

Environmental Burden of Disease Series, No. 2

Lead

Assessing the environmental burden of disease at national and local levels

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A Microsoft Excel spreadsheet for calculating the estimates described in this document can be obtained from WHO/PHE
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TABLE OF CONTENTS

Preface	v
Affiliations and acknowledgements.....	vi
Summary.....	vii
1. Background.....	1
1.1 Summary of the method.....	1
2. Sources of lead and exposure pathways	3
3. Lead toxicity	5
3.1 Nervous system effects and intelligence.....	5
3.2 Systemic effects	6
3.3 Effects of lead on reproduction.....	7
4. Exposure–risk relationships.....	8
4.1 Anaemia and gastrointestinal effects	9
4.2 Loss of IQ points and estimation of mild mental retardation	10
4.3 Increase in blood pressure and cardiovascular disease.....	13
5. Exposure assessment	16
5.1 Assessing levels of lead in blood.....	16
5.2 Overall output	19
6. Estimating the disease burden.....	21
6.1 An example problem: assessing the disease burden effects of a programme to reduce lead in gasoline	21
6.2 Adjusting blood lead levels for the effects of the programme to reduce lead in gasoline.....	22
6.3 Calculating weighted means	22
6.4 Combining standard deviations	23
6.5 Calculating the population at risk.....	24
6.6 Estimating disease rates in children.....	28
6.7 Estimating the disease burden due to increased blood pressure	29
6.8 Summary of steps for estimating the disease burden.....	30
7. Uncertainties	31
7.1 Blood lead measurements	31
7.2 Are the data representative?.....	31
7.3 Adequacy of adjustment factors	31
7.4 Ranges of reported exposure-response relationships.....	32
7.5 Quantitative estimation of uncertainty.....	32
8. Research needs and recommendations	33
9. Disease burden and policy	34
References.....	35
Annex 1 Country groupings for global assessment.....	39
Annex 2 Measuring blood lead.....	40
Annex 3 Using exposure scenarios to inform policy actions	43

Annex 4	Estimating the global disease burden of environmental lead exposure	50
Annex 5	Calculation spreadsheet for lead	65

List of Tables

Table 1	Health effects of lead	9
Table 2	Distribution of a normal population within specified IQ increments	11
Table 3	Regional adjustment ratios for excess mental retardation rates caused by communicable disease or iodine deficiency	13
Table 4	Relative risk values for cardiovascular disease, for defined increases in blood pressure	15
Table 5	Blood lead data for country X.....	21
Table 6	Adjusted mean blood lead levels for urban children in country X	23
Table 7	Weighted mean blood lead levels for urban children in country X	23
Table 8	Weighted standard deviation for urban children in country X	24
Table 9	Blood lead levels in children of country X	27
Table 10	Proportion of children within specified blood lead intervals....	27
Table 11	Total children at risk of lead-related health effects.....	28

List of Figures

Figure 1	Framework for lead exposure	4
Figure 2	IQ point loss, by blood lead level	10
Figure 3	Shift to MMR as a result of lead-induced IQ loss	11
Figure 4	Reduction in blood lead levels during a programme to reduce lead in gasoline in the United States	19
Figure 5	Typical distribution of blood lead levels in a population, with a health-effect interval	25
Figure 6	Flow chart for estimating the disease burden.....	30

Preface

The disease burden of a population, and how that burden is distributed across different subpopulations (e.g. infants, women), are important pieces of information for defining strategies to improve population health. For policy-makers, disease burden estimates provide an indication of the health gains that could be achieved by targeted action against specific risk factors. The measures also allow policy-makers to prioritize actions and direct them to the population groups at highest risk. To help provide a reliable source of information for policy-makers, WHO recently analysed 26 risk factors worldwide, including lead, in the *World Health Report* (WHO, 2002).

The Environmental Burden of Disease (EBD) series continues this effort to generate reliable information, by presenting methods for assessing the environmental burden of lead at national and local levels. The methods in the series use the general framework for global assessments described in the *World Health Report* (WHO, 2002). The introductory volume in the series outlines the general method (Prüss-Üstün et al., 2003a), while subsequent volumes address specific environmental risk factors. The guides on specific risk factors are organized similarly, first outlining the evidence linking the risk factor to health, and then describing a method for estimating the health impact of that risk factor on the population. All the guides take a practical, step-by-step approach and use numerical examples. The methods described in the guides can be adapted both to local and national levels, and can be tailored to suit data availability.

Affiliations and acknowledgements

Lorna Fewtrell is from the Centre for Research into Environment and Health, University of Wales, Aberystwyth, UK. Rachel Kaufmann is from the US Centers for Disease Control and Prevention, USA. Annette Prüss-Üstün, Carlos Corvalán and Diarmid Campbell-Lendrum are from the World Health Organization and Alistair Woodward is from the Wellington School of Medicine, New Zealand.

In preparing this document, we drew on the methods developed for estimating the global burden of disease caused by exposure to lead. We therefore thank the additional co-authors in the global analysis, Philip Landrigan of the Mount Sinai School of Medicine and José Luis Ayuso-Mateos of the Hospital Universitario de la Princesa, as well as all those having peer reviewed that analysis.

We also thank the US Environmental Protection Agency for having supported the development of the Environmental Burden of Disease approaches. Finally, we are grateful to Kevin Farrell and Eileen Brown who put this document into its final format.

Summary

This guide outlines a method for estimating the disease burden at national, city or local levels caused by environmental exposure to lead. The method described in the guide assesses lead exposure from the distribution of lead levels in blood samples representative of the study population. For children, the exposure distribution is then converted into a distribution of IQ points lost, resulting mild mental retardation, and into rates of anaemia and gastrointestinal symptoms. For adults, the exposure distribution is converted mainly into increased blood pressure, which may cause various cardiovascular diseases, including ischaemic heart disease and cerebrovascular disease.

The method can be used to highlight the health impacts on population subgroups at particular risk, provided that exposure in these subgroups is assessed separately. Such subgroups can include children of lower-income families living in degraded housing, people living around “hotspots” (such as certain industrial activities), or occupational groups. Global estimates of the disease burden from lead are given for 14 different regions and several age groups (Annex 4). It is estimated that lead exposure accounts for almost one percent of the global burden of disease, and most of the exposure affects children in the developing world.

To select the most suitable interventions for reducing the disease burden, an inventory of the main sources of exposure to lead is required. In countries where it is still used, leaded gasoline will likely be a major contributor to exposure, either directly through the air, or indirectly through food and dust. Other sources may also be locally relevant, such as the use of leaded ceramics. Workplace exposures and cottage industries can affect workers and their families and neighborhoods, although the emphasis here is on environmental exposure. In developed countries, where leaded gasoline has usually been phased out, the highest environmental exposures to lead generally affect children of lower-income families living in degraded housing.

The burden of disease caused by relatively low and widespread exposures to lead is often underestimated by policy makers. For example, loss of IQ points is not considered a disease *per se*, yet it reflects subtle neurological impairment that will be most marked on the social and psychological development of children who already have a low IQ score. Subtle effects on IQ loss are expected from blood lead levels as low as 5 µg/dl and the effects gradually increase with increasing levels of lead in the blood. The effects of losing IQ points will be greater in children with an IQ score just above 69 (with mild mental retardation defined as an IQ score between 50–69), than in children with a higher IQ. At higher levels, lead exposure also leads to gastrointestinal symptoms and anaemia (about 20% of children are affected when blood lead levels exceed 60–70 µg/dl). In adults, relatively low levels of lead exposure (5 µg/dl) may increase blood pressure, which can then lead to cardiovascular diseases.

Summary

Quantification of the health impacts in a given country or region by methods such as that presented in this guide provides an opportunity to highlight the magnitude of disease burden that could be avoided. The results of such an analysis can therefore present important arguments for policy action to reduce the exposure to this risk factor, and thus reduce the current burden of disease of the population.

1. Background

The toxic nature of lead has been well known since 2000 BC (Needleman, 1999). Despite this, lead has become widely dispersed throughout the environment because of the number of human uses for it. Even though interventions for removing lead have been implemented around the world, its toxic effects are felt everywhere. For example, a range of adverse health outcomes have been attributed to lead, some of which are manifest at low concentrations. In a recent estimate of the global burden of disease, lead accounted for 0.9% of the total disease burden, based solely on its role in lead-induced mental retardation and in the consequences of increased blood pressure, such as cardiovascular disease (Fewtrell et al., 2003). As would be expected, the burden was not evenly distributed and those regions still using leaded gasoline were most heavily affected. Data such as these indicate that lead is an important environmental pollutant.

Although lead in gasoline is a reasonable predictor of environmental lead (Landrigan, Boffetta & Apostoli, 2000), the burden of disease from this toxin is more meaningfully assessed at local (i.e. regional or country) level, since lead use is often localized. Analysis of the problem at national level could provide the necessary input for a cost-benefit analysis prior to the implementation of a lead reduction programme. And decisions about extending or redirecting mitigation programmes could also be based, in part, on assessments of the health burden from lead exposures in the population.

The following gives a brief summary of a method for estimating the disease burden of lead. Subsequent chapters outline the sources of lead in the environment and its toxic effects, and issues relating to the lead exposure-response relationship. The method presented here is similar to one that has been applied at global level (Fewtrell et al., 2003; Prüss-Üstün et al., 2003a).

1.1 Summary of the method

The quantitative assessment of the health impacts of lead at population level is based on three components:

1. Assessing exposure from the distribution of blood lead levels in the general population.
2. Mapping the exposure distribution onto health effects for the study population.
3. Quantification of the following selected health effects:
 - The loss of IQ points in children (which results in mild mental retardation (MMR) when this loss leads to IQ scores below 70 points), using an absolute rate of disease.
 - Increased blood pressure in adults (which results in cardiovascular diseases, including ischaemic heart disease, cerebrovascular disease, hypertensive disease and other cardiac diseases). This estimate is based on

relative risks that are converted to the fraction of disease attributable to lead.

- Gastrointestinal symptoms in children, using an absolute rate of disease.
- Anaemia in children and adults, using an absolute rate of disease.

Where absolute rates of diseases are used to calculate the disease burden (from MMR, gastrointestinal symptoms, anaemia), each blood lead level is converted into a rate of disease.

To estimate the consequences of increased blood pressure on health, we use a relative approach. First, the attributable fraction is estimated from the impact fraction, IF, using:

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

where:

P_i = proportion of the population at exposure category 'i' (exposed and unexposed);

RR_i = relative risk at exposure category 'i', compared to the reference level.

The impact fraction is then multiplied by the total number of cases or deaths from the disease in the study population (e.g. the country population). Further information is provided in section four of the introductory volume for EBD assessment (Prüss-Üstün et al., 2003a).

2. Sources of lead and exposure pathways

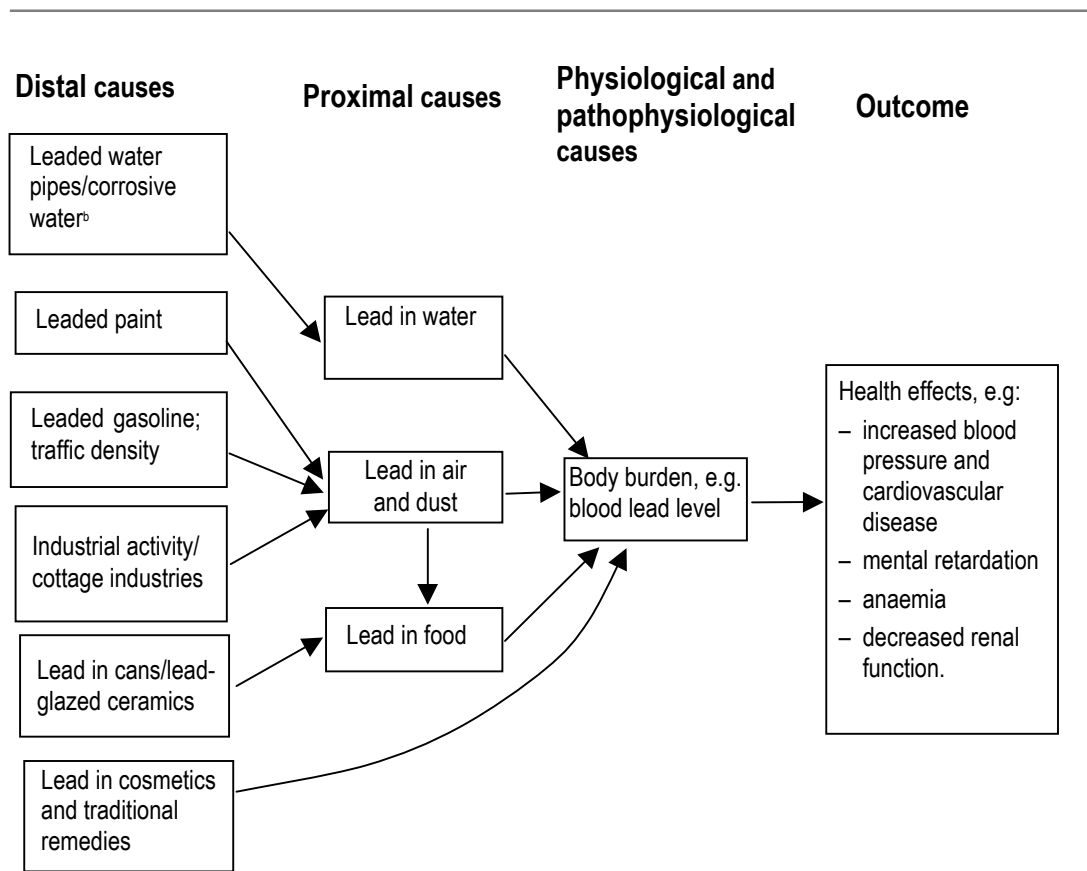
Lead exists in the earth's crust, and occurs naturally in the environment through a variety of mechanisms including volcanic emissions and geochemical weathering. The majority of lead pollution, however, derives from human activity to extract and exploit the metal. Lead has been put to many uses and is important in plumbing materials, gasoline additives, batteries, pigments and ammunition. Potential sources of lead exposure may vary, both within and between countries. In the United States of America (USA), for example, lead in paint is an important source of exposure, while for Mexico this source is largely irrelevant and lead-glazed ceramics are more important (Hernandez-Avila et al., 1999). Identifying lead-containing materials is not necessarily straightforward and van Alphen (1999) lists, alphabetically, some of the possible idiosyncratic sources and consumer goods containing lead. The following list covers those beginning with "c":

- cable sheaths
- ceramic glazes
- chalking paint
- charging batteries
- coffee machines (with brass and soldered plumbing)
- coffin lining, burial stone inlays
- collapsible tubes (e.g. art paint, ointments, toothpaste)
- corrosion-resistant equipment
- crayons
- crystal glassware
- curtain weights.

A framework for a number of lead exposure pathways is given in Figure 1. In the decision-making process for a national study, this framework can form a starting point, by acting as a checklist for likely local exposure pathways. It should be remembered that some exposure pathways can be quite obscure, as highlighted in the preceding "c" list. Another illustration of an unexpected source is provided by the outbreak of lead poisoning in Egypt that was caused by lead solder used in flour mill grinding stones (Falk, 2002).

Assessments of the role of lead at global level only account for "general population" exposures and do not include exposures in high-risk groups (such as those exposed to pollution 'hotspots' around a lead mine or smelter or occupationally-exposed groups, including those engaging in cottage industries that use lead). A national assessment may allow a more detailed examination of the role of lead through all its exposure pathways and hence a more accurate assessment of population exposure.

Figure 1 Framework for lead exposure ^a



^a Source: Fewtrell et al. (2003).

^b Corrosive water is water that is highly acidic or alkaline, and that can dissolve certain metals (such as antimony cadmium, copper, lead or nickel) in pipes and fixtures. When corrosive water stands in contact with fittings the concentrations of these metals can be elevated, even though their levels may be normal in “flushed” samples.

3. Lead toxicity

The aim of this section is to outline some of the main effects of lead toxicity. More details are given in reviews (ATSDR, 1999; WHO, 1995; National Research Council, 1993).

Some of the earliest toxic effects of lead to be recognized were colic (gastrointestinal effects) and anaemia. As measurement techniques have increased in sophistication, however, it has become clear that lead can have effects on the human body at levels lower than initially suspected, and the nervous system appears to be the principal target (although other organ systems are far from immune).

The health outcomes described below were selected because of the strength of the evidence supporting a causal relationship with lead. The evidence was rated according to the Agency for Toxic Substances and Disease Registry (ATSDR, 1999). Increased blood pressure was also selected as a health outcome, based on the recommendations of a peer review group in the WHO Comparative Risk Assessment process (Ezzati et al., 2003), and on evidence from meta-analyses and large population surveys such as NHANES (Schwartz, 1988).

3.1 Nervous system effects and intelligence

The effects of lead on the nervous system have been recognized for some time, with Benjamin Franklin and Charles Dickens writing about them in the late 18th and 19th centuries. In occupational studies, where workers have been exposed to high levels of lead, symptoms such as loss of appetite, malaise, lethargy, headache, forgetfulness and dizziness have been reported. At lower lead levels, decreases in reaction time, deficits in hand-eye coordination and decreased nerve conduction velocities have all been reported. At its most severe, lead poisoning can result in encephalopathy (which affects brain function). Symptoms include seizures and convulsions, which can be followed by coma and death, although such cases of severe poisoning are rarely observed in environmental exposures today. Therefore, these severe effects are not considered in the burden of disease calculations presented here.

Prior to the 1940s, it was assumed that children who survived severe lead poisoning made a full recovery. In 1943, however, it was reported that children who had previously suffered from lead poisoning had behavioural disorders, short attention spans and generally made poor progress at school (Byers & Lord, 1943). This led to further studies on the effect of lead on children's intellectual abilities and behaviour, particularly at low levels of lead. Many of those studies showed that the effects of lead exposure included longer reaction times, increased delinquent activity and increased school drop-out rates (Needleman et al., 1990; 1996).

The effect of lead on child intelligence quotient (IQ) scores has been extensively studied. Although the studies have used different measures of IQ and different

biological markers (e.g. level of lead in the blood, teeth etc.), most have shown lead to have a detrimental effect on IQ at relatively low levels of exposure. In a meta-analysis, Schwartz (1994) showed that an increase in blood lead from 10 µg/dl to 20 µg/dl was associated with a mean decrease of 2.6 IQ points. The results suggested that the effect is likely to continue below 10 µg/dl. Two studies examined higher blood lead levels and IQ, and concluded that above 20 µg/dl, an average loss of 2–5 IQ points could occur (de la Burde & Choate, 1972; Rummo, Routh & Rummo, 1979). In this guide, we use the midpoint of this range, 3.5 IQ points, to estimate health effects. However, there is some evidence that cognitive effects of lead could occur at blood levels below 5 µg/dl (Lanphear et al., 2000).

3.2 Systemic effects

Elevated blood pressure

This is another effect that is seen at low blood lead levels. Although in a strict sense it is not a health outcome, elevated blood pressure has been associated with an increased risk of cardiovascular and cerebrovascular disease. The association between the blood lead level and blood pressure is strongest for increases in systolic blood pressure in adult males. Schwartz (1995) showed that decreases in blood lead from 10 µg/dl to 5 µg/dl were associated with a decrease of 1.25 mmHg in systolic blood pressure; other studies found decreases of 2 mmHg for reductions in blood lead from 20 µg/dl to 15 µg/dl, and from 15 µg/dl to 10 µg/dl (Schwartz, 1988; Pirkle et al., 1985). In women, the association between systolic blood pressure and blood lead is weaker and less-well documented. The most recent and comprehensive study included 24 000 female subjects, and it was estimated that systolic blood pressure increased by 0.8 mmHg for a doubling in blood lead (Nawrot et al, 2002). This result is not significantly different from that reported for men.

Gastrointestinal effects

One of the earliest clinical signs of lead poisoning can be nonspecific, gastrointestinal effects. Symptoms include abdominal pain, constipation, cramps, nausea, vomiting, anorexia and weight loss.

Anaemia

The haemopoietic system is very sensitive to the effects of lead, and subclinical effects on a number of enzymes involved with haem biosynthesis have been seen at very low lead levels. At higher levels, lead-induced anaemia may result, owing to a combination of reduced erythrocyte survival (due to haemolysis) and reduced haemoglobin formation.

Renal effects

Reduced renal function is a recognized symptom of both acute and chronic lead toxicity. Acute effects are generally seen in children, when exposure is primarily through the oral route, while chronic effects are more common in adults

occupationally exposed to lead, where the principal exposure route is inhalation (ATSDR, 1999).

3.3 Effects of lead on reproduction

The effects of lead on reproduction are well established for both men and women, with reports dating to the 19th century. At one stage, lead was even used to induce abortions (Hall & Cantab, 1905). Although the majority of human studies have been based on small numbers of subjects, there is nevertheless general agreement that women, especially those exposed to lead during pregnancy, report higher rates of miscarriages, stillbirths and preterm deliveries. The effects of lead on sperm include decreasing sperm count and an increasing number of abnormal sperm.

4. Exposure–risk relationships

Methods for quantifying disease burden are only provided for certain health effects and are based on:

- the strength of evidence;
- the availability of quantitative information on the association between blood lead and the health effect;
- whether the effects constitute well-defined health outcomes, or can be converted into such.

Furthermore, the effects of lead at very high exposure levels have not been considered, but such exposures rarely result from current environmental conditions outside of uncontrolled workplace settings.

The health effects outlined in the previous section appear at considerably different lead levels. For the most part, formal dose–response data do not exist and many of the most serious health effects are based on case reports. For example, the levels of lead in the blood of children with encephalopathy have been reported to be between 90–800 µg/dl, while in fatal cases the levels were between 125–750 µg/dl (NAS, 1972). Woolf (1990) reported similar results, where blood lead levels in children ranged between 60–950 µg/dl.

Table 1 summarizes selected health outcomes, blood lead levels at which the population is considered to be “at risk”, and the quantitative relationship to the specified health outcomes. However, the levels in the table do not necessarily indicate the lowest levels at which lead exerts an effect, and further research is required to quantify the health effects of lead in more detail. For example, the effects of lead on reproduction have not been included as a health outcome in Table 1 because the available data do not allow the effective levels of lead to be estimated (ATSDR, 1999).

Table 1 Health effects of lead

Outcome	Blood lead threshold ^a (µg/dl)		Relationship
	Children	Adults	
IQ reduction ^b	5	ND	Linear relationship between 5–20 µg/dl BPb ^c (loss of 1.3 IQ points per 5 µg/dl BPb); loss of 3.5 IQ points above 20 µg/dl.
Increased systolic blood Pressure ^d	ND	5	Linear relationship assumed between 5–20 µg/dl (increase of 1.25 mmHg per increase of 5 µg/dl BPb for males, and 0.8 mmHg for females); above 20 µg/dl, an increase of 3.75 mmHg for males, and 2.4 mmHg for females.
Gastrointestinal effects	60	ND	20% of children are affected above these rates ^e .
Anaemia	70	80	20% of people are affected above these rates ^e .

^a Thresholds for gastrointestinal effects and anaemia are levels “at risk”, as defined by ATSDR (1999).

^b The disease burden is always estimated for one particular year and the effects of previous exposures are not accounted for in the year of assessment. As a result, only children aged 0–1 year old were considered in the calculations, since the effects of lead on previous cohorts were considered in previous years.

^c BPb: blood lead level (in µg/dl).

^d Adults aged 20–79 years only.

^e Based on Schwartz et al. (1990); see section 4.1.

ND No documented effects or insufficient evidence.

4.1 Anaemia and gastrointestinal effects

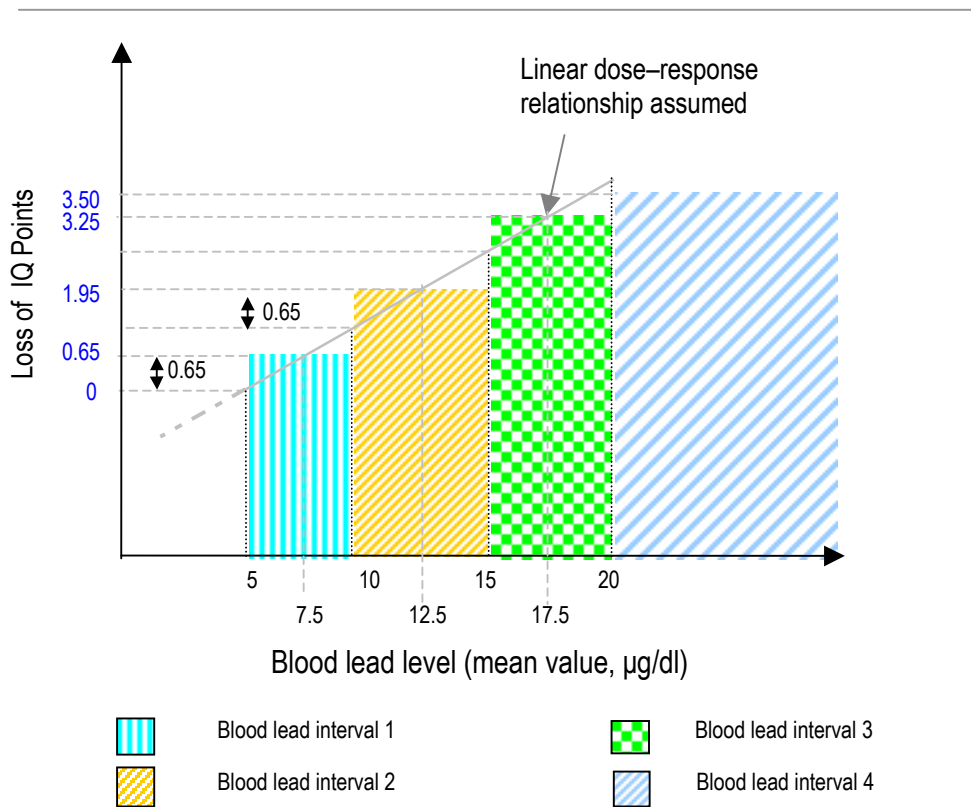
As specific dose–response relationships are rare, it is necessary to make assumptions about the percentages of people who will develop the defined health outcomes. For “serious” outcomes, estimates of the populations “at risk” were based on the work of Schwartz et al. (1990), who showed that children “at risk” had a 20% probability of experiencing anaemia. As there were no specific data for gastrointestinal effects, the same adjustment factor was assumed. A different approach was taken for IQ, and for cardiovascular disease that resulted from increased blood pressure.

4.2 Loss of IQ points and estimation of mild mental retardation

IQ loss

The loss of IQ points is quantified assuming a linear relationship of 1.3 IQ points lost per 5 $\mu\text{g}/\text{dl}$ of blood lead between 5–20 $\mu\text{g}/\text{dl}$ (Figure 2). This ratio is based on data by Schwartz (1994), who reported a 2.6 IQ point loss for a 10 $\mu\text{g}/\text{dl}$ interval. To calculate the ratio, the mean loss of IQ points for each blood lead level interval is assigned to the midpoint of the interval. Thus, 0.65 (the average loss of IQ points for the 5–10 $\mu\text{g}/\text{dl}$ interval) is ascribed to a blood lead level of 7.5 $\mu\text{g}/\text{dl}$ (the midpoint of the interval). Similarly, 1.95 and 3.25 are ascribed to 12.5 $\mu\text{g}/\text{dl}$ and 17.5 $\mu\text{g}/\text{dl}$, respectively.

Figure 2 IQ point loss, by blood lead level^a



^a Based on data by Schwartz (1994)

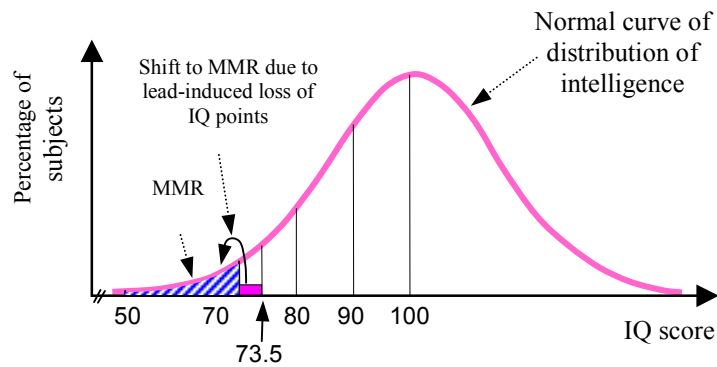
A loss of 3.5 IQ points was assumed for all blood lead levels over 20 $\mu\text{g}/\text{dl}$. This value is the midpoint of the 2–5 IQ point loss range reported earlier (De la Burde & Choate, 1972; Rummo, Routh & Rummo, 1979). Ideally, the calculations would be performed on the basis of the linear dose–response relationship. The stepwise

approach has only been adopted for ease of calculation and further processing of the data.

Mild mental retardation from lead-related IQ loss

IQ loss is not considered to be a disease and therefore the analysis only addresses instances when IQ loss results in mental retardation. By convention, mental retardation (MMR) occurs when the IQ is below 70 points but above 50 points. Mental retardation (MR) includes cases in which the IQ is below 50 points. Intelligence in human populations approximates to a normal distribution (except for an excess below 50 IQ points, representing brain damage and disorder), generally with a mean of 100 and a standard deviation of 15 IQ points (Lezak, 1995). Thus, to attribute a disease burden to the loss of IQ points, it is necessary to calculate the number of people just above the threshold who would enter the MMR range through loss of IQ points due to lead exposure (Figure 3).

Figure 3 Shift to MMR as a result of lead-induced IQ loss



From the normal distribution of IQ, it is possible to estimate the percentage of subjects between 70 and each of 70.65, 71.95, 73.25 and 73.5 points (i.e. the intervals of IQ loss outlined above). This is shown in Table 2.

Table 2 Distribution of a normal population within specified IQ increments^a

IQ health band	IQ interval	Population in IQ interval (%)
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

^a Source: Lezak (1995)

The rate of MMR is estimated by multiplying the numbers of children with the defined IQ point losses, by the respective percentage of the population within that increment. It should be noted, however, that the standard IQ distribution will not necessarily reflect regional or country distributions. It is possible to account for this in two ways. If a country-specific distribution is available, this should be applied instead of the standard curve. In the absence of this information, it is possible to use a regional or country correction factor, which accounts for the difference in the prevalence of risk factors that affect IQ scores.

MMR adjustment ratio

Several diseases result in mental retardation. These include anaemia, meningitis, pertussis, Japanese encephalitis, ascariasis, trichuriasis, hookworm infection, cretinoidism and cretinism due to iodine deficiencies (WHO, 2001a). Using the prevalences of cognitive impairment and mental retardation as consequences of these diseases (WHO, 2001b), it is possible to estimate the number of additional cases of MMR attributable to these disease risks in countries where such diseases are significant. The adjustment is based on the assumption that noncongenital causes of impaired cognitive function are separable and additive, compared to other risk factors. It assumes that the increase in frequency of MMR (50–69 IQ points) due to other risk factors is proportional to the increase in frequency of IQ point values just above 70 points (i.e. between 70–73.5 points). It has been reported that there are differences of prevalence rates for MMR in developed and developing regions (Roeleveld, Zielhuis & Gabreels, 1997), and most of these differences could be explained by noncongenital causes.

Therefore, we estimated the prevalence of mental retardation and cognitive impairment from known noncongenital causes (those mentioned above), compared the values from developed and developing countries, and estimated a rate accounting for the increased risk of mental retardation in developing countries:

$$AR = \frac{P_R - P_{\text{baseline}} + P_{\text{MR standard}}}{P_{\text{MR standard}}}$$

where:

- AR = adjustment ratio
- MR = mental retardation
- P_R = region-specific prevalence of MR from known causes
- P_{baseline} = prevalence of MR from known, noncongenital causes in developed countries
- $P_{\text{MR standard}}$ = prevalence of MR according to the standard distribution of IQ score.

We calculated adjustment ratios (Table 3) for the regions used by WHO in burden of disease assessments (Annex 1). The calculations used the typical baseline prevalence in developed countries of 0.42 cases of mental retardation from known noncongenital causes per 100 people, and a total rate of mental retardation of 2.27 cases per 100 people (from the standard distribution). The calculations assume that the adjustment ratios are valid for an IQ range of 70–73.5. This implies a number

of assumptions, but it is an attempt to account for additional risks prevailing in developing regions. However, protein malnutrition, potentially the most important risk factor for MMR, cannot not be taken into account, as the occurrence and the impact of protein malnutrition on mental retardation have not been sufficiently quantified at the global level. As a result, the cumulative effects of lead and malnutrition on MMR are probably underestimated.

Table 3 Regional adjustment ratios for excess mental retardation rates caused by communicable disease or iodine deficiency

Region ^a	AfrD	AfrE	AmrA	AmrB	AmrD	EmrB	EmrD	EurA	EurB	EurC	SearB	SearD	WprA	WprB
AR ^b	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

^a WHO regions: Afr = Africa; Amr = Americas; Emr = Eastern Mediterranean; Eur = Europe; Sear = South-East Asia; Wpr = Western Pacific. A: very low child, very low adult mortality; B: low child, low adult mortality; C: low child, high adult mortality; D: high child, high adult mortality; E: high child, very high adult mortality. See Annex 1 for a list of countries in each WHO region.

^b AR = adjustment ratio, compared to standardized rates.

4.3 Increase in blood pressure and cardiovascular disease

Blood pressure increases attributable to lead

As outlined earlier, blood pressure increases in adults have been related to the levels of lead in the blood. To estimate the increase due to lead, a similar approach can be taken to that for IQ point loss, with blood lead levels divided into intervals and a blood pressure increase associated with each interval. For men, a 1.25 mmHg increase is associated with each 5 µg/dl increase in blood lead between 5–20 µg/dl, with an increase of 3.75 mmHg above 20 µg/dl. For women, a 0.8 mmHg increase in systolic blood pressure is associated with each 5 µg/dl increase between 5–20 µg/dl, with a 2.4 mmHg increase above 20 µg/dl.

Cardiovascular disease burden attributable to lead

To calculate the level of cardiovascular disease resulting from lead exposure it is necessary to calculate the attributable fraction due to lead. To do this, the population distribution of lead levels causing increased blood pressure is combined with the relative risk for each blood pressure level, using the formula for the impact fraction (Last, 2001):

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

where:

IF = impact fraction

P_i = proportion of the population at exposure interval *i*

RR_i = relative risk at exposure interval *i*, compared to the reference level.

For the purpose of this analysis, the relative risk is of specific cardiovascular diseases associated with increased blood pressure. P_i is the proportion of the population with blood lead levels within each specified lead level interval, i (i.e. intervals 5–10; 10–15; 15–20; and >20 $\mu\text{g}/\text{dl}$). Relative risks were defined according to a comparative risk analysis (Prüss-Üstün et al., 2003b; Lawes et al., 2003), and are listed in Table 4 for salient increases in blood pressure .

Table 4 Relative risk values for cardiovascular disease, for defined increases in blood pressure

Disease	Age (yrs)				
	15–29	30–44	45–59	60–69	70–79
Males					
0.625 mmHg increase					
IHD ^a	1.041	1.041	1.032	1.018	1.014
CVA ^b	1.056	1.056	1.044	1.029	1.020
Hypertensive disease	1.122	1.122	1.059	1.036	1.027
Other cardiac diseases	1.013	1.013	1.009	1.006	1.003
1.875 mmHg increase					
IHD	1.130	1.130	1.100	1.055	1.043
CVA	1.177	1.177	1.137	1.089	1.061
Hypertensive disease	1.413	1.413	1.189	1.111	1.083
Other cardiac diseases	1.039	1.039	1.026	1.017	1.010
3.125 mmHg increase					
IHD	1.225	1.225	1.172	1.093	1.072
CVA	1.312	1.312	1.239	1.152	1.104
Hypertensive disease	1.779	1.779	1.334	1.192	1.142
Other cardiac diseases	1.067	1.067	1.044	1.029	1.017
3.750 mmHg increase					
IHD	1.276	1.276	1.210	1.112	1.087
CVA	1.385	1.385	1.293	1.185	1.126
Hypertensive disease	1.996	1.996	1.413	1.235	1.172
Other cardiac diseases	1.081	1.081	1.053	1.035	1.020
Females					
0.4 mmHg increase					
IHD	1.026	1.026	1.021	1.011	1.009
CVA	1.035	1.035	1.028	1.018	1.013
Hypertensive disease	1.076	1.076	1.038	1.023	1.017
Other cardiac diseases	1.008	1.008	1.005	1.004	1.002
1.2 mmHg increase					
IHD	1.081	1.081	1.063	1.035	1.027
CVA	1.110	1.110	1.086	1.056	1.039
Hypertensive disease	1.247	1.247	1.117	1.070	1.052
Other cardiac diseases	1.025	1.025	1.017	1.011	1.006
2.0 mmHg increase					
IHD	1.139	1.139	1.107	1.058	1.046
CVA	1.190	1.190	1.147	1.095	1.065
Hypertensive disease	1.446	1.446	1.203	1.119	1.088
Other cardiac diseases	1.042	1.042	1.028	1.018	1.011
2.4 mmHg increase					
IHD	1.169	1.169	1.130	1.070	1.055
CVA	1.232	1.232	1.179	1.115	1.079
Hypertensive disease	1.556	1.556	1.248	1.145	1.107
Other cardiac diseases	1.051	1.051	1.033	1.022	1.013

^a Ischaemic heart disease.^b Cerebrovascular disease.

5. Exposure assessment

There are several measures for assessing lead exposure, including proximal measurements, such as the lead concentration in air, dust, food and water; or pathophysiological measurements that assess the body burden of lead (Figure 1). The problem with proximal measurements is in determining how they translate to actual population exposure, since lead absorption depends on a wide range of factors, including individual behaviour, diet, etc. (Mahaffey, McKinney & Reigart, 1992).

Measures of the lead body burden, such as lead in blood, teeth, bone and hair, are closely related to outcome and should more accurately reflect exposure. There are, however, good and bad aspects to each of these measurements. Bone lead is an excellent indicator of long-term exposure, but requires sophisticated measuring equipment. Blood lead is the most commonly assessed parameter because it is straightforward to measure. However, while the level of lead in blood reflects the long-term equilibrium of lead in the body, it will also be elevated by recent exposure to higher-than-normal lead doses. Ultimately, all measurements are likely to involve some compromise, and it is important to balance accuracy and ease of sampling.

Blood lead is the suggested measure for exposure assessment because of the wealth of population studies using this as a measure, the relative ease of sampling, and its close relationship to health outcome.

5.1 Assessing levels of lead in blood

There are a number of ways of assessing blood lead levels, including obtaining data from:

- national institutes, administrations or research bodies (“grey” literature)
- peer-reviewed literature
- special surveys.

Whichever source(s) is used, the data required for the exposure assessment are: the geometric mean value; standard deviation; sample size; population studies; and year of study (as opposed to the year of publication). However, whether assessing exposure through reference to the literature, or through a specifically designed sampling programme, the following should be remembered:

- *Possible contamination:* blood lead measurements can be fraught with contamination problems, especially if capillary samples (rather than venous samples) are used. Scrupulous cleaning of the skin prior to sampling is important. It is also vital that any kit and reagents used to collect blood samples are checked to ensure that they are lead-free, otherwise results will be meaningless. If deriving data from the literature, both of these contamination issues can present problems, since it will often not be possible to determine if quality control was appropriate, or even if samples are venous or capillary.

- *Representative population*: it is important to ensure that exposure data relate to a representative population, or that appropriate adjustments can be made to extrapolate the data to the population for which the disease burden is to be calculated.

Annex 2 provides information on the practical aspects of assessing blood lead levels.

Blood lead surveys

For national burden of disease estimates, the ideal scenario is to have blood lead data from one or more random, population-based studies that are representative of the entire population. Often, however, such data are not available. In many countries, the only data on blood lead levels come from adults in occupational settings, or from school children living in areas surrounding industrial point sources. While these studies are of value they cannot represent an entire population. Nor do they necessarily represent a “worst-case” scenario for very young children (the individuals most at risk), because very young children ingest and absorb more lead from their environment than older children and adults. Children may also be exposed to lead sources that others do not face (e.g. colic remedies containing lead are used in Latin America; and lead poisoning from traditional medicines used in the Middle East, south Asia and China have also been reported (CDC, 1991). Therefore, in many cases it may be advisable to perform additional studies.

The ideal study would use a probability sample and be representative of the entire population. However, such studies are expensive to mount. Typically, much more of the cost is related to items, such as sample design, interviewer salaries, transport and other logistics, rather than to blood drawing and the analysis itself. Therefore it is worth considering whether blood lead testing may be added to an ongoing survey. For example, India chose to add blood lead testing to its 1998–1999 National Survey on Family Growth, a periodic population-based survey that primarily focuses on reproductive health.

If it is not possible to perform national surveys, it will be necessary to make strategic choices of the sites to be studied and to use the results from these sites to draw inferences about similar, but unmeasured, areas. Doing this well is difficult, since many factors related to exposure sources and risk behaviours will vary from place to place. When choosing survey sites, all available information on important lead sources and their prevalence around the country must be considered. This could include information on: air quality data; factories and cottage industries using lead; smelters; the use of lead-glazed ceramics; the use of lead-containing remedies and cosmetics etc.

It is also worth considering whether it is necessary to include people of all ages in the study. As very young children are at risk from development effects, including them should receive highest priority when it is not possible to include representatives of all population groups.

As a rule, random population-based samples are preferable to convenience samples, because the selection biases inherent in convenience samples can seriously distort results. The rationale and steps for performing random, population-based sampling are discussed elsewhere (Kalton, 1983). In some instances, it may be possible to readily arrange population-based sampling by using existing societal systems. For example, in a study of blood lead levels among children in Wuxi, China, toddlers were selected for inclusion when they attended clinics for their universal, mandatory, 12-month health check-up (Gao et al., 2001). Information on practical aspects of blood lead measurements are discussed in Annex 2.

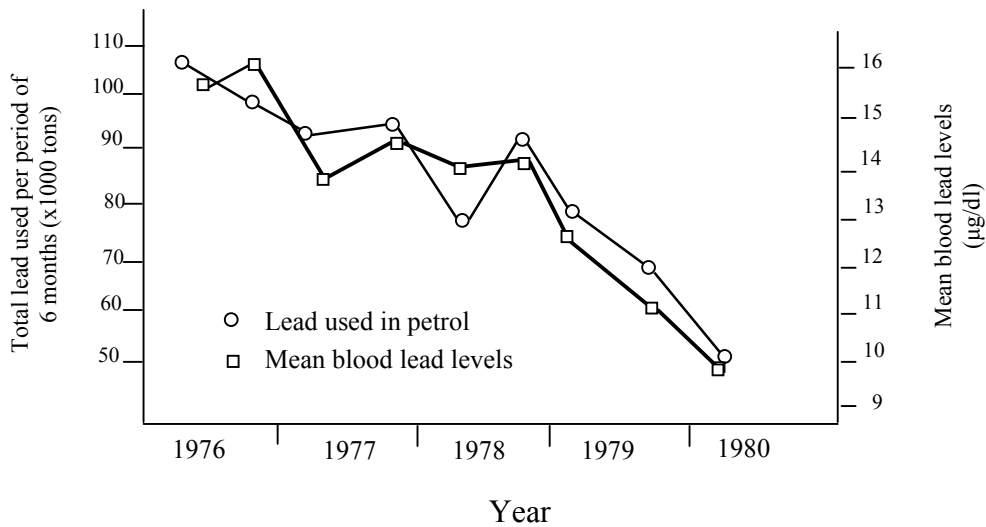
Deriving lead levels from the literature

There is a wealth of literature on lead levels, and a country- or region-specific literature search is a good starting point for an exposure assessment. Population exposure data can be obtained from a variety of sources, including national centres of expertise (universities, environmental institutions, etc.), or government authorities. Additionally, data may also be identified through MEDLINE searches, using a variety of key words (e.g. lead paired with any of the following: newborn, cord, child, adult, pregnancy, blood, smelter, ceramics, pottery, gasoline, cosmetics, kohl, surma, medicine, poisoning, exposure, neurological deficit and cognitive function). Depending on the amount and quality of the data available in the literature, it could form the basis of the exposure assessment or supplement it. As mentioned earlier, there are a number of factors to consider, including: the population; the type of exposure (occupational, local hotspot, general population); applicability of the study (e.g. was it done before changes to the levels of lead in gasoline); and quality control.

Type of exposure

Many studies in the literature relate to occupational or local hotspots, where lead is known or strongly suspected to cause a problem. In the assessment of disease burden at global level, the exposure assessment concentrated only on general population data, as resources did not permit estimates of the number of people exposed due to hotspots and occupational exposure. In a national assessment, with the advantage of country-specific knowledge, such data could provide a valuable addition. If, for example, it is shown in the literature that three similar smelters in an area have a combined surrounding population of 10 000, with a geometric mean blood level of 30 ± 10 µg/dl, a specific estimate of the disease burden for this population could be added to a general population estimate. Any data in the literature that combines blood lead levels with an examination of health outcomes in the population would be valuable and allow specific estimates of the disease burden to be derived. Equally, blood lead level measurements from surma users, for example, can be incorporated into the overall estimate, provided the approximate percentage of users is known. The control groups of occupational or hotspot studies can sometimes be used to characterize a general population not exposed to locally-specific sources.

Figure 4 Reduction in blood lead levels during a programme to reduce lead in gasoline in the United States



Applicability of the study

The applicability of the study will probably depend upon various parameters, such as whether the sample is representative of the study population, or whether any changes have occurred in the population since the exposure measurements. If significant changes occurred since the exposure measurement (e.g. the initiation or completion of a lead reduction programme, such as removal of lead in gasoline), the study data may still be useful but will need some adjustment. Numerous studies have shown that reductions in blood lead parallel decreases in the level of lead in gasoline. In the USA, for example, average blood lead levels dropped 37% in the early stages of lead reduction programme (Annest 1983; Annest et al. 1983; Figure 4). Other studies conducted in various countries have shown similar results (Elinder et al., 1986; Wietlisbach et al., 1995; Schuhmacher et al., 1996), with decreases over a five-year period ranging between 30–48%. In the global burden of disease study, a number of countries had “old” data that did not reflect the implementation of lead reduction programmes. Therefore, the midpoint of the reported ranges (i.e. a 39% decrease in blood lead for a five-year period) was chosen as a reduction factor and applied to the mean blood lead levels in the population. A numerical example on the use of this correction factor is given in section 6, *Estimating the disease burden*.

5.2 Overall output

Whichever method or combination of exposure assessment methods is chosen, the final output should be either a single value of mean blood lead and its standard deviation, or a series of values that can be combined to derive an overall estimate of the burden of disease. Preferably, child and adult data should be assessed and

analyzed separately, as well as data for urban and rural populations, as these groups often have very different patterns of lead exposure and health effects. This will allow the best estimate of the disease burden to be made. If there are exposure hotspots, such as around a smelter, these can be accounted for, provided an estimate of the exposed population can be made.

6. Estimating the disease burden

The outcome assessment is derived from combining the exposure information and the data on health effects. Depending upon the amount of data available, it may be necessary to combine the data to form a single or series of blood lead distributions. For example:

- If the study population is urban and the study sample is representative of it, a single mean and standard deviation can be used to estimate the disease burden (preferably, separate values should be used for children and adults).
- If the study population is composed of urban and rural populations, or if there are several samples for several towns or regions, it is possible to combine the means and standard deviations by weighting each by the population it represents (see section 6.3: *Calculating weighted means*).

The calculations need to be repeated for each population subgroup, and the numbers of people affected can be summed at the end.

A step-by-step numerical application of the methods is given in the following sections. The hypothetical example assesses the disease burden in country X, following the introduction of a programme to reduce the amount of lead in gasoline.

6.1 An example problem: assessing the disease burden effects of a programme to reduce lead in gasoline

In a hypothetical search of the literature, it was found that a number of studies had measured blood lead levels in the population of country X (Table 5). However, in 1996, a programme to reduce the lead content of gasoline was started in country X.

Table 5 Blood lead data for country X

Study No.	Year of study	Age group	Location	Sample size (N)	Blood lead level (µg/dl) ^a	Standard deviation (µg/dl)
1	1996	Adults	Urban	245	8.4	NR ^b
2	1996	0–4 years	Urban	145	7.9	2.4
3	1997	Children	Urban	650	6.2	2.1
4	1998	Children	Urban	458	5.9	1.8
5	1999	15–45 years	Urban	750	6.7	2.3
6	1999	Children	Urban	750	5.6	NR
7	2000	Children	Urban	60	4.8	2.2
8	2000	Adults	Urban	420	6.0	NR
9	2000	Adults	Rural	1500	3.5	1.2
10	2000	Children	Rural	1500	3.8	1.3

^a The blood lead level is reported as the geometric mean of the population sample.

^b NR: not reported

Thus, to estimate the disease burden for the year 2001, the empirical blood lead data for 1996–2000 first need to be adjusted for the expected annual reduction in lead levels produced by the programme. This step yields estimates of the adjusted mean blood lead levels for the year 2001, from each of the studies. The estimates can then be pooled to generate a distribution of blood lead levels, from which the disease burden for 2001 can be assessed by comparing the distribution with known health effects (e.g. Figure 2).

The adjustment is normally applied only to urban populations, since rural populations are generally less affected by high-density traffic and would be less affected by a programme to cut lead in gasoline. Similarly, data would not need to be adjusted if the environmental exposure had not changed in the time period of interest (e.g. if the programme to reduce lead in gasoline had not been introduced, the disease burden for 2001 could be estimated directly from the data in Table 5, without adjustment). In countries where environmental exposure has varied significantly in recent years, it is advisable not to include blood lead levels older than five years in the calculations. They can, however, be used to examine trends and to check for consistency.

6.2 Adjusting blood lead levels for the effects of the programme to reduce lead in gasoline

As a result of the programme to reduce leaded gasoline, blood lead levels are considered to decrease by 39% over a five-year period (or 7.8% per year; see section 5.1: *Assessing levels of lead in blood*). However, the pace or pattern of programme implementation may be different for each study, and if alternative data on blood lead reduction are given in the study, they should be used to calculate the correction factor, rather than the generic rate of 7.8% per year. Whichever data are used, the correction factor can then be used to adjust the mean level of blood lead for each study for the length of time the leaded-gasoline programme has been in effect in the study population.

The correction factor is calculated by subtracting the date of the study from 2001, then multiplying the difference by the yearly decline of 7.8% (or other rate derived from study data). In Study 1 (Table 5), for example, the period since data assessment is 5 years (2001-1996). The correction factor is thus 5 years \times 0.078 per year = 0.39. To calculate the adjusted mean blood lead level for the adults in Study 1, the unadjusted mean level for 1996 (Table 5) is multiplied by (1-correction factor): $8.4 \mu\text{g/dl} \times (1-0.39) = 5.13 \mu\text{g/dl}$. Essentially, this value is an estimate of the mean blood lead level for the year 2001, based on data taken in 1996.

6.3 Calculating weighted means

Using the method above, adjusted mean blood lead levels for urban children were calculated for five studies (Table 6). The adjusted means can be combined to form a single, sample-size weighted, geometric mean value, that describes the blood lead distribution of urban children in country X.

Table 6 Adjusted mean blood lead levels for urban children in country X^a

Study No.	Year	Age group	Location	Sample size (N)	Mean blood lead level ($\mu\text{g/dl}$) ^b	(1-correction factor)	Adjusted mean blood lead level ($\mu\text{g/dl}$)
2	1996	0–4 years	Urban	145	7.9	1-0.390	4.8
3	1997	Children	Urban	650	6.2	1-0.312	4.3
4	1998	Children	Urban	458	5.9	1-0.234	4.5
6	1999	Children	Urban	750	5.6	1-0.156	4.7
7	2000	Children	Urban	60	4.8	1-0.078	4.4

^a The mean blood lead levels were adjusted to account for the implementation of a lead reduction programme in 1996, and are given as geometric means.

^b Means from studies compiled in Table 5.

To weight the data for sample size, the adjusted mean blood lead level from each study should be transformed into the natural logarithm, (owing to the log-normal distribution of blood lead levels), and then multiplied by the sample size. An average is then obtained by summing all the resulting values and dividing by the total sample size. The natural antilogarithm of this average then gives the weighted mean value (Table 7).

Table 7 Weighted mean blood lead levels for urban children in country X

Study No.	Sample size (N)	(A) Adjusted mean blood lead level ($\mu\text{g/dl}$)	ln(A)	ln(A) x N
2	145	4.8	1.57	228
3	650	4.3	1.45	943
4	458	4.5	1.51	691
6	750	4.7	1.55	1165
7	60	4.4	1.49	89
Σ	2063			3116
Weighted mean ^a	4.5			

^a The average of $\Sigma[\ln(A) \times N]/N = 3116/2063 = 1.51$. The natural antilogarithm of this value is then $e^{1.51} = 4.5$, which is the weighted geometric mean blood lead level.

6.4 Combining standard deviations

A similar method is used to derive a sample-size weighted, standard deviation, although this is calculated as the variance (i.e. the square of the standard deviation), and no adjustments are made for lead reduction programmes. This is illustrated for urban children in Table 8.

Table 8 Weighted standard deviation for urban children in country X

Study No. ^a	Sample size (N)	SD ^b	SD ²	ln(SD ²)	ln(SD ²) x N
2	145	2.4	5.76	1.75	254
3	650	2.1	4.41	1.48	965
4	458	1.8	3.24	1.18	538
7	60	2.2	4.84	1.58	95
Σ	1313				1852
Square root					1.19
Weighted standard deviation ^c					3.29

^a Study No. 6 (Table 5) was excluded because no information on the standard deviation was available.

^b SD = standard deviation.

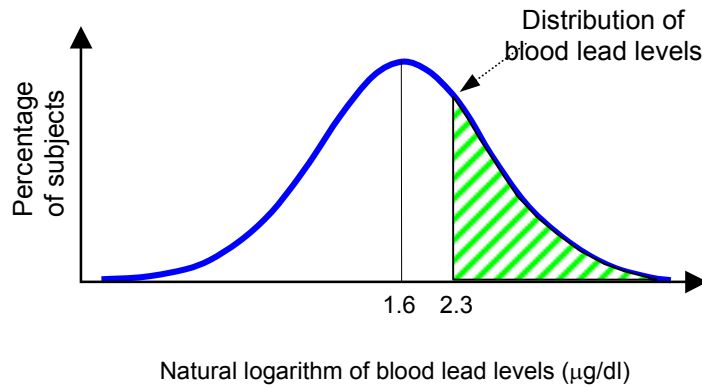
^c The average of $\sum[\ln(\text{SD}^2) \times N]/N = 1852/1313 = 1.41$. Since $\sqrt{1.41} = 1.19$, the weighted standard deviation is $e^{1.19} = 3.28$.

Thus, the blood lead distribution of urban children in country X has mean value of 4.53µg/dl and a standard deviation of 3.28µg/dl.

6.5 Calculating the population at risk

To assess the disease burden, the health-effect levels must be superimposed onto each blood lead distribution, from which the number of people affected can be calculated. A typical blood lead distribution, such as that calculated in the previous section, is shown in Figure 5. The previously-defined health-effect intervals (e.g. Figure 2) can then be combined with this distribution. Although in Figure 2 the health effects are shown as discrete bands, it is important to note that the “at risk” population in each band is also at risk of health effects that occur at lower blood lead levels.

Figure 5 Typical distribution of blood lead levels in a population, with a health-effect interval



The proportion of the population above a certain blood lead level can be calculated using the function, LOGNORMDIST, in recent versions of Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). The function returns the cumulative log-normal distribution of x , where $\ln(x)$ is normally distributed. To obtain the population proportion above a certain blood lead level, the function, $1 - \text{LOGNORMDIST}(x, \mu, \sigma)$, should be used.¹ These functions are already incorporated into a Microsoft Excel spreadsheet that can be requested from WHO's Department of Protection of the Human Environment (PHE) at e-mail address EBDAssessment@who.int (see cover note).

The distribution of blood lead takes the form:

$$\frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

where the variable, x , is the blood lead level above which a health effect occurs. The population above this level is the proportion at risk of the health effect;

μ , is the mean blood lead value (derived from a single large-scale study, or from the literature);

σ , is the standard deviation of the mean blood lead value.

For example, in Figure 5, the shaded area corresponds to the number of people with blood lead levels above 10 $\mu\text{g/dl}$ ($\ln 10 = 2.3$), for a population with a geometric mean blood lead level of 5.0 $\mu\text{g/dl}$ ($\ln 5 = 1.6$) and a standard deviation

¹ Additional information can be obtained from the "Help" function in Microsoft Excel.

of 3.9 µg/dl. The number of people, N , within the shaded area can be calculated using the Microsoft Excel function, $1 - \text{LOGNORMDIST}$, which takes the following form:

$$N = 1 - \text{LOGNORMDIST}(10, 1.6, 1.36)$$

where 10 µg/dl is the lower bound of the health interval of interest (corresponding to 2.3 µg/dl in Figure 5); 1.6 is the natural logarithm of the mean value of the distribution (5.0 µg/dl); and 1.36 is the natural logarithm of the standard deviation (3.9 µg/dl).

The output from this function shows that 30.5% of the population represented in Figure 5 have blood lead levels greater than 10 µg/dl.

Next, to assess the predefined health effects of lead, it is necessary to calculate the number of people in the following blood lead intervals (which correspond to the levels outlined in Table 1).

- Level 1 5–10 µg/dl
- Level 2 10–15 µg/dl
- Level 3 15–20 µg/dl
- Level 4 > 20 µg/dl
- Level 5 ≥ 60 µg/dl
- Level 6 ≥ 70 µg/dl
- Level 7 ≥ 80 µg/dl

This is accomplished by first using the method described in section 6.5 *Calculating the population at risk*, to calculate the proportion of the population with blood lead levels above a given value (5 µg/dl, 10 µg/dl, 15 µg/dl etc; see Table 9), and then calculating the proportion of people in the intervals (5–10 µg/dl, 10–15 µg/dl, etc.) using these data (see Table 10). This is illustrated for the children listed in Table 5.

In country X, 74% of the people live in urban areas. The blood lead distribution for urban children has a mean of 4.5 µg/dl and a SD of 3.28 µg/dl (see Tables 7, 8). The blood lead distribution for rural children has a mean of 3.8 µg/dl and a SD of 1.32 µg/dl (Study No. 10, Table 5). From these data, the percentage of children at, or above, the specified blood lead levels were calculated using the LOGNORMDIST function in Microsoft Excel (Table 9). The data in Table 9 clearly illustrate the importance of accounting for the exposure of urban and rural groups separately. Once the distribution of urban and rural individuals into the blood lead level intervals have been estimated, they can be added up (see below).

Table 9 Blood lead levels in children of country X

Blood lead level ($\mu\text{g}/\text{dl}$)	Urban children (%)	Rural children (%)
5	46.7	16.1
10	25.3	0
15	15.7	0
20	10.6	0
60	1.5	0
70	1.1	0
80	0.8	0

To calculate the number of children within specific intervals (5–10 $\mu\text{g}/\text{dl}$, 10–15 $\mu\text{g}/\text{dl}$ etc.) from the data in Table 9, the figure for the upper band of the interval is subtracted from the lower one and divided by 100.

For example, the proportions of urban and rural children in the 5–10 $\mu\text{g}/\text{dl}$ interval are $(46.7-25.3)/100 = 0.214$ and $(16.1-0.0)/100 = 0.161$, respectively. Table 10 shows the proportion of children within each health effect interval. These proportions represent the children at risk for the health effects of lead.

Table 10 Proportion of children within specified blood lead intervals

Blood lead interval ($\mu\text{g}/\text{dl}$)	Proportion of urban children	Proportion of rural children
Level 1 5–10	0.214	0.161
Level 2 10–15	0.096	0
Level 3 15–20	0.051	0
Level 4 > 20	0.106	0
Level 5 ≥ 60	0.015	0
Level 6 ≥ 70	0.011	0

If a single, combined proportion for both urban and rural children at risk is required, the data for each blood lead interval have to be adjusted for the proportion of the population that is urban (74%) or rural (26%):

combined proportion of children in interval $L = [(\text{proportion of urban children in interval } L) \times (\% \text{ of the urban population})] + [(\text{proportion of rural children in interval } L) \times (1-\% \text{ of the urban population})]$.

For example, the combined proportion for the 5–10 $\mu\text{g}/\text{dl}$ interval = $(0.214 \times 0.74) + [0.161 \times (1-0.74)] = 0.200$.

6.6 Estimating disease rates in children

To assess the health burden of blood lead, the proportions of at-risk children in each interval shown in Table 10 are equated with the rates at which health effects appear for the interval. Blood lead levels 1–4 (Table 10) equate to IQ loss in young children, for example, while levels 5 and 6 equate to gastrointestinal effects and anaemia, respectively. Health effect rates are expressed as the number of children with the effect per 1000 children.

The continuing example of how to assess health effects uses combined proportions of both urban and rural children at risk (Table 11). The total proportions of children at risk were calculated as described in section 6.5 *Calculating the population at risk*, and multiplied by 1000 to give the total number of children at risk per 1000 children (“Rate per 1000 children”, Table 11).

Table 11 Total children at risk of lead-related health effects

Blood lead interval (µg/dl)	Total proportion of children at risk	Health effect ^a	Rate per 1000 children ^b	Normal population in IQ interval (%) ^c
5–10	0.200	IQ(1) loss of 0.65 points	200	0.24
10–15	0.070	IQ(2) loss of 1.95 points	70	0.80
15–20	0.038	IQ(3) loss of 3.25 points	38	0.45
> 20	0.078	IQ(4) loss of 3.50 points	78	1.59
≥ 60	0.011	Gastrointestinal effects	2.2	NA
≥ 70	0.008	Anaemia	1.6	NA

^a The loss of IQ points is largely irreversible and for the purpose of this estimate is considered to occur only once (rather than every year), so this loss should only be applied to the cohort of children aged one year or younger.

^b The rates for gastrointestinal effects and anaemia require a 0.2 correction factor (Table 1).

^c Distribution of a normal population into the specified intervals, from Table 2. The proportion of children in each interval represents those potentially affected by loss of IQ points due to lead.

NA: not applicable.

The final step in the health effects calculation is to convert the IQ loss figures into a rate of MMR per 1000 population. This is done by multiplying the number of people affected at each blood lead level by the figures from Table 2, summing, and then multiplying by the regional adjustment rate for MMR (Table 3).

For example, assume country X is in EurC; the MMR adjustment ratio is therefore 1.19 (Table 3). Using the data in Table 2 and 11, the incidence rate of MMR is then calculated as:

$$\begin{aligned}
 I(\text{MMR}) &= 1.19 [(200 \text{ children}/1000 \times 0.0024) + (70 \text{ children}/1000 \times 0.008) + \\
 &\quad (38 \text{ children}/1000 \times 0.0145) + (78 \text{ children}/1000 \times 0.0159)] \\
 &= 3.37 \text{ children per } 1000 \text{ children in country X.}
 \end{aligned}$$

NB: This rate applies only to the children of one cohort, i.e. the children who are aged 0–1 years in the year for which the disease burden is being estimated. The burden of older children (between 1–4 years) is attributed to previous years

In summary, in country X in 2001, exposure to lead is expected to result in 3.37 cases of MMR for every 1000 children at risk in the age group 0–1 years. The corresponding rate for the 0–4 year-old age group is a fifth of this rate (i.e. $3.37/1000$ divided by $5 = 0.67/1000$), as this age group includes the 5-year old children, but cases occur in the first year only. In addition, 2.2 cases/1000 of gastrointestinal effects and 1.6/1000 cases of anaemia in children under the age of five years are also expected because of lead exposure. The MMR rate is one of the output parameters from the Microsoft Excel lead spreadsheet (Annex 5), and can be used as input into the DALY calculation template.

Interventions to reduce exposure to lead, such as phasing lead out of gasoline, reducing lead levels in drinking water, and removing leaded paints from housing can drastically reduce blood lead levels. In countries where such measures have been taken, blood lead levels can typically reach means as low as $2 \mu\text{g}/\text{dl}$. If this were the case in country X, and assuming a standard deviation of $2.3 \mu\text{g}/\text{dl}$, the number of people affected by health effects could be reduced by as much as 80% in the medium term.

Although the foregoing example only uses inputs relating to urban and rural children, if a mean and standard deviation are available for children exposed to a hotspot of pollution (e.g. a smelter) this can also be factored in, provided the population exposed can be estimated.

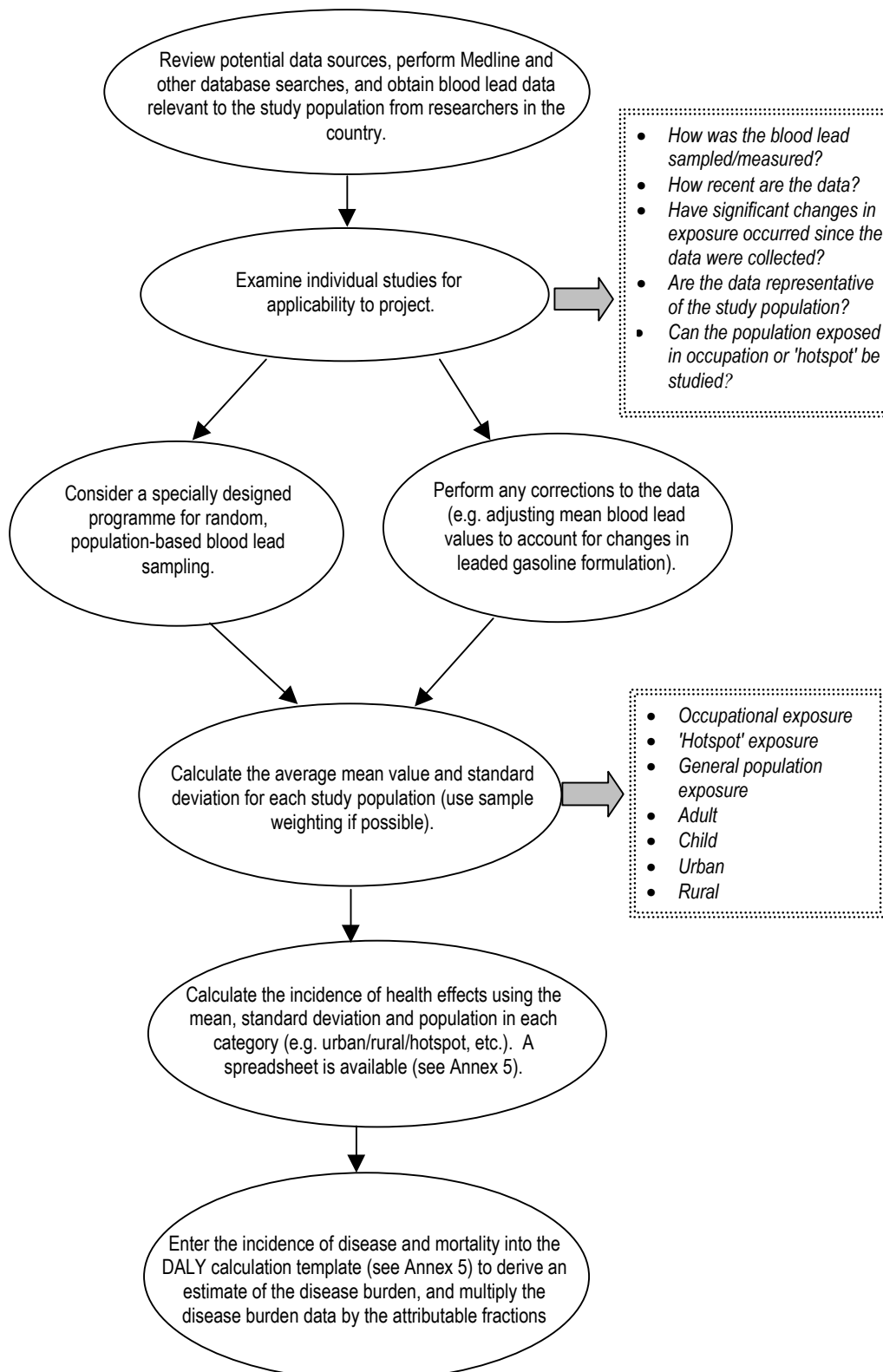
6.7 Estimating the disease burden due to increased blood pressure

The procedure for estimating the disease burden due to increased blood pressure in adults is basically the same as that for estimating MMR rates in children. The proportions of the population within specified blood lead levels are estimated as outlined in section 6.5, using data on adult populations. The proportions of the adult population exposed in the various levels (see Table 10 for comparable data for children) are combined with the relative risks for cardiovascular diseases (Table 4) to calculate the impact fraction (section 4.3). The resulting impact fractions, estimated for each age group, are then multiplied by the total disease burden or incidence rates that are available for the outcomes of concern (ischaemic heart disease, cerebrovascular disease, hypertensive disease, other cardiac diseases) in the country or study area of concern (see also Chapter 5).

6.8 Summary of steps for estimating the disease burden

The process for estimating the disease burden is summarized in the form of a flow chart (Figure 6).

Figure 6 Flow chart for estimating the disease burden



7. Uncertainties

There are uncertainties in the approach described in the foregoing section and they derive from:

- uncertainties inherent in data compiled for the analysis (e.g. how accurate are the measurements of blood lead levels in a sample population, and how representative are they of the population as a whole);
- uncertainties due to parameters used in a model, such as exposure-response relationships derived from the literature;
- uncertainties associated with the method used to adjust exposure data (if applicable).

These sources are discussed in the following sections 7.1–7.4.

7.1 Blood lead measurements

As mentioned earlier (section 5.1, *Assessing levels of lead in blood*), measurements of blood lead levels can be fraught with contamination problems. Nevertheless, if measurements are conducted according to the methods outlined in this guide, this should not be an issue. On the other hand, data derived from the literature are more likely to have a greater degree of uncertainty associated with them, as the studies often do not report their quality-control procedures.

7.2 Are the data representative?

Regardless of how the data are derived, there will be uncertainties as to whether they represent the general population. This will be less of a problem if studies use good design and quality-control procedures, and study diverse populations.

7.3 Adequacy of adjustment factors

The main adjustment factor in the approach is in translating the population distribution “at risk” of a lead-related health effect, based on blood lead measurements, to the population intervals for actual health effects. Uncertainties can arise in this process, because the same health effects can occur at very different lead levels in individuals (for a number of reasons, including genetics and nutritional status). The blood lead levels in Table 1, for example, were used because health effects are widely seen at these levels, but health effects may occur at lower levels. A correction factor of 0.2 was chosen (i.e. a fifth of those at risk would develop symptoms), but in the global burden of disease study, upper and lower levels were determined using correction factors of 0.15 and 0.25. This is the largest source of uncertainty in the estimate and it is discussed further in section 8, *Research needs and recommendations*.

The other main adjustment factor is the downward adjustment of blood lead levels to account for decreases in environmental lead levels (e.g. because of a lead reduction programme). This adjustment would not be necessary if environmental

lead levels have remained constant over time. Also, over- or underestimation of the blood lead levels may be introduced here because the phasing out of lead may occur at a more-or-less rapid pace, depending on the effort and investments the country dedicates to it.

7.4 Ranges of reported exposure-response relationships

The meta-analysis used to estimate the exposure-response relationship (Schwartz, 1995) reported that the confidence interval around the exposure-response relationship between blood lead level and blood pressure is about 30%. The meta-analysis covering the association between blood lead and loss of IQ points reports a loss of 2.6 with a standard error of ± 0.41 IQ points (i.e. $\pm 16\%$) for an increase in blood lead from 10 to 20 $\mu\text{g}/\text{dl}$. In the absence of a confidence interval for the exposure-response relationships between blood lead and gastrointestinal effects and anaemia, a similar interval (i.e. 30%) has been assumed.

7.5 Quantitative estimation of uncertainty

The final estimates of disease burden related to lead should not only provide the “best estimate”, but should also reflect an uncertainty interval around this estimate. To do so, lower and upper estimates for exposure estimates can be defined (e.g. using the confidence interval around the mean exposure). Examples of such estimates include the bounds for the 0.2 adjustment factor (0.15, 0.25), or the confidence interval for the relationship of lead levels and blood pressure ($\pm 30\%$; see Schwartz, 1995). In addition, to estimate MMR, the mean IQ score in the population can be varied. By recalculating the results using combinations of these higher and lower input parameters, instead of the “best estimate”, “low” and “high” estimates of the impact can be obtained. Such evaluations of uncertainties do not have any statistical meaning, but rather serve as an indication of the lower and higher estimates of the health impacts from the risk factor.

If quantified uncertainty were available for all the input parameters, then it would be possible to model the uncertainty around results with a Monte-Carlo analysis, which would be a more systematic approach. Often, however, the uncertainty of all the input parameters is difficult to quantify, which is why the approach mentioned above is often chosen even though it only provides an indication of possible values of the results rather than an uncertainty interval *per se*.

8. Research needs and recommendations

The greatest improvements in estimating the disease burden of lead will come from characterizing the exposure-response relationships for health effects. At present, it is necessary to make assumptions about the number of people likely to suffer symptoms at specified exposure levels, based on limited evidence. Clearly, it is likely that the proportion of people who become ill will change with increasing blood lead level, but additional evidence is needed to quantify this change, particularly for population subgroups (e.g. children of different age groups or nutritional status). A single adjustment factor could be adopted for all blood lead levels and for all health outcomes. It is also likely that, as the characterization of health effects improves, it will be possible to account for lead-related health effects that cannot be accounted for currently, such as its effects on reproduction, or on violence and delinquent behaviour (with consequent injuries) (Nevin, 2000).

To reduce the disease burden caused by exposure to lead it is important to determine the groups at highest risk, and the main pathways of exposure that contribute to the health impacts. The assessment of exposure could therefore be refined by assessing various subgroups and, if necessary, collecting parallel measurements of lead levels in the environment.

9. Disease burden and policy

Having established an estimate of disease burden it is important to consider these results in policy formulations. For this, it is necessary to estimate the relative contributions of lead sources to the total exposure, to inform possible reduction strategies. These estimates can be obtained from environmental measurements by models developed for this purpose, such as the United States Environmental Protection Agency (USEPA) integrated exposure and biokinetic model (USEPA, 1994a,b). A simpler way of obtaining estimates is to use environmental indicators of exposure (i.e. distal causes, Figure 1) in conjunction with typical exposure scenarios compiled from the literature (see Annex 3). Once the main sources of exposure are identified, targeted measures can be taken at national or local level. In countries where leaded gasoline is still being used, this is generally the most important source, be it direct, through air and dusts, or indirect, through food. Phasing out leaded gasoline should be a priority.

Besides phasing out leaded gasoline, effective measures to reduce exposure include enforcing regulations that limit:

- industrial emissions
- worker exposure to lead in formal and cottage industries
- the lead content of lead-glazed pottery used for cooking, eating or drinking
- lead in school materials, such as paint
- the use of leaded solder in food cans
- the use of leaded paints
- lead levels in other environmental media.

Local measures to reduce environmental lead may include the renovation of degraded housing (including the removal of leaded paint and leaded pipes for drinking-water); termination of emissions and abatement of contamination by local cottage industries (such as battery recycling); and screening and treatment of children at particular risk. Other local measures for specific exposures may also be important. For further information, consult the policy recommendations published by several organizations (Alliance to end childhood lead poisoning, 2001; CDC, 2002; USEPA, 2002; Environmental Health Center, 2002).

In addition to disease burden, lead exposure may contribute to causation of other socioeconomic burdens. In the USA, for example, it has been estimated that 45 000 cases of lead-related reading disabilities could be prevented, at a savings of more than US\$ 900 million per year in remedial education (Glotzer, Freedberg & Bauchner, 1995). Another study estimated that each one-point rise in IQ raises worker productivity by 1.76%–2.38%, resulting in an economic benefit of US\$ 110–319 billion for each year's cohort of children (Grosse et al., 2002).

References

- Alliance to end childhood lead poisoning (2001) Washington, (Internet communication of January 2001 at web site www.aeclp.org).
- Annest JL. (1983) Trends in blood lead levels of the US population. In: Rutter M, Jones RR, eds. *Lead versus Health*. New York, John Wiley and Sons, pp. 33–58.
- Annest JL, Pirkle JL, Makuc D, Neese JW, Bayse DD and Kovar MG. (1983) Chronological trend in blood lead levels between 1976 and 1980. *New England Journal of Medicine*, 308:1373–1377.
- ATSDR (1999) *Toxicological profile for lead (update)*. Atlanta, GA, Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry.
- Byers RK, Lord EE. (1943) Late effects of lead poisoning on mental development. *American Journal of Diseases in Children*, 66:471–494.
- CDC (1991) *Preventing lead poisoning in young children: a statement by the Centers for Disease Control*. Atlanta, GA, USA, Centers for Disease Control and Prevention, p. 25.
- CDC (2002) *CDC childhood lead poisoning prevention program*. Atlanta, GA, USA, Centers for Disease Control and Prevention (internet communication of October 2002 at web site www.cdc.gov/nceh/lead/lead.htm).
- de la Burde B, Choate MS, Jr. (1972) Does asymptomatic lead exposure in children have latent sequelae? *Journal of Pediatrics*, 81:1088–1091.
- Elinder CG, Friberg L, Lind B, Nilsson B, Svartengren M, Overmark I. (1986) Decreased blood lead levels in residents of Stockholm for the period 1980–1984. *Scandinavian Journal of Work and Environmental Health*, 12(2):114–120.
- Environmental Health Center (2002) *Lead poisoning prevention outreach program*. Washington, DC, National Safety Council (internet communication of October 2002 at web site www.nsc.org/ehc/lead.htm).
- Ezzati M, Lopez AD, Rodgers A, Murray CJL (Eds). (2003) *Comparative quantification of health risks: global and regional burden of disease due to selected major risk factors*. Geneva, World Health Organization (in press).
- Falk H (2002) International environmental health for the pediatrician: case study of lead poisoning. *Pediatrics* (in press).
- FAO (1989) *Exposure of infants and children to lead*. Rome, Food and Agriculture Organization of the United Nations (Food and Nutrition Paper No. 45).
- Fewtrell L, Prüss-Üstün A, Ayuso-Mateos JL. (2003) *Estimating the global burden of disease of mild mental retardation and cardiovascular diseases from environmental lead exposure*. (in press)
- Gao WZ, Li Z, Wang ZG, Kaufmann RB, Jones RL, Wang NF, Zhou XQ, Chen YF. (2001) Blood lead levels of children aged 1 to 5 years in Wuxi, China. *Environmental Research*, 87:11–19.
- Glotzer DE, Freedberg KA, Bauchner H (1995) Management of childhood lead poisoning: clinical impact and cost-effectiveness. *Medical Decision Making*, 15(1):13–24.

- Grosse SD, Matte TD, Schwartz J, Jackson RJ. (2002) Economic gains resulting from the reduction in children's exposure to lead in the United States. *Environmental Health Perspectives*, 110(6):563–569.
- Hall A, Cantab MD (1905) The increasing use of lead as an abortifacient: a series of 30 cases of plumbism. *British Medical Journal*, i:584–587.
- Hernandez-Avila M, Cortez-Lugo M, Munoz I, Tellez M and Rojo-Soliz M. (1999) Lead exposure in developing countries. In: George, AM, ed. *Lead poisoning prevention and treatment: implementing a national program in developing countries*. Bangalore, India, The George Foundation, pp. 87–94.
- Kalton G (1983) *Introduction to survey sampling*. London, Sage Publications.
- Landrigan PJ, Boffetta P, Apostoli P (2000) The reproductive toxicity and carcinogenicity of lead: a critical review. *American Journal of Industrial Medicine*, 38:231–243.
- Lanphear BP, Dietrich K, Auinger P, Cox C. (2000) Cognitive deficits associated with blood lead concentrations <10 µg/dl in US children and adolescents. *Public Health Reports*, 15:521–529.
- Last JM, ed. (2001) *A dictionary of Epidemiology*. New York, Oxford University Press, International Epidemiological Association.
- Lawes C, Vander Hoorn S, Rodgers A, Elliott P, MacMahon S. (2003) High blood pressure. In: Ezzati M et al., eds. *Comparative quantification of health risks: global and regional burden of disease due to selected major risk factors*. Geneva, World Health Organization.
- Lezak MD (1995) *Neuropsychological Assessment*. New York, Oxford University Press.
- Mahaffey KR, McKinney J, Reigart JR (1992) Lead and compounds. In: Lippmann M, ed. *Environmental toxicants. Human exposures and their health effects*. New York, Van Nostrand Reinhold, pp. 360–391.
- NAS (1972) *Lead. Airborne lead in perspective*. Washington, DC, National Academy of Sciences.
- National Research Council (1993) *Measuring lead exposure in infants, children and other sensitive populations*. Washington, DC, National Academy Press.
- Nawrot T, Thijs L, Den Hond EM, Roels HA, Staessen JA. (2002) An epidemiological reappraisal of the association between blood pressure and blood lead: a meta-analysis. *Journal of Human Hypertension*, 16(2):123–131.
- Needleman HL (1999) History of lead poisoning in the world. In: George AM, ed. *Lead poisoning prevention and treatment: implementing a national program in developing countries*. Bangalore, India, The George Foundation, pp. 17–25.
- Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. (1990) The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. *New England Journal of Medicine*, 322(2):83–88.
- Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greathouse JB. (1996) Bone lead levels and delinquent behaviour. *Journal of the American Medical Association*, 275(5):363–369.
- Nevin R (2000) How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. *Environmental Research*, 83(1),1–22.

- Pirkle JL, Schwartz J, Landis JR and Harlan WR. (1985) The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. *American Journal of Epidemiology*, 121(2):46–258.
- Prüss-Üstün A, Woodward A, Corvalán C. (2003a) *Assessment of environmental burden of disease: introduction and methods*. Geneva, World Health Organization (in press).
- Prüss-Üstün A, Fewtrell L, Landrigan P, Ayuso-Mateos JL. (2003b) Exposure to lead in the environment. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL (Eds). *Comparative quantification of health risks: global and regional burden of disease due to selected major risk factors*. Geneva, World Health Organization (in press).
- Roeleveld N, Zielhuis GA, Gabreels F (1997) The prevalence of mental retardation: a critical review of recent literature. *Developmental Medicine and Child Neurology*, 39(2):125–132.
- Rummo JH, Routh DK, Rummo NJ (1979) Behavioural and neurological effects of symptomatic and asymptomatic lead exposure in children. *Archives of Environmental Health*, 34:120–125.
- Schuhmacher M et al. (1996) Impact of reduction of lead in gasoline on the blood and hair levels in the population of Tarragona Province, Spain, 1990–1995. *Science of the Total Environment*, 184:203–209.
- Schwartz J (1988) The relationship between blood lead and blood pressure in the NHANES II survey. *Environmental Health Perspectives*, 78:15–22.
- Schwartz J (1994) Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. *Environmental Research*, 65:42–55.
- Schwartz J (1995) Lead, blood pressure, and cardiovascular disease in men. *Archives of Environmental Health*, 50(1), 31–37.
- Schwartz J, Landrigan PJ, Baker EL Jr., Orenstein WA, von Lindern IH. (1990) Lead-induced anemia: dose-response relationships and evidence for a threshold. *American Journal of Public Health*, 80(2):165–168.
- USEPA (1994a) *Guidance manual for the integrated exposure uptake biokinetic model for lead in children*. Washington, DC, US Environmental Protection Agency (EPA/540/R-93. PB93-963510).
- USEPA (1994b) *Technical support document: parameters and equations used in integrated exposure uptake biokinetic model for lead in children (v0.99d)*. Washington, DC, US Environmental Protection Agency (EPA/540/R-94-040. PB94-963505).
- USEPA (2002) *Lead awareness program*. Washington, DC, US Environment Protection Agency (Internet communication of October 2002 at web site www.epa.gov/opptintr/lead).
- van Alphen M (1999) Identifying the source of lead poisoning in each individual case. In: George AM, ed. *Lead poisoning prevention and treatment: implementing a national program in developing countries*. Bangalore, India, The George Foundation, pp. 149–157.
- WHO (1995) *Inorganic lead. Environmental health criteria 165. International programme on chemical safety*. Geneva, World Health Organization.
- WHO (2001a) *World Health Report 2001*. Geneva, World Health Organization.
- WHO (2001b) *GBD calculation sheets for meningitis, iodine deficiency, anaemia, pertussis, trichuriasis, ascariasis and Japanese encephalitis*.

References

- Geneva, World Health Organization (unpublished document available from Evidence and Information for Policy (EIP) cluster, 1211 Geneva 27, Switzerland).
- WHO (2002) *World health report 2002: reducing risks, promoting healthy life*. Geneva, World Health Organization.
- Wietlisbach V, Rickenbach M, Berode M and 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. *Environmental research*, 68(2):82–90.
- Woolf DA (1990) Aetiology of acute lead encephalopathy in Omani infants. *Journal of Tropical Pediatrics*, 36:328–330.