastern Mediterranean Regional Office*), and *African Index Medicus* were searched with the same keywords, with MEDLINE consulted again to ensure coverage of the most recent publications (up to the end of 2000).

Table 1
Regions for burden of disease

WHO region	Mortality stratum	Countries
Afr	D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, São Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo
Afr	E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
Amr	A	Canada, Cuba, United States of America
Amr	B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
Amr	D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
Emr	B	Bahrain, Cyprus, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
Emr	D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
Eur	A	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
Eur	B	Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, the Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan, Yugoslavia
Eur	C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
Sear	B	Indonesia, Sri Lanka, Thailand
Sear	D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal
Wpr	A	Australia, Brunei Darussalam, Japan, New Zealand, Singapore
Wpr	B	Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Vietnam

Occupational exposures or studies of "hotspots," i.e., areas of unusually high lead levels of local relevance (such as areas around smelters), were excluded. The rationale for this was threefold:

- It was not possible to assess all hot spots at a global level, as this would have required specific examination of each hot spot (using other methods employing more distal indicators, such as a country's lead production, and would have yielded very speculative results).
- To a certain extent, the exposure to hot spots will be reflected in blood samples taken from the general public, especially when the population around hot spots is significant.
- Occupational exposures to lead should be accounted for in the assessment of burden of disease from occupation (WHO, 1996).

More refined exposure assessments taking into account hot spots and occupational exposures are likely to be possible at national or subnational levels.

Geometric mean blood lead levels from individual countries were combined on a regional basis, with separate levels compiled for children and adults when data were available. The 14 regions used in this analysis (Table 1) correspond to continents divided into mortality strata A–E (i.e., the level of child and adult mortality of a country determines the regional category to which it

is attributed), as described in the Annex of the annual World Health Report (WHO, 2002).

In relating population blood lead measurements to the exposure assessment it was necessary to account for the implementation of lead-reduction programs in many countries where such efforts took place during or after assessment. For these countries, only the most recent blood lead measurements were considered in order to avoid overestimating exposure. Where no recent data were available an alternative approach, based on the level of leaded gasoline, was used. While leaded gasoline is not the only source of lead in the environment (although it contributes to direct exposures through the air and indirect exposures through food and dust), it is a good indicator of a country's efforts at reducing the exposure of its population to lead (Landrigan et al., 2000), and adjustments in population exposure, at country level, have therefore been based mainly on the progress in phasing out leaded gasoline.

Annest and colleagues showed that in the USA over a 5-year period (representing the early stages of a lead-reduction program) average blood lead levels dropped by 37% (Annest, 1983; Annest et al., 1983). Other studies conducted in various countries have shown very similar results, with decreases over a 5-year period ranging between 30% and 48% (Elinder et al., 1986; Schuhmacher et al., 1996; Wietlisbach et al., 1995). We selected 39%, the midpoint, as the reduction factor for a 5-year period. Full implementation of lead-reduction programs, over a decade or more, have shown reductions in blood lead levels in children reaching 90% or more (CDC, 1997). Only recent data, less than 5-years old, were considered for countries with significant lead-reduction activities; a maximum correction factor of 39% (i.e., 7.8% per year) was used to adjust for changes having occurred since the measurements. Each country's use of leaded gasoline was analyzed, and blood lead levels were individually adjusted where necessary (Earth Watch Summit, 2000).

Where leaded gasoline is still in use, lead levels in rural populations are generally lower than those seen in urban populations. Thomas et al. (1999) showed that after the removal of leaded gasoline, population blood lead levels tend to converge on $3.1 \pm 2.3\,\mu g/dL$. This value is very similar to the mean of rural data points of $3.0\,\mu g/dL$ seen in a number of countries in which gasoline lead has not been fully phased out (Nriagu et al., 1997a; Piomelli et al., 1980; Vasilios et al., 1997). As a conservative estimate, we used this value as a reasonable proxy for rural lead levels and used it for countries in which urban values were higher. In Latin America and the Caribbean (Amr B, Amr D), however, higher rural blood lead levels were assumed, as sources such as ceramics and the recycling of batteries contribute significantly to lead exposure (Romieu, 2001a). A value of $4.3\,\mu g/dL$ based on Garcia and Mercer (2001) and Sepulveda et al. (2000) was used to represent rural blood lead levels here. After the complete eradication of leaded gasoline, blood lead levels continue to decrease (mainly due to additional efforts to reduce lead in the environment). Recent assessments from the USA (Amr A) have reported mean blood levels as low as $1.6\,\mu g/dL$ (CDC, 2001). In such cases the same blood lead levels were used for characterizing both urban and rural populations, as higher exposures in urban environments were not justifiable. Rural population figures were derived from the Human Development Report of the UN Development Programme (2000).

For each country with more than one blood lead sample, geometric means were calculated by weighting according to sample size, after adjusting (where required) as outlined above. Regional means were calculated by weighting country means by the size of the urban population. Means of urban and rural populations were estimated separately. If regions were made up of countries with differing levels of progress in phasing out leaded gasoline (all regions but Eur A and Afr D), urban means were assessed separately for two groups of countries based on their level of progress (i.e., the more and the less advanced). In summary, we superimposed two or three log normal distributions for each region to characterize the distribution of blood lead levels in the population, each of them weighted by the population they represented.

In addition to the geometric mean, population exposure was described by standard deviations. Fewer values of standard deviation were available than for mean blood lead levels. In order to estimate standard deviations for data-poor areas, we grouped regions according to economic and lead use patterns and calculated the average standard deviation for each grouping, based on similar lead-use patterns (Amr A; Eur A and Wpr A; Amr B and D; remaining B and C regions; D and E regions). Sample size-weighted country averages were estimated, which were then averaged into the regional mean standard deviations by weighting for urban population size. For the grouping of D and E regions we did not weight by population size because the available standard deviations for the large countries of these two groupings were not representative for other countries.

2.2. Health outcomes

Lead has been implicated in many health outcomes, but here only decreased IQ (leading to mild mental retardation) and increased blood pressure resulting in a number of cardiac diseases have been examined. Health outcomes relating to gastrointestinal effects and lead-induced anemia have also been quantified and are published elsewhere (Prüss et al., 2001). Reproductive effects, effects on violence and, as a consequence,

injuries, and other effects have not been included, as the available data did not permit an estimate of effect levels (ATSDR, 1999).

2.3. Loss of IQ points and mild mental retardation (MMR)

The meta-analysis of Schwartz (1994) showed a reduction of 2.6 IQ points for an increase in blood lead from 10 to 20 μg/dL. This analysis included eight cross-sectional and longitudinal studies, the largest longitudinal study being the Port Pirie cohort study in Australia, with about 500 participants and a follow-up of several years (Baghurst et al., 1992). The meta-analysis also reports that the effect is likely to continue between 10 and 5 μg/dL, with an even steeper curve. Above a blood lead level of 20 μg/dL, a loss of 3.5 IQ points has been assumed (which is the midpoint of the range of 2–5 IQ points reported by the ATSDR report (1999), derived from evidence from de la Burde and Choate, 1972; Rummo et al., 1979).

The loss of IQ points was quantified as follows:

- We assumed a linear relationship with a loss of 1.3 IQ points per 5-μg/dL blood lead interval for blood lead levels between 5 and 20 μg/dL (based on Schwartz's 2.6 IQ point loss for a 10-μg/dL interval). For simplification we divided the linear relationship into three intervals and assigned the mean IQ loss in each interval to its mean blood lead level. Thus, an IQ loss of 0.65 for the 5- to 10-μg/dL interval was ascribed to a blood lead level of 7.5 μg/dL, representing the midpoint of the 5- to 10-μg/dL interval; a 1.95 IQ loss for the 10- to 15-μg/dL interval was ascribed to a blood lead level of 12.5 μg/dL; and a 3.25 IQ loss for the 15- to 20-μg/dL interval was ascribed to a blood lead level of 17.5 μg/dL.
- A loss of 3.5 IQ points was assumed for blood lead levels above 20 μg/dL.

As loss of IQ points per se is not considered to be a disease, we have converted the loss into cases of MMR.

MMR is defined as having an IQ score of 50–69. Intelligence in human populations approximates a "normal" distribution (Lezak, 1995), except for an excess below 50 (representing brain damage and disorder). For estimating how many children will suffer MMR as a consequence of IQ loss due to lead, it is necessary to estimate the ratio of children who already have a low IQ score and for whom a loss of a few points will result in a score of less than 70. We therefore estimated the percentage of the population between 70 and 70.65, 71.95, 73.25, and 73.5 (i.e., the intervals defined by the loss of IQ points outlined above), assuming a normal distribution with a mean of 100 and a standard deviation of 15 (Fryers, 2000; Lezak, 1995) as shown in Table 2. The rate of MMR was estimated by multiplying the numbers of children with the defined IQ point losses with the respective percentage of the population within that increment. However, several diseases result in mental retardation, including anemia, meningitis and pertussis, Japanese encephalitis, ascariasis, trichuriasis, hookworm infection, and cretinoidism and cretinism due to iodine deficiencies (WHO, 2001b). In regions where the incidences of these diseases are significant, the prevalences of low IQ scores will be proportionately higher, and these needed to be accounted for in our calculations. Using prevalences of cognitive impairment and mental retardation as a consequence of these diseases (WHO, 2001b), we estimated the number of additional cases that are likely to be observed because of these additional risks (Prüss-Üstün et al., 2003). The calculated regional adjustment ratios accounting for excess mental retardation rates caused by these communicable diseases or iodine deficiency as compared to the standardized rates are shown in Table 3. The severity weight used for the DALY calculation for MMR was based on a mean of 0.361, as proposed by Murray and Lopez (1996).

Table 2
Distribution of a normal population within specified IQ increments

IQ health band	IQ increment	Percentage of population (assuming a normal distribution) (%)
IQ(1)	70–70.65	0.24
IQ(2)	70–71.95	0.80
IQ(3)	70–73.25	1.45
IQ(4)	70–73.50	1.59

Data are from Lezak (1995).

Table 3
Adjustment ratios to account for excess mental retardation rates caused by communicable diseases or iodine deficiency compared to the standardized rates

	Region													
	Afr D	Afr E	Amr A	Amr B	Amr D	Emr B	Emr D	Eur A	Eur B	Eur C	Sear B	Sear D	Wpr A	Wpr B
Adjustment ratio	2.05	2.01	1.00	2.71	2.64	1.90	1.90	1.00	1.53	1.19	3.25	2.06	1.00	3.03

vl, very low; l, low; h, high; vh, very high.

Table 4
Relative risk values relating blood pressure increases to specified cardiovascular diseases

Disease	BPb increment/bp increase	Age (males)					BPb increment/bp increase	Age (females)				
		15–29	30–44	45–59	60–69	70–79		15–29	30–44	45–59	60–69	70–79
	1: 5–10 μg/dL/0.625 mm Hg						1: 5–10 μg/dL/0.4 mm Hg					
IHD		1.04	1.04	1.03	1.02	1.01		1.03	1.03	1.02	1.01	1.01
CVA		1.06	1.06	1.04	1.03	1.02		1.04	1.04	1.03	1.02	1.01
HTD		1.12	1.12	1.06	1.04	1.03		1.08	1.08	1.04	1.02	1.02
OCD		1.01	1.01	1.01	1.01	1.00		1.01	1.01	1.01	1.00	1.00
	2: 10–15 μg/dL/1.875 mm Hg						2: 10–15 μg/dL/1.2 mm Hg					
IHD		1.13	1.13	1.10	1.05	1.04		1.08	1.08	1.06	1.03	1.03
CVA		1.18	1.18	1.14	1.09	1.06		1.11	1.11	1.09	1.06	1.04
HTD		1.41	1.41	1.19	1.11	1.08		1.25	1.25	1.12	1.07	1.05
OCD		1.04	1.04	1.03	1.02	1.01		1.03	1.03	1.02	1.01	1.01
	3: 15–20 μg/dL/3.125 mm Hg						3: 15–20 μg/dL/2.0 mm Hg					
IHD		1.23	1.23	1.17	1.09	1.07		1.14	1.14	1.11	1.06	1.05
CVA		1.31	1.31	1.24	1.15	1.10		1.19	1.19	1.15	1.10	1.07
HTD		1.78	1.78	1.33	1.19	1.14		1.45	1.45	1.20	1.12	1.09
OCD		1.07	1.07	1.04	1.03	1.02		1.04	1.04	1.03	1.02	1.01
	4: <20 μg/dL/3.75 mm Hg						4: <20 μg/dL/2.4 mm Hg					
IHD		1.28	1.28	1.21	1.11	1.09		1.17	1.17	1.13	1.07	1.06
CVA		1.38	1.38	1.29	1.18	1.13		1.23	1.23	1.18	1.11	1.08
HTD		2.00	2.00	1.41	1.23	1.17		1.56	1.56	1.25	1.14	1.11
OCD		1.08	1.08	1.05	1.03	1.02		1.05	1.05	1.03	1.02	1.01

BP, blood lead; bp, blood pressure; IHD, ischemic heart disease; CVA, cerebrovascular disease; HTD, hypertensive disease; OCD, other cardiac diseases. This table is based on data found in Lawes et al. (2003).

2.4. Blood pressure increases

Hypertension (i.e., the elevation of arterial blood pressure above the normal range) has been associated with blood lead levels. Although not a health outcome per se, increases in blood pressure have been associated with increases in risk of cardiovascular and cerebrovascular disease. The association between lead and blood pressure is strongest for increases in systolic blood pressure in adult males.

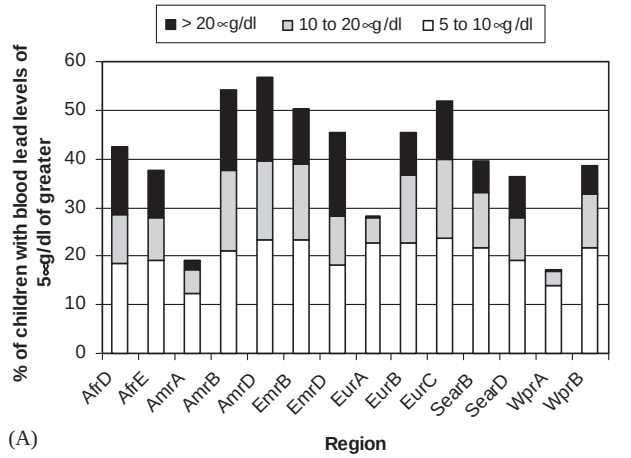
The categories defined for changes in systolic blood pressure have been informed principally by the meta-analysis of Schwartz (1995) and the analysis of the Second National Health and Nutrition Examination Survey (NHANES II—Schwartz, 1988; Pirkle et al., 1985). In his meta-analysis, Schwartz (1988) reported a decrease in the systolic blood pressure of 1.25 mm Hg (95% CI = 0.87–1.63 mm Hg) in men associated with a decrease of blood lead from 10 to 5 μg/dL. The NHANES II describes blood pressure changes in relation to higher blood lead levels, reporting decreases of 2 mm Hg for a reduction in blood lead from 20 to 15 μg/dL and also from 15 to 10 μg/dL. To keep the estimate conservative, the same decrease of 1.25 mm Hg was chosen for all three categories. The findings relating to the higher blood lead levels were based on large studies carried out in the USA (Pirkle et al., 1985; Schwartz, 1988), and are assumed to apply globally. The recent review by Nawrot et al. (2002) provides a similar estimate for an increase of 1.2 mm Hg "for a doubling of blood lead levels" (with the majority of studies addressing the 5- to 10-μg/dL interval).

In women, the association between systolic blood pressure and blood lead is weaker and less well documented. The most recent and comprehensive estimate consists of a 0.8-mm Hg increase in systolic blood pressure for a doubling in blood lead (Nawrot et al., 2002).

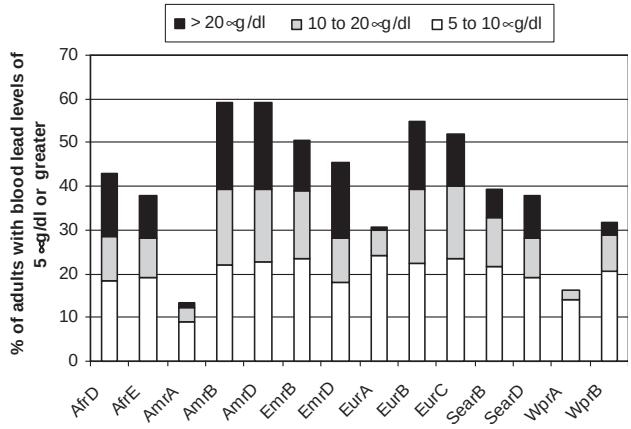
For the calculation of blood pressure increases, we took an approach similar to that used for IQ point loss, with blood lead split into intervals and a blood pressure increase associated with each interval. For men, a 1.25-mm Hg increase was associated with each 5-μg/dL increase between 5 and 20 μg/dL and an increase of 3.75 mm Hg was assumed above 20 μg/dL. For women, a 0.8-mm Hg increase in systolic blood pressure was associated with each 5-μg/dL increase between 5 and 20 μg/dL, and a 2.4-mm Hg increase was assured above 20 μg/dL.

2.4.1. Blood pressure increases and cardiovascular disease

To calculate the occurrence of cardiovascular disease resulting from lead exposure, it is necessary to calculate the attributable fraction due to lead. For this the distribution in the population of blood lead levels causing increased blood pressure is combined with the relative risk for each blood pressure level with the



(A)



(B)

Fig. 2. Percentages of people with specified blood lead levels: (A) childrens and (B) adults.

formula for the "impact fraction" (IF) (Last, 2001):

$$IF = \frac{\sum P_i\ RR_i - 1}{\sum P_i\ RR_i},$$

where P_i is the proportion of the population at exposure category i and RR_i is the relative risk at the exposure category compared to that at the reference level.

The RR is, for the purpose of this analysis, the relative risk of increased blood pressure associated with a particular blood lead level. The proportion of the exposed (P_i) is the proportion of the population with blood lead levels within each specified interval (i.e., 5–10; 10–15; 15–20, and >20 μg/dL) associated with increased blood pressure.

Relative risks for ischemic heart disease, cerebrovascular disease, hypertensive disease, and other cardiac diseases have been defined based on the comparative risk analysis (Lawes et al., 2003; Prüss-Üstün et al., 2003) and are listed in Table 4 for the blood pressure increase intervals of concern.

For the selected health outcomes DALYs were calculated as described in the Global Burden of Disease study (Murray and Lopez, 1996), with age weighting and health discounted by 3% a year. These parameters were chosen to allow comparison with other risk factors and diseases (Ezzati et al., 2003).

3. Results

The regional urban mean blood lead levels, along with details on the countries and studies that contributed to the blood lead information, are summarized in Table 5. The regional means vary widely, ranging from 1.7 μg/dL in adults in region Amr A to 15.4 μg/dL in Emr D. Fig. 2 shows the percentage of the population with blood lead levels between 5 and 10 and 10 and 20 μg/dL and those >20 μg/dL. These percentages equate to 120 million people having blood lead levels between 5 and 10 μg/dL and about the same number again with levels greater than 10 μg/dL. Levels of illness per 1000 population for IQ loss and the number of DALYs associated with MMR and cardiovascular outcomes are shown in Table 6 and Fig. 3. The global disease burden of lead-induced MMR amounts to 9.8 million DALYs and the burden of cardiovascular disease results in 229,000 premature deaths and 3.1 million DALYs.

4. Discussion and conclusions

Regional blood lead levels vary widely, but worldwide a large number of people are exposed to potentially harmful levels of lead. The largest disease burden is seen in developing countries, in particular in areas where leaded gasoline is still heavily used. Forty percent of all children have blood lead levels above 5 μg/dL and 20% have levels above 10 μg/dL. Ninety percent of these children live in developing regions. In total, the outcomes attributable to lead amount to about 12.9 million DALYs, representing 0.9% of the global burden of disease. This places lead in the 16th position in terms of leading risk factors for health at a global level (WHO, 2002), but can be more important in certain regions.

The method used for estimating lead-induced mental retardation has been used by Fryers (2000) to assess the total number of cases of mental retardation from all causes. A comparison of the lead-induced burden of MMR with total burden from that condition estimated by the same approach shows that about 13% of this disease burden is lead-induced. A limitation of this approach is that potential regional differences in IQ distribution could only partly be considered. Additionally, population means (to which all IQ scores are related) change over time. In our estimate the same normal distribution has been applied worldwide because data on test means and standard deviations are not available for most populations.

Table 5
Blood lead levels in urban children and adults, by region

Subregion	Afr D[a]	Afr E[a]	Amr A	Amr B	Amr D	Emr B	Emr D	Eur A	Eur B	Eur C	Sear B	Sear D	Wpr A	Wpr B
Mean blood lead, urban children (μg/dL)[b]	11.1	9.8	2.2	7.0	9.0	6.8	15.4	3.5	5.8	6.7	7.4	7.4	2.7	6.6
Mean blood lead, urban adults (μg/dL)[b]	11.6	10.4	1.7	8.5	10.8	6.8	15.4	3.7	9.2	6.7	7.4	9.8	2.7	3.6
Standard deviation (μg/dL)	5.6	5.6	2.9	3.9	3.9	3.9	5.6	1.9	3.0	3.0	3.0	5.6	1.9	3.0
Percentage of urban population	36%	25%	77%	74%	58%	67%	37%	78%	62%	72%	31%	26%	80%	32%
Countries with data used in the calculation process	Nigeria[1]	South Africa[2]	Canada[3], USA[4]	Argentina[5], Brazil[6], Chile[7], Jamaica[8], Mexico[9], Uruguay[10], Venezuela[11]	Ecuador[12], Nicaragua[13], Peru[14]	Saudi Arabia[15]	Egypt[16], Morocco[17], Pakistan[18]	Denmark[19], France[20], Germany[21], Greece[22], Israel[23], Sweden[24]	Poland[25], Turkey[26], Yugoslavia[27]	Hungary[28], Russian Federation[29]	Indonesia[30], Thailand[31]	Bangladesh[32], India[33]	Australia[34], Japan[35], New Zealand[36], Singapore[37]	China[38], Philippines[40], Republic of Korea[41]

[1]Nriagu et al. (1997b), Omokhodion (1994). [2]Deveaux et al. (1986), Grobler (1992), Karimi et al. (1999), Maresky and Grobler (1993), Nriagu et al. (1997a), von Schirnding et al. (2001), White et al. (1982). [3]Koren et al. (1990), Levallois et al. (1991), Rhainds and Levallois (1993), Smith and Rea (1995). [4]CDC (2000, 2001). [5]Cordeiro et al. (1996), Garcia and Mercer (2001). [6]dos Santos et al. (1994), Paolielo et al. (1997). [7]Sepulveda et al. (2000). [8]Matte et al. (1991). [9]Azcona-Cruz et al. (2000), Farias et al. (1998), Hernandez-Avila et al. (1996), Junco-Munoz et al. (1996), Lacasaña-Navarro et al. (1996), López Lara et al. (2000), Romieu (2001b), Rothenberg et al. (1996). [10]Schutz et al. (1997). [11]Feo et al. (1993), Mujica (2001). [12]Counter et al. (1998). [13]Bonilla et al. (1998). [14]Jacoby (1998), Ramirez et al. (1997). [15]Al-Saleh (1995), Al-Saleh et al. (1995, 1999). [16]Kamal et al. (1991). [17]Khassouani et al. (1997). [18]Bashir et al. (1995), Hafeez and Malik (1996), Khan et al. (1994), Khan et al. (1995), Khwaja (2002), Sadaruddin et al. (1995). [19]Nielsen et al. (1998). [20]Flurin et al. (1998). [21]Jacob et al. (2000). [22]Vasilios et al. (1997). [23]Tepferberg and Almog (1999). [24]Bergdahl et al. (1997), Osterberg et al. (1997). [25]Dutkiewicz et al. (1993), Osman et al. (1999), Zejda et al. (1995), Zedja et al. (1997). [26]Vural and Gulvendik (1988). [27]Blanusa et al. (1991), Factor-Litvak et al. (1996, 1998), Kostial et al. (1991). [28]Bitto et al. (1997). [29]Tepferberg and Almog (1999). [30]Heinze et al. (1998). [31]Wananukul et al. (1998). [32]Kaiser et al. (2001). [33]Awasthi et al. (1996), D'Souza et al. (1994), Gogte et al. (1991), Lal et al. (1991), Saxena et al. (1994), Shenoi et al. (1991), Wahid et al. (1997). [34]Australian Institute of Health and Welfare (1996). [35]Watanabe et al. (1996), Zhang et al. (1997). [36]Fawcett et al. (1996). [37]Chia et al. (1996, 1997), Neo et al. (2000). [38]Gao et al. (2001), Murata et al. (1995), Shen et al. (1996), Shen et al. (2001), Wan et al. (1996), Yan et al. (1999), Zhang et al. (1997). [39]Zhang et al. (1998). [40]Moon et al. (1995), Yang et al. (1996).

[a] Blood lead level data combined for AFR D and AFR E; only 1999 South African data were used to represent countries with efforts in lead reduction in African regions; older data were used to represent countries without such efforts.

[b] High and low urban blood lead means were used in regions where countries were in different stages of phasing out leaded petrol; the distribution is therefore a superposition of two or three log-normal distributions, and the means and standard deviations outlined above do not therefore reflect the distribution seen within the population as a whole.

Table 6
Levels of illness/1000 population and DALY associated with health outcomes

	Region														
	Afr D	Afr E	Amr A	Amr B	Amr D	Emr B	Emr D	Eur A	Eur B	Eur C	Sear B	Sear D	Wpr A	Wpr B	Total
Loss of IQ (number of people affected/1000 population)															
0.65	186	191	124	222	232	233	181	227	227	236	218	192	141	218	
1.95	66	61	33	104	105	102	66	41	92	106	76	61	23	75	
3.25	34	28	14	59	58	54	35	10	46	57	36	28	6	34	
3.5	139	95	21	167	172	114	172	5	89	119	65	83	3	58	
MMR (proportion of people affected/ 1000 population)	7.5	5.8	1.1	13.2	10.2	7.6	8.0	1.1	5.2	4.9	8.7	5.5	0.7	7.7	
DALY due to MMR (thousands)	871	768	82	1393	225	334	868	55	212	153	582	1912	16	2341	9813
Attributable DALY (thousands) due to cardiovascular outcomes															
IHD	44	38	19	112	12	51	125	30	125	249	49	447	3	86	1391
CVA	58	60	10	134	16	19	70	25	111	196	54	250	6	256	1266
HTD	16	17	4	46	10	16	34	3	33	22	25	46	0	57	329
OCD	10	9	2	12	2	4	11	4	11	15	5	32	0	8	126
Total[a]	128	124	35	304	40	90	241	63	280	482	133	775	9	407	3112
Attributable mortality (thousands) due to lead-related cardiovascular outcomes															
Total	8	8	2	20	3	6	17	5	22	39	9	57	1	31	229

MMR, mild mental retardation, DALYs, disability-adjusted life years; IHD, ischemic heart disease; CVA, cerebrovascular disease; HTD, hypertensive disease; OCD, other cardiac diseases.
[a]Total cardiac diseases.

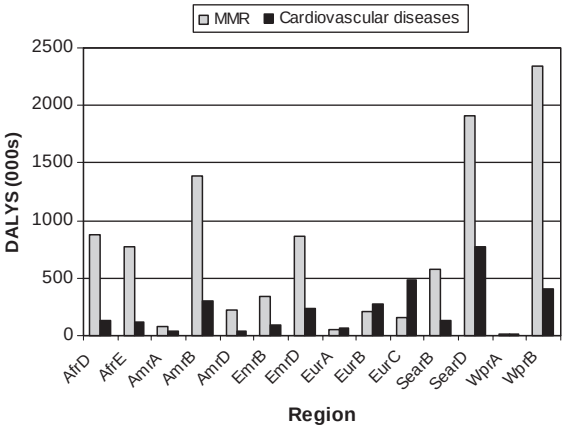


Fig. 3. DALYs due to lead-induced mild mental retardation (MMR) and cardiovascular diseases in the year 2000.

An alternative to this approach, which focuses on subjects with borderline IQ who, due to environmental lead exposure, develop MMR, is provided by the Dutch Burden of Disease study (de Hollander et al., 1999). This study uses a severity weight of 0.06 for any loss of IQ between 1 and 4 points, whether resulting in mental retardation or remaining within the normal IQ range. This results in a much greater burden estimate in relation to lead exposure and is not considered in our estimate, as we have restricted our analysis to well-defined disease outcomes. It should be noted, however, that although in most instances a loss of IQ points will not lead to a recognizable health condition, it will potentially negatively impact function.

The burden of cardiovascular diseases related to lead exposure amounts to 3.1 million DALYs, which is about 2% of the total cardiovascular disease burden. It is estimated that lead exposure leads to 229,000 deaths as a result of cardiac disease, most of which are due to cerebrovascular disease and ischemic heart disease. In our estimate the relationship between increases in blood pressure and blood lead levels was derived from studies conducted in developed countries. It is, however, possible that this relationship varies, leading to possible over- or underestimates of effect.

The burden of various disease outcomes caused by lead cold not be quantified in this assessment. With quantification of additional outcomes discussed in this article, in particular increased delinquent behavior and its impact on injuries, the burden would most probably exceed 1%.

All of this lead-induced disease burden is, in principle, preventable by phasing out the use of leaded gasoline, reducing industrial emissions, removing lead from products such as ceramics, folk remedies, cans, and paints, and replacing leaded pipes used for drinking water. Population blood lead levels have been shown to drop quickly in response to reduced lead exposure, meaning that the burden of disease could be reduced over a reasonable time frame. This could lead to economic benefits as well as health benefits. Considering only the effects of lead on decreasing IQ and hence worker productivity, Grosse et al. (2002) have estimated that each IQ point raises worker productivity between 1.8% and 2.4%. In the USA alone, one of the least affected areas (attributable to long-standing remedial actions), the reduction of blood lead levels over the last three decades could amount to an economic benefit of 110–319 billion US$ for each year's cohort of children.

This represents the first attempt to estimate the global burden of disease due to lead-related health outcomes. The results are based on 89 studies from over 40 countries, and clearly the estimate depends upon the accuracy and representativeness of the data used; this is especially the case for the more limited standard deviation data. We believe, however, that this estimate represents the best that is possible at present and, together with guidance on performing burden estimates at the local level (Fewtrell et al., 2003), will stimulate further research into this important area of environmental health.

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References

Al-Saleh, I., 1995. Lead exposure in Saudi Arabia and its relationship to smoking. BioMetals 8, 243–245.

Al-Saleh, I., Khalil, M.A., Taylor, A., 1995. Lead, erythrocyte protoporphyrin, and hematological parameters in normal maternal and umbilical cord blood from subjects of the Riyadh region, Saudi Arabia. Arch. Environ. Health 50, 66–73.

Al-Saleh, I., Nester, M., DeVol, E., Shinwari, N., Al-Shahria, S., 1999. Determinants of blood lead levels in Saudi Arabian schoolgirls. Int. J. Occup. Environ. Health 5, 107–114.

Annest, J.L., 1983. Trends in blood lead levels of the US population. In: Rutter, M., Jones, R.R. (Eds.), Lead Versus Health. Wiley, New York, pp. 33–58.

Annest, J.L., Pirkle, J.L., Makuc, D., Neese, J.W., Bayse, D.D., Kovar, M.G., 1983. Chronological trend in blood lead levels between 1976 and 1980. N. Engl. J. Med. 308, 1373–1377.

ATSDR, 1999. Toxicological profile for lead (update). Agency for Toxic Substances and Disease Registry. US Department of Health and Human Services, Atlanta, GA.

Australian Institute of Health and Welfare, 1996. Lead in Australian Children: Summary of the National Survey of Lead. Environment Protection Agency, Australia.

Awasthi, S., Awasthi, R., Pande, V.K., Srivastav, R.C., Frumkin, H., 1996. Blood lead in pregnant women in the urban slums of Lucknow, India. Occup. Environ. Med. 53, 836–840.

Azcona-Cruz, M.I., Rothenberg, S.J., Schnaas-Arrieta, L., Romero-Placeres, M., Perroni-Hernandez, E., 2000. Relationship of blood lead levels with visual–motor and equilibrium disturbances in children aged 8–10 years [Spanish]. Salud Publica Mex. 42, 279–287.

Baghurst, P.A., McMichael, A.J., Wigg, N.R., Vimpani, G.V., Robertson, E.F., Roberts, R.J., Tong, S.L., 1992. Environmental exposure to lead and children's intelligence at the age of seven years: the Port Pirie Cohort Study. N. Engl J. Med. 327, 1279–1284.

Bashir, R., Khan, D.A., Saleem, M., Zaman, K.U., Malik, I.A., 1995. Blood lead levels and anemia in lead exposed workers. J. Pak. Med. Assoc. 45, 64–66.

Bergdahl, I.A., Schutz, A., Gerhardsson, L., Jensen, A., Skerfving, S., 1997. Lead concentrations in human plasma, urine and whole blood. Scand J. Work Environ. Health 23, 359–363.

Bitto, A., Horvath, A., Sarkany, E., 1997. Monitoring of blood lead levels in Hungary. Cent. Eur. J. Public Health 5, 75–78.

Blanusa, M., Telisman, S., Hrsak, J., Fugas, M., Prpic-Majic, D., Saric, M., 1991. Assessment of exposure to lead and cadmium through air and food in inhabitants of Zagreb. Arch. Ind. Hyg. Toxicol. 42, 257–266.

Bonilla, C.M., Mauss, L., Mauss, E.A., 1998. A community-initiated study of blood lead levels of Nicaraguan children living near a battery factory. Am. J. Public Health 88, 1843–1845.

CDC, 1997. Update: Blood lead levels—United States, 1991–1994. MMWR 46, 141–146.

CDC, 2000. Blood lead levels in young children—United States and selected states. MMWR 49, 1133–1137.

CDC, 2001. National Report on Human Exposure to Environmental Chemicals. Centers for Disease Control and Prevention, Atlanta.

Chia, S.E., Chia, H.P., Ong, C.N., Jeyaratnam, J., 1996. Cumulative concentrations of blood lead and postural stability. Occup. Environ. Med. 53, 264–268.

Chia, S.E., Chia, H.P., Ong, C.N., Jeyaratnam, J., 1997. Cumulative blood lead levels and neurobehavioral test performance. Neurotoxicology 18, 793–803.

Cordeiro, R., Lima, Filho, E.C., Salgado, E., 1996. Neurological disorders in workers with low levels of lead in the blood. I. Peripheral neuropathy [Portuguese]. Rev. Saude Publica 30, 248–255.

Counter, S.A., Buchanan, L.H., Rosas, H.D., Ortega, F., 1998. Neurocognitive effects of chronic lead intoxication in Andean children. J. Neurosci. 160, 47–53.

de Hollander, A.E.M., Melse, J.M., Lebret, E., Kramers, P.G.N., 1999. An aggregate public health indicator to represent the impact of multiple environmental exposures. Epidemiology 10, 606–617.

de la Burde, B., Choate Jr., M.S., 1972. Does asymptomatic lead exposure in children have latent sequelae? J. Pediatr. 81, 1088–1091.

Deveaux, P., Kibel, M.A., Dempster, W.S., Pocock, F., Formenti, K., 1986. Blood lead levels in pre-school children in Cape Town. SAMJ 29, 421–424.

dos Santos, A.C., Colacciopo, S., Dal Bo, C.M., dos Santos, N.A., 1994. Occupational exposure to lead, kidney function tests, and blood pressure. Am. J. Ind. Med. 26, 635–643.

D'Souza, S.J., Narurkar, L.M., Narurkar, M.V., 1994. Effect of environmental exposures to lead and cadmium on human lymphocytic detoxifying enzymes. Bull. Environ. Contam. Toxicol. 53, 458–463.

Dutkiewicz, T., Sokolowska, D., Kulka, E., 1993. Health risk assessment in children exposed to lead compounds in the vicinity of mine-smelter plant "Orzel Bialy". Pol. J. Occup. Med. 6, 71–78.

Earth Watch Summit, 2000. The Global Phaseout of Leaded Gasoline: A Successful Initiative. Internet communication of August 2000. URL: http://www.earthsummitwatch.org/gasoline.html.

Elinder, C.G., Friberg, L., Lind, B., Nilsson, B., Svartengren, M., Overmark, I., 1986. Decreased blood lead levels in residents of Stockholm for the period 1980–1984. Scand. J. Work Environ. Health 12, 114–120.

Ezzati, M., Lopez, A.D., Rodgers, A., Murray C.J.L. (eds.), 2003. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Due to Selected Major Risk Factors. WHO, Geneva.

Factor-Litvak, P., Kline, J.K., Popovac, D., Hadzialjevic, S., Lekic, V., Preteni-Rexhepi, E., Capuni-Paracka, S., Slavkovich, V., Graziano, J., 1996. Blood lead and blood pressure in young children. Epidemiology 7, 633–637.

Factor-Litvak, P., Slavkovich, V., Liu, X., Popovac, D., Preteni, E., Capuni-Paracka, S., Hadzialjevic, S., Lekic, V., LoIacono, N., Kline, J., Graziano, J., 1998. Hyperproduction of erythropoietin in nonanemic lead-exposed children. Environ. Health Perspect. 106, 361–364.

Farias, P., Hu, H., Rubenstein, E., Meness-Gonzalez, F., Fishbein, E., Palazuelos, E., Aro, A., Hernandez-Avil, M., 1998. Determinants of bone and blood lead levels among teenagers living in urban areas with high lead exposure. Environ. Health Perspect. 106, 733–737.

Fawcett, J.P., Williams, S.M., Heydon, J.L., Walmsley, T.A., Menkes, D.B., 1996. Distribution of blood lead levels in a birth cohort of New Zealanders at age 21. Environ. Health Perspect. 104, 1332–1335.

Feo, O., Fernandez, M., Santaella, N., Valera, L., 1993. Plumbemia en madres y sus hijos recien nacidos en el Hospital Central de Maracay (Lead in mothers and newborn children in the Maracay Central Hospital). Salud Trab. (Maracay) 1, 69–76.

Fewtrell, L., Kaufmann, R., Prüss-Üstün, A., 2003. Lead: Assessing the Burden of Disease at National and Local Levels. World Health Organization, Geneva.

Flurin, V., Mauras, Y., Le Bouil, A., Krari, N., Kerjan, A., Allain, P., 1998. Lead blood levels in children under 6 years of age in the Le Mans region [French]. Presse Méd. 27, 57–59.

Fryers, T., 2000. Epidemiology of mental retardation. In: Gelder, M.G., Lopez-Ibor Jr., J.J., Andreasen, C. (Eds.), New Oxford Textbook of Psychiatry. Oxford University Press, New York.

Gao, W., Li, Z., Kaufmann, R.B., Jones, R.L., Wang, Z., Chen, Y., Zhao, X., Wang, N., 2001. Blood lead levels among children aged 1–5 years in Wuxi City, China. Environ. Res. 87, 11–19.

Garcia, S., Mercer, R., 2001. The problems related to lead and health in children in Argentina [Spanish]. Presented at: Latin American Situation. Lead Poisoning in Children: Evaluation, Prevention and Treatment. World Health Organization, Lima, Peru, 7–10 May, 2001.

Gogte, S.T., Basu, N., Sinclair, S., Ghai, O.P., Bhide, N.K., 1991. Blood lead levels of children with pica and surma use. Indian J. Pediatr. 58, 513–519.

Grobler, S.R., Maresky, L.S., Kotze, T.J., 1992. Lead reduction of petrol and blood lead concentrations of athletes. Arch. Environ. Health 47, 139–142.

Grosse, S.D., Matte, T.D., Schwartz, J., Jackson, R.J., 2002. Economic gains resulting from the reduction in children's exposure to lead in the United States. Environ. Health Perspect. 110, 563–569.

Hafeez, A., Malik, Q.U., 1996. Blood lead levels in pre-school children in Rawalpindi. J. Pak. Med. Assoc. 46, 272–274.

Heinze, I., Gross, R., Stehle, P., Dillon, D., 1998. Assessment of lead exposure in schoolchildren from Jakarta. Environ. Health Perspect. 106, 499–501.

Hernandez-Avila, M., Gonzalez-Cossio, T., Palazuelos, E., Romieu, I., Aro, A., Fishbein, E., Peterson, K.E., Hu, H., 1996. Dietary and environmental determinants of blood and bone lead levels in lactating postpartum women living in Mexico City. Environ. Health Perspect. 104, 1076–1082.

Jacob, B., Ritz, B., Heinrich, J., Hoelscher, B.B., Wichmann, H.E., 2000. The effect of low-level blood lead on hematologic parameters in children. Environ. Res. 82, 150–159.

Jacoby, E., 1998. Environmental lead is a problem in Lima, Peru. Environ. Health Perspect. 106, A170.

Junco-Munoz, P., Ottman, R., Lee, J.H., Barton, S.A., Rivas, F., Cerda-Flores, R.M., 1996. Blood lead concentrations and associated factors in residents of Monterrey, Mexico. Arch. Med. Res. 27, 547–551.

Kaiser, R., Henderson, A.K., Daley, W.R., Naughton, M., Khan, M.H., Rahman, M., Kieszak, S., Rubin, C.H., 2001. Blood lead levels of primary school children in Dhaka, Bangladesh. Environ. Health Perspect. 109, 563–566.

Kamal, A.A., Eldamaty, S.E., Faris, R., 1991. Blood lead level of Cairo traffic policemen. Sci. Total Environ. 105, 165–170.

Karimi, P.G., MoodLey, J., Jinabhai, C.C., Nriagu, J., 1999. Maternal and fetal blood lead levels. SAMJ 89, 676–679.

Khan, D.A., Malik, I.A., Saleem, M., Hashim, R., Bashir, R., 1994. Screening for chronic lead poisoning in lead factory workers. J. Pak. Med. Assoc. 44, 239–241.

Khan, M.H., Khan, I., Shah, S.H., Rashid, O., 1995. Lead poisoning - a hazard of traffic and industries in Pakistan. J. Environ. Pathol. Toxicol. Oncol. 14 (2), 117–120.

Khassouani, C.E., Allain, P., Soulaymani, R., 1997. Lead impregnation in inhabitants of the Rabat region. Presse Méd. 26, 1714–1716 (French).

Khwaja, M.A., 2002. Studies on Blood Lead Levels in School Children Resulting from Lead Exposure Due to Lead Petrol Use and Increasing Road Traffic in Pakistan. Presented at Environmental Threats to the Health of Children: Hazards and Vulnerability, Bangkok, Thailand, March 3–7.

Koren, G., Chang, N., Gonen, R., Klein, J., Weiner, L., Demshar, H., Pizzolato, S., Radde, I., Shime, J., 1990. Lead exposure among mothers and their newborns in Toronto. Can. Med. Assoc. J. 142, 1241–1244.

Kostial, K., Dekanic, D., Telisman, S., Blanusa, M., Duvancic, S., Prpic-Majic, D., Pongracic, J., 1991. Dietary calcium and blood lead levels in women. Biol. Trace Elem. Res. 28, 181–185.

Lacasaña-Navarro, M., Romieu, I., Sanìn-Aguirre, L.H., Palazuelos-Rendón, E., Hernández-Avila, M., 1996. Consumption of calcium and blood lead level in women of reproductive age [Spanish: Consumo de calcio y plomo en sangre de mujeres en edad reproductiva]. Rev. Invest. Clin. 48, 425–430.

Lal, M., Joseph, D., Choudhury, R.K., Bajpai, H.N., Gauba, I., Lokeshwar, M.R., Wagle, C.S., 1991. Studies of blood lead levels in children by proton-induced X-ray emission (PIXE). Sci. Total Environ. 103, 209–214.

Landrigan, P.J., Boffetta, P., Apostoli, P., 2000. The reproductive toxicity and carcinogenicity of lead: a critical review. Am. J. Ind. Med. 38, 231–243.

Last, J., 2001. A Dictionary of Epidemiology. Oxford University Press, New York.

Lawes, C., Vander Hoorn, S., Rodgers, A., Law, M., Elliott, P., MacMahon, S., 2003. High blood pressure. In: Ezzati, M., Lopez, A.D., Rodgers, A., Murray, C.J.L. (Eds.), Comparative Quantification of Health Risks: Global and Regional Burden of Disease Due to Selected Major Risk Factors. WHO, Geneva.

Levallois, P., Lavoie, M., Goulet, L., Nantel, A.J., Gingras, S., 1991. Blood lead levels in children and pregnant women living near a lead-reclamation plant. CMAJ 144, 877–885.

Lezak, M.D., 1995. Neuropsychological Assessment. Oxford University Press, New York.

López Lara, B., Cantú Martinez, P.C., Hernández Arizpe, H., Gómez-Gúzman, L.G., 2000. Blood lead levels and its relation to birth weight in newborns [Spanish: Niveles de plomo en sangre en recién nacidos y su relación con el peso al nacer]. Salud Pública Nutr. 1, 1–7.

Maresky, L.S., Grobler, S.R., 1993. Effect of the reduction of petrol lead on the blood lead levels of South Africans. Sci. Total Environ. 136, 43–48.

Matte, T.D., Figueroa, J.P., Ostrowski, S., Burr, G., Jackson-Hunt, L., Baker, E.L., 1991. Lead exposure from conventional and cottage lead smelting in Jamaica. Arch. Environ. Contam. Toxicol. 21, 65–71.

McMichael, A., Pastides, H., Prüss, A., Corvalán, C., Kay, D., 2001. Update on WHO's initiative to assess environmental burden of disease. Epidemiology 12, 1–3.

Moon, C.S., Zhang, Z.W., Shimbo, S., Watanabe, T., Moon, D.H., Lee, C.U., Lee, B.K., Ahn, K.D., Lee, S.H., Ikeda, M., 1995. Dietary intake of cadmium and lead among the general population in Korea. Environ. Res. 71, 46–54.

Mujica, N., 2001. Niveles de Plomo en Personas no Expuestas Ocupationalmente: Valores de Referencia [Spanish]. Presented at Latin American Situation: Lead Poisoning in Children: Evaluation, Prevention and Treatment, WHO, Lima, Peru, May 7–10.

Murata, K., Araki, S., Yokoyama, K., Nomiyama, K., Nomiyama, H., Tao, Y.X., Liu, S.J., 1995. Autonomic and central nervous system effects of lead in female glass workers in China. Am. J. Ind. Med. 28, 233–244.

Murray, C.J.L., Lopez, A.D., 1996. The Global Burden of Disease. World Health Organization, Harvard School of Public Health, World Bank.

Murray, C.J.L., Lopez, A.D., 1999. On the comparable quantification of health risks: lessons learned from the global burden of disease study. Epidemiology 10, 594–605.

Nawrot, T., Thijs, L., Den Hond, E.M., Roels, H.A., Staessen, J.A., 2002. An epidemiological re-appriasal of the association between blood pressure and blood lead: a meta-analysis. J. Hum. Hypertens. 16, 123–131.

Neo, K.S., Goh, K.T., Sam, C.T., 2000. Blood lead levels of a population group not occupationally exposed to lead in Singapore. Southeast Asian J. Trop. Med. Public Health 31, 295–300.

Nielsen, J.B., Grandjean, P., Jorgensen, P.J., 1998. Predictors of blood lead concentrations in the lead-free gasoline era. Scand. J. Work Environ. Health 24, 153–156.

Nriagu, J., Jinabhai, C.C., Naidoo, R., Coutsoudis, A., 1997a. Lead poisoning of children in Africa. II. Kwaulu/Natal, South Africa. Sci. Total Environ. 197, 1–11.

Nriagu, J., Oleru, N.T., Cudjoe, C., Chine, A., 1997b. Lead poisoning of children in Africa. III. Kaduna Nigeria. Sci. Total Environ. 197, 13–19.

Omokhodion, F.O., 1994. Blood lead and tap water lead levels in Ibadan, Nigeria. Sci. Total Environ. 151, 187–190.

Osman, K., Elinder, C., Schutz, A., Grubb, A., 1999. Biomarkers of nephrotoxicity in children environmentally exposed to lead in Poland. J. Environ. Med. 1, 33–38.

Osterberg, K., Borjesson, J., Gerhardsson, L., Schutz, A., Skerfving, S., 1997. A neurobehavioural study of long-term occupational inorganic lead exposure. Sci. Total Environ. 201, 39–51.

Paolielo, M.M., Gutierrez, P.R., Turini, C.A., Matsuo, T., Mezzaroba, L., Barbosa, D.S., Alvarenga, A.L., Carvalho, S.R., Figueiroa, G.A., Leite, V.G., Gutierrez, A.C., Nogueira, K.B., Inamine, W.A., Zavatti, A.M., 1997. Reference values for lead levels in

blood for the urban population [Portugese]. Rev. Saude Publica 31, 144–148.
Piomelli, S., Corash, L., Corash, M.B., Seaman, C., Mushak, P., Gloer, B., Padgett, R., 1980. Blood lead concentrations in a remote Himalayan population. Science 210, 1135–1137.
Pirkle, J.L., Schwartz, J., Landis, J.R., Harlan, W.R., 1985. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am. J. Epidemiol. 121, 246–258.
Prüss, A., Corvalán, C.F., Pastides, H., de Hollander, A.E.M., 2001. Methodological considerations in estimating the burden of disease from environmental risk factors at national and global level. Int. J. Occup. Environ. Health 7, 58–67.
Prüss-Üstün, A., Fewtrell, L., Landrigan, P.J., Ayuso-Mateos, J.L., 2003. Exposure to lead in the environment. In: Ezzati, M., Lopez, A.D., Rodgers, A., Murray, C.J.L. (Eds.), Comparative Quantification of Health Risks: Global and Regional Burden of Disease Due to Selected Major Risk Factors, WHO, Geneva.
Ramirez, A.V., Paucar, J.C., Medina, J.M., 1997. Blood lead in the inhabitants of 4 Peruvian localities [Spanish]. Rev. Panam. Salud Pública 1, 344–348.
Rhainds, M., Levallois, P., 1993. Umbilical cord blood lead levels in the Quebec City area. Arch. Environ. Health 48, 421–427.
Romieu, I., 2001a. Lead in Latin America and the Caribbean [Plomo en America Latina y el Caribe]. Presented at Latin American Situation: Lead Poisoning in Children: Evaluation, Prevention and Treatment [Taller Latinoamericano: Envenenamiento de Niños por Plomo: Evaluación, Prevención y Tratamiento], World Health Organization, Lima, Peru, May 7–10, 2001.
Romieu, I., 2001b. Epidemiological studies: design, interpretation and use of lead data [Estudios epidemiológicos: diseño, interpretación y uso de datos de plomo]. Presented at Latin American Situation: Lead Poisoning in Children: Evaluation, Prevention and Treatment [Taller Latinoamericano: Envenenamiento de Niños por Plomo: Evaluación, Prevención y Tratamiento], World Health Organization, Lima, Peru, May 7–10.
Rothenberg, S.J., Karchmer, S., Schnaas, L., Perroni, E., Zea, F., Salinas, V., Fernandez Alba, J., 1996. Maternal influences on cord blood lead levels. J. Expo. Anal. Environ. Epidemiol. 6, 211–227.
Rummo, J.H., Routh, D.K., Rummo, N.J., 1979. Behavioural and neurological effects of symptomatic and asymptomatic lead exposure in children. Arch. Environ. Health 34, 120–125 (Cited in ATSDR, 1999).
Sadaruddin, A., Agha, F., Khatoon, N., Sultana, K., 1995. Blood lead levels in young children in Chakshahzad, Islamabad. J. Pak. Med. Assoc. 45, 215–218.
Saxena, D.K., Singh, C., Murthy, R.C., Mathur, N., Chandra, S.V., 1994. Blood and placental lead levels in an Indian city: a preliminary report. Arch. Environ. Health 49, 106–110.
Schuhmacher, M., Belles, M., Rico, A., Domingo, J.L., Corbella, J., 1996. Impact of reduction of lead in gasoline on the blood and hair lead levels in the population of Tarragona Province, Spain, 1990–1995. Sci. Total Environ. 184, 203–209.
Schutz, A., Barregard, L., Sallsten, G., Wilske, J., Manay, N., Pereira, L., Cousillas, Z.A., 1997. Blood lead in Uruguayan children and possible source of exposure. Environ. Res. 74, 17–23.
Schwartz, J., 1988. The relationship between blood lead and blood pressure in the NHANES II Survey. Environ. Health Perspect. 78, 15–22.
Schwartz, J., 1994. Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ. Res. 65, 42–55.
Schwartz, J., 1995. Lead, blood pressure, and cardiovascular disease in men. Arch. Environ. Health 50, 31–37.
Sepulveda, A.V., Vega Morales, J., Delgaso, B.I., 2000. Childhood environmental lead exposure in Antofagasta, Chile [Spanish]. Rev. Med. Chil. 128, 221–232.
Shen, X.M., Rosen, J.E., Guo, D., Wu, S.M., 1996. Childhood lead poisoning in China. Sci. Total Environ. 181, 101–109.
Shen, X.M., Sheng, S.H., Yan, C.H., 2001. Impacts of low-level lead exposure on development of children: recent studies in China. Clin. Chim. Acta 313, 217–220.
Shenoi, R.P., Khandekar, R.N., Jaykar, A.V., Raghunath, R., 1991. Sources of lead exposure in urban slum school children. Indian J. Pediatr. 28, 1021–1027.
Smith, L.F., Rea, E., 1995. Low blood lead levels in Northern Ontario—what now? Can. J. Public Health 86, 373–376.
Tepferberg, M., Almog, S., 1999. Prenatal lead exposure in Israel: an international comparison. Isr. Med. Assoc. J. 1, 250–253.
Thomas, V.M., Socolow, R.H., Fanelli, J.J., Spiro, T.G., 1999. Effects of reducing lead in gasoline: an analysis of the international experience. Environ. Sci. Technol. 33, 3942–3948.
UN (United Nations) Development Programme, 2000. Human Development Report 2000. UNDP, New York.
Vasilios, D., Theodor, S., Konstantinos, S., Evangelos, P.E., Fotini, K., Dimitrios, L., 1997. Lead concentrations in maternal and umbilical cord blood in areas with high and low air pollution. Clin. Exp. Obstet. Gynecol. 24, 187–198.
von Schirnding, Y., Mathee, A., Robertson, P., Strauss, N., Kibel, M., 2001. Distribution of blood lead levels in schoolchildren in selected Cape Peninsula suburbs subsequent to reductions in petrol lead. SAMJ 91, 870–872.
Vural, N., Gulvendik, G., 1988. Blood lead level distribution by age group in inhabitants of Ankara. Biol. Trace Elem. Res. 18, 85–93.
Wahid, A., Koul, P.A., Shah, S.U., Khan, A.R., Bhat, M.S., Malik, M.A., 1997. Lead exposure in papier mache workers. Hum. Exp. Toxicol. 16, 281–283.
Wan, B.J., Zhang, Y., Tian, C.Y., Cai, Y., Jiang, H.B., 1996. Blood lead dynamics of lead-exposed pregnant women and its effects on fetus development. Biomed. Environ. Sci. 9, 41–45.
Wananukul, W., Sirivarasai, J., Sriapha, C., Chanatara, V., Chunvimaluang, N., Keanpoompuang, A., Boriboon, W., Pumala, K., Kaojarern, S., 1998. Lead exposure and accumulation in healthy Thais: assessed by lead levels, EDTA mobilization and heme synthesis-related parameters. J. Med. Assoc. Thai. 81, 110–116.
Watanabe, T., Nakatsuka, H., Shimbo, S., Iwami, O., Imai, Y., Moon, C.S., Zhang, Z.W., Iguchi, H., Ikeda, M., 1996. Reduced cadmium and lead burden in Japan in the past 10 years. Int. Arch. Occup. Environ. Health 68, 305–314.
White, N.W., Dempster, W.S., Pocock, F., Kibel, M.A, 1982. Lead absorption in Cape children: a preliminary report. SAMJ 62, 799–802.
Wietlisbach, V., Rickenbach, M., Berode, M., Guillemin, M., 1995. Time trend and determinants of blood lead levels in a Swiss population over a transition period (1984–1993) from leaded to unleaded gasoline use. Environ. Res. 68, 82–90.
Williams, A., 1999. Calculating the burden of disease: time for a strategic reappraisal? Health Econ. 8, 1–8.
WHO, 1996. Global Burden of Disease and Injury Due to Occupational Factors—Discussion Paper, WHO/EHG/96.20. World Health Organization, Geneva.
WHO, 2001a. Methodology for Assessment of Environmental Burden of Disease—ISEE Session on Environmental Burden of Disease. World Health Organization Consultation, Buffalo, August 2000, Geneva (WHO/WSH/00.7).
WHO, 2001b. GBD Calculation Sheets for Meningitis, Iodine Deficiency, Anaemia, Pertussis, Trichuriasis, Ascariasis and Japanese Encephalitis. World Health Organization, Evidence for Information and Policy (unpublished data).
WHO, 2002. World Health Report 2002. World Health Organization, Geneva. http://www.who.int/whr/

WOH/ILO (International Labour Office), 1998. Methods for Health Impact Assessment in Environmental and Occupational Health: Report of a WHO/ILO Consultation. WHO, Geneva, 1998, WHO/EHG/98.4.

Yan, C.H., Shen, X.M., Zhang, Y.W., 1999. A study on relationship between blood level and physical growth and development of babies and young children in Shanghai. Chin. J. Prev. Med. 33, 269–271.

Yang, J.S., Kang, S.K., Park, I.I., Rhee, K.Y., Moon, Y.H., Sohn, D.H., 1996. Lead concentrations in blood among the general population of Korea. Int. Arch. Occup. Environ. Health 68 (3), 199–202.

Zhang, Z.W., Moon, C.S., Watanabe, T., Shimbo, S., He, F.S., Wu, Y.Q., Zhou, S.F., Su, D.M., Qu, J.B., Ikeda, M., 1997. Background exposure of urban populations to lead and cadmium: comparison between China and Japan. Int. Arch. Occup. Environ. Health 69, 273–281.

Zhang, Z.W., Subida, R.D., Agetano, M.G., Nakatsa, H., Inoguchi, N., Watanabe, T., Shimbo, S., Higashikawa, K., Ikeda, M., 1998. Non-occupational exposure of adult women in Manila, the Philippines, to lead and cadmium. Sci. Total Environ. 215, 157–165.

Zedja, J.E., Grabecki, J., Krol, B., Panasiuk, Z., Jedrzejczak, A., Jarkowski, M., 1997. Blood lead levels in urban children of Katowice Voivodship, Poland: Surveillance program. Cent. Eur. J. Public Health 5 (2), 60–64.

Zejda, J.E., Sokal, A., Grabecki, J., Panasiuk, Z., Jarkowski, M., Skiba, M., 1995. Blood lead concentrations in school children of Upper Silesian Industrial Zone, Poland. Cent. Eur. J. Public Health 3, 92–96.