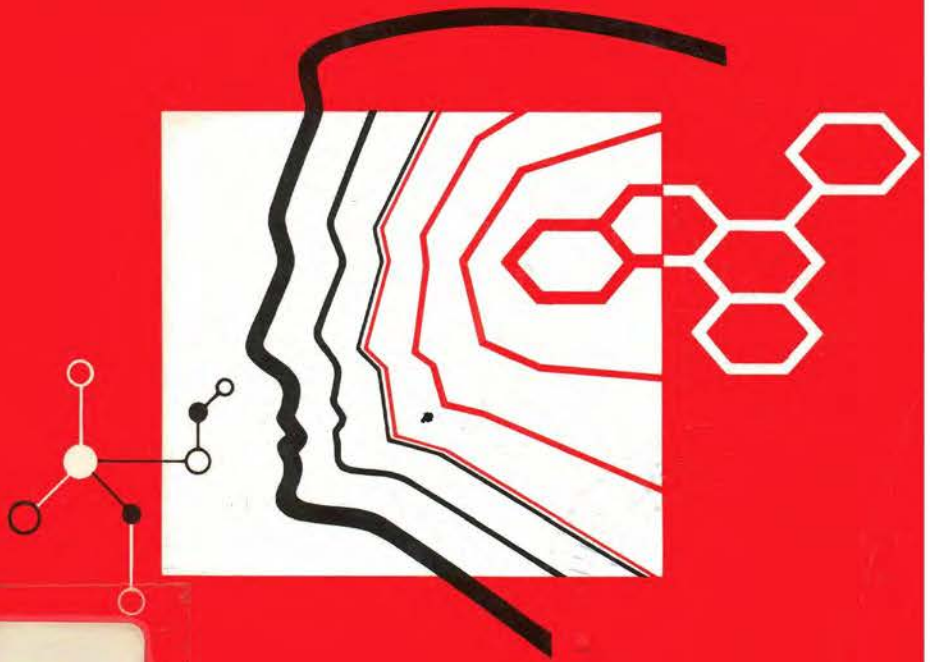
IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 165

Inorganic Lead



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Under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization

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Environmental Health Criteria 165

INORGANIC LEAD

Published under the joint sponsorship of
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and the World Health Organization

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Geneva, 1995

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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CONTENTS

ENVIRONMENTAL HEALTH CRITERIA FOR INORGANIC LEAD

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (Telephone No. 9799111).

* * *

This publication was made possible by grant number 5 U01 ES02617-15 from the National Institute of Environmental Health Sciences, National Institutes of Health, USA, and by financial support from the European Commission.

Environmental Health Criteria

P R E A M B L E

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the importance of occupational health and environmental

effects was fully recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary - a review of the salient facts and the risk evaluation of the chemical
- Identity - physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

Procedures

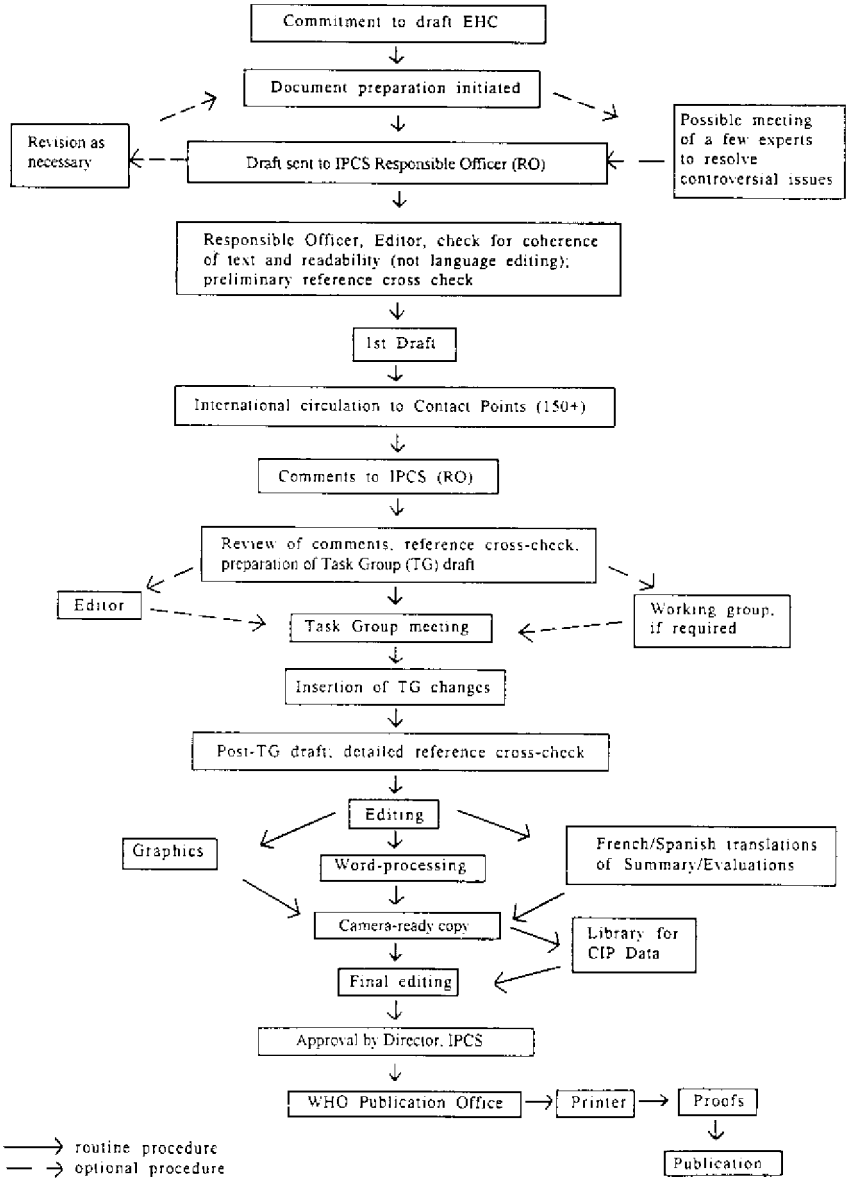
The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson.

EHC PREPARATION FLOW CHART



Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

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ENVIRONMENTAL HEALTH CRITERIA FOR INORGANIC LEAD

A WHO Task Group on Environmental Health Criteria for Inorganic Lead met in Brisbane, Australia, from 1 to 6 February 1993. The meeting was sponsored by a consortium of Australian Commonwealth and State Governments through a national Steering Committee chaired by Dr Keith Bentley, Director, Health and Environmental Policy, Department of Human Services and Health, Canberra. The meeting was hosted and organized by the Queensland Department of Health, Dr G.R. Neville being responsible for the arrangements. Dr G. Murphy, Director of Public Health, Queensland, welcomed the participants on behalf of the Organizers, and Dr T. Adams, Chief Commonwealth Medical Advisor and Dr G. Johns, Parliamentary Secretary to Federal Minister for Health, Housing and Community Services, welcomed the participants on behalf of the Commonwealth Government. Dr Johns stressed the importance attached to this IPCS meeting by the Commonwealth and State Governments of Australia. Dr G.C. Becking, IPCS, welcomed the participants on behalf of Dr M. Mercier, Director of the IPCS and the three cooperating organizations (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria monograph, and made an evaluation of the risks to human health from exposure to inorganic lead.

The Task Group draft was prepared by Dr A.E. Robinson, Toronto, Canada, using texts made available by Dr K.R. Mahaffey[a] (National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA) and Dr E. Silbergeld (University of Maryland School of Medicine, Baltimore, Maryland, USA), and the comments received from the IPCS contact points for environmental health criteria monographs. The draft was revised extensively by the Task Group taking into account the comments from the IPCS contact points.

Dr G.C. Becking (IPCS Central Unit, Interregional Research Unit) and Dr P.G. Jenkins (IPCS Central Unit, Geneva) were responsible for the overall scientific content and technical editing, respectively, of this monograph.

The efforts of all who helped in the preparation and finalization of this publication are gratefully acknowledged.

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ABBREVIATIONS

AAS	atomic absorption spectrometry
AES	atomic emission spectroscopy
ALA	δ-aminolaevulinic acid
ALAD	δ-aminolaevulinic acid dehydratase
ASV	anodic stripping voltametry
EDTA	ethylenediaminetetraacetic acid
FEP	free erythrocyte porphyrin
GFAAS	graphite furnace atomic absorption spectrometry
ICP	inductively coupled plasma
IDMS	isotope dilution mass spectrometry
MPb	mobilization yield of lead
MSW	municipal solid waste
PbB	blood lead
PbT	tooth lead
TML	tetramethyllead
XRFS	X-ray fluorescence spectroscopy
ZPP	zinc protoporphyrin

PREFACE

Although many countries have initiated programmes to lower the level of lead in the environment, human exposure to lead remains of concern to public health officials worldwide. For over 20 years the World Health Organization (WHO) and the International Programme on Chemical Safety (IPCS) have been concerned about the health and environmental effects of the levels of inorganic lead in the environment. The evaluation of human health risks arising from food-borne lead has been carried out by WHO on four occasions since 1972. In addition, health-based guidance values for lead in water, air and the workplace have been developed by various Task Groups convened by WHO. Environmental Health Criteria 3: Lead, published in 1977, examined the effects of lead on human health and Environmental Health Criteria 85: Lead - Environmental Aspects was published in 1989.

Since the publication of Environmental Health Criteria 3: Lead, a large body of knowledge has accumulated concerning the effects of lead on humans at low levels of exposure. Studies have emphasized the effects of inorganic lead on infants and children, a high-risk population. This monograph on inorganic lead reflects this research emphasis; a major part of the monograph deals with the neurotoxic effects of lead with emphasis on neurobehavioural development in children. Less detail is presented on the health effects of the higher levels of inorganic lead found in some workplaces, although such exposures are still considered to pose a risk to humans in many regions of the world.

This monograph deals only with the human health effects of inorganic lead. No attempt has been made to evaluate the human health effects of organo-lead compounds, although it was recognized that such compounds when added to petrol (gasoline) are a major source of inorganic lead in the environment. In view of the toxicity of many organo-lead derivatives and the possible methylation of inorganic lead in the environment, the IPCS plans to evaluate the risk to humans from exposure to organo-lead compounds in a separate monograph.

As with all IPCS criteria monographs, no attempt has been made to prepare an exhaustive bibliography of the extremely large amount of lead-related literature published since 1977. Rather, an effort has been made to review critically the studies on humans

and experimental animals that are essential for the evaluation of risks to human health from exposure to all sources of inorganic lead.

1. SUMMARY

This monograph focuses on the risks to human health associated with exposure to lead and inorganic lead compounds. Emphasis has been given to data which have become available since the publication of Environmental Health Criteria 3: Lead (IPCS, 1977). The environmental effects of lead are discussed in Environmental Health Criteria 85: Lead - Environmental Aspects (IPCS, 1989).

1.1 Identity, physical and chemical properties, and analytical methods

Lead is a soft, silvery grey metal, melting at 327.5 °C. It is highly resistant to corrosion, but is soluble in nitric and hot sulfuric acids. The usual valence state in inorganic lead compounds is +2. Solubilities in water vary, lead sulfide and lead oxides being poorly soluble and the nitrate, chlorate and chloride salts are reasonably soluble in cold water. Lead also forms salts with such organic acids as lactic and acetic acids, and stable organic compounds such as tetraethyllead and tetramethyllead.

The most commonly used methods for the analysis of low concentrations of lead in biological and environmental materials are flame, graphite furnace and inductively coupled plasma atomic absorption spectroscopy and anode stripping voltametry. Depending on sample pretreatment, extraction techniques and analytical instrumentation, detection limits of 0.12 μmoles lead/litre blood (2.49 μg/dl) can be achieved. However, reliable results are obtained only when specific procedures are followed to minimize the risk of contamination during sample collection, storage, processing and analysis.

1.2 Sources of human exposure

The level of lead in the earth's crust is about 20 mg/kg. Lead in the environment may derive from either natural or anthropogenic sources. Natural sources of atmospheric lead include geological weathering and volcanic emissions and have been estimated at 19 000 tonnes/year, compared to an estimate of 126 000 tonnes/year emitted to the air from the mining, smelting and consumption of over 3 million tonnes of lead per year.

Atmospheric lead concentrations of 50 pg/m^3 have been found in remote areas. Background levels of lead in soil range between 10 and 70 mg/kg and a mean level near roadways of 138 mg/kg has been reported. Present levels of lead in water rarely exceed a few micrograms/litre; the natural concentration of lead in surface water has been estimated to be 0.02 μg/litre.

Lead and its compounds may enter the environment at any point during mining, smelting, processing, use, recycling or disposal. Major uses are in batteries, cables, pigments, petrol (gasoline) additives, solder and steel products. Lead and lead compounds are also used in solder applied to water distribution pipes and to seams of cans used to store foods, in some traditional remedies, in bottle closures for alcoholic beverages and in ceramic glazes and crystal tableware. In countries where leaded petrol is still used, the major air emission is from mobile and stationary sources of petrol combustion (urban centres). Areas in the vicinity of lead mines and smelters are subject to high levels of air emissions.

Airborne lead can be deposited on soil and water, thus reaching humans through the food chain and in drinking-water. Atmospheric lead is also a major source of lead in household dust.

1.3 Environmental transport, distribution and transformation

The transport and distribution of lead from fixed, mobile and natural sources are primarily via air. Most lead emissions are deposited near the source, although some particulate matter (< 2 μm in diameter) is transported over long distances and results in the contamination of remote sites such as arctic glaciers. Airborne lead can contribute to human exposures by the contamination of food, water and dust, as well as through direct inhalation. The removal of airborne lead is influenced by atmospheric conditions and particulate size. Large amounts of lead may be discharged to soil and water. However, such material tends to remain localized because of the poor solubility of lead compounds in water.

Lead deposited in water, whether from air or through run-off from soils, partitions rapidly between sediment and aqueous phase, depending upon pH, salt content, and the presence of organic chelating agents. Above pH 5.4, hard water may contain about 30 μg lead/litre and soft water about 500 μg lead/litre. Very little lead deposited on soil is transported to surface or ground water

except through erosion or geochemical weathering; it is normally quite tightly bound (chelated) to organic matter.

Airborne lead can be transferred to biota directly or through uptake from soil. Animals can be exposed to lead directly through grazing and soil ingestion or by inhalation. There is little biomagnification of inorganic lead through the food chain.

1.4 Environmental levels and human exposure

In the general non-smoking adult population, the major exposure pathway is from food and water. Airborne lead may contribute significantly to exposure, depending upon such factors as use of tobacco, occupation, proximity to motorways, lead smelters, etc., and leisure activities (e.g., arts and crafts, firearm target practice). Food, air, water and dust/soil are the major potential exposure pathways for infants and young children. For infants up to 4 or 5 months of age, air, milk, formulae and water are the significant sources of lead exposure.

Levels of lead found in air, food, water and soil/dust vary widely throughout the world and depend upon the degree of industrial development, urbanization and lifestyle factors. Ambient air levels over 10 $\mu g/m^3$ have been reported in urban areas near a smelter, whereas lead levels below 0.2 $\mu g/m^3$ have been found in cities where leaded petrol is no longer used. Lead intake from air can, therefore, vary from less than 4 μg/day to more than 200 μg/day.

Levels of lead in drinking-water sampled at the source are usually below 5 μg/litre. However, water taken from taps (faucets) in homes where lead is present in the plumbing can contain levels in excess of 100 μg/litre, particularly after the water has been standing in the pipes for some hours.

The level of dietary exposure to lead depends upon many lifestyle factors, including foodstuffs consumed, processing technology, use of lead solder, lead levels in water, and use of lead-glazed ceramics.

For infants and children, lead in dust and soil often constitutes a major exposure pathway. Lead levels in dust depend upon such factors as the age and condition of housing, the use of lead-based paints, lead in petrol and urban density. The intake of lead will be influenced by the age and behavioural characteristics of the child and bioavailability of lead in the source material.

Inhalation is the dominant pathway for lead exposure of workers in industries producing, refining, using or disposing of lead and lead compounds. During an 8-h shift, workers can absorb as much as 400 μg lead, in addition to the 20-30 μg/day absorbed from food, water and ambient air; significant intake may occur from ingestion of large inhaled particulate material.

1.5 Kinetics and metabolism in laboratory animals and humans

Lead is absorbed in humans and animals following inhalation or ingestion; percutaneous absorption is minimal in humans. Depending upon chemical speciation, particle size, and solubility in body fluids, up to 50% of the inhaled lead compound may be absorbed. Some inhaled particulate matter (larger than 7 μm) is swallowed following mucociliary clearance from the respiratory tract. In experimental animals and humans, absorption of lead from the gastrointestinal tract is influenced by the physico-chemical nature of the ingested material, nutritional status, and type of diet consumed. In adult humans approximately 10% of the dietary lead is absorbed; the proportion is higher under fasting conditions. However, in infants and young children as much as 50% of dietary lead is absorbed, although absorption rates for lead from dusts/soils and paint chips can be lower depending upon the bioavailability. Diets that are deficient in calcium, phosphate, selenium or zinc may result in increased lead absorption. Iron and vitamin D also affect absorption of lead.

Blood lead (PbB) levels are used as a measure of body burden and absorbed (internal) doses of lead. The relationship between blood lead and the concentration of lead in exposure sources is curvilinear.

Once it has been absorbed, lead is not distributed homogeneously throughout the body. There is rapid uptake into blood and soft tissue, followed by a slower redistribution to bone. Bone accumulates lead over much of the human life span and may serve as an endogenous source of lead. The half-life for lead in blood and other soft tissues is about 28-36 days, but it is much longer in the various bone compartments. The percentage retention of lead in body stores is higher in children than adults. Transfer of lead to the human fetus occurs readily throughout gestation.

Blood lead is the most commonly used measure of lead exposure. However, techniques are now available for measuring lead in teeth and bone, although the kinetics are not fully understood.

1.6 Effects on laboratory animals and *in vitro* systems

In all species of experimental animals studied, including non-human primates, lead has been shown to cause adverse effects in several organs and organ systems, including the haematopoietic, nervous, renal, cardiovascular, reproductive and immune systems. Lead also affects bone and has been shown to be carcinogenic in rats and mice.

Despite kinetic differences between experimental animal species and humans, these studies provide strong biological support and plausibility for the findings in humans. Impaired learning/memory abilities have been reported in rats with PbB levels of 0.72–0.96 μmoles/litre (15–20 μg/dl) and in non-human primates at PbB levels not exceeding 0.72 μmoles/litre (15 μg/dl). In addition, visual and auditory impairments have been reported in experimental animal studies.

Renal toxicity in rats appears to occur at a PbB level in excess of 2.88 μmol/litre (60 μg/dl), a value similar to that reported to initiate renal effects in humans. Cardiovascular effects have been seen in rats after chronic low-level exposures resulting in PbB levels of 0.24–1.92 μmol/litre (5–40 μg/dl). Tumours have been shown to occur at dose levels below the maximum tolerated dose of 200 mg lead (as lead acetate) per litre of drinking-water. This is the maximum dose level not associated with other morphological or functional changes.

1.7 Effects on humans

In humans, lead can result in a wide range of biological effects depending upon the level and duration of exposure. Effects at the subcellular level, as well as effects on the overall functioning of the body, have been noted and range from inhibition of enzymes to the production of marked morphological changes and death. Such changes occur over a broad range of doses, the developing human generally being more sensitive than the adult.

Lead has been shown to have effects on many biochemical processes; in particular, effects on haem synthesis have been studied extensively in both adults and children. Increased levels of serum erythrocyte protoporphyrin and increased urinary excretion of coproporphyrin and δ-aminolaevulinic acid are observed when PbB concentrations are elevated. Inhibition of the

enzymes δ-aminolaevulinic acid dehydratase and dihydrobiopterin reductase are observed at lower levels.

The effects of lead on the haemopoietic system result in decreased haemoglobin synthesis, and anaemia has been observed in children at PbB concentrations above 1.92 μmol/litre (40 μg/dl).

For neurological, metabolic and behavioural reasons, children are more vulnerable to the effects of lead than adults. Both prospective and cross-sectional epidemiological studies have been conducted to assess the extent to which environmental lead exposure affects CNS-based psychological functions. Lead has been shown to be associated with impaired neurobehavioural functioning in children.

Impairment of psychological and neurobehavioural functions has been found after long-term lead exposure of workers. Electrophysiological parameters have been shown to be useful indicators of subclinical lead effects in the CNS.

Peripheral neuropathy has long been known to be caused by long-term high-level lead exposure at the workplace. Slowing of nerve conduction velocity has been found at lower levels. These effects have often been found to be reversible after cessation of exposure, depending on the age and duration of exposure.

The effect of lead on the heart is indirect and occurs via the autonomic nervous system; it has no direct effect on the myocardium. The collective evidence from population studies in adults indicates very weak associations between PbB concentration and systolic or diastolic blood pressure. Given the difficulties of allowing for relevant confounding factors, a causal relationship cannot be established from these studies. There is no evidence to suggest that any association of PbB concentration with blood pressure is of major health importance.

Lead is known to cause proximal renal tubular damage, characterized by generalized aminoaciduria, hypophosphataemia with relative hyperphosphaturia and glycosuria accompanied by nuclear inclusion bodies, mitochondrial changes and cytomegaly of the proximal tubular epithelial cells. Tubular effects are noted after relatively short-term exposures and are generally reversible, whereas sclerotic changes and interstitial fibrosis, resulting in decreased kidney function and possible renal failure, require chronic exposure to high lead levels. Increased risk from

nephropathy was noted in workers with a PbB level of over 3.0 μmol/litre (about 60 μg/dl). Renal effects have recently been seen among the general population when more sensitive indicators of function were measured.

The reproductive effects of lead in the male are limited to sperm morphology and count. In the female, some adverse pregnancy outcomes have been attributed to lead.

Lead does not appear to have deleterious effects on skin, muscle or the immune system. Except in the case of the rat, lead does not appear to be related to the development of tumours.

1.8 Evaluation of human health risks

Lead adversely affects several organs and organ systems, with subcellular changes and neurodevelopmental effects appearing to be the most sensitive. An association between PbB level and hypertension (blood pressure) has been reported. Lead produces a cascade of effects on the haem body pool and affects haem synthesis. However, some of these effects are not considered adverse. Calcium homoeostasis is affected, thus interfering with other cellular processes.

a) The most substantial evidence from cross-sectional and prospective studies of populations with PbB levels generally below 1.2 μmol/litre (25 μg/dl) relates to decrements in intelligence quotient (IQ). It is important to note that such observational studies cannot provide definitive evidence of a causal relationship with lead exposure. However, the size of the apparent IQ effect, as assessed at 4 years and above, is a deficit between 0 and 5 points (on a scale with a standard deviation of 15) for each 0.48 μmol/litre (10 μg/dl) increment in PbB level, with a likely apparent effect size of between 1 and 3 points. At PbB levels above 1.2 μmol/litre (25 μg/dl), the relationship between PbB and IQ may differ. Estimates of effect size are group averages and only apply to the individual child in a probabilistic manner.

   Existing epidemiological studies do not provide definitive evidence of a threshold. Below the PbB range of 0.48-0.72 μmol/litre (10-15 μg/dl), the effects of confounding variables and limits in the precision in analytical and psychometric measurements increase the uncertainty attached to any estimate of effect. However, there is some evidence of an association below this range.

b) Animal studies provide support for a causal relationship between lead and nervous system effects, reporting deficits in cognitive functions at PbB levels as low as 0.53-0.72 μmol/litre (11-15 μg/dl) which can persist well beyond the termination of lead exposure.

c) Reduction in human peripheral nerve conduction velocity may occur with PbB levels as low as 1.44 μmol/litre (30 μg/dl). In addition, sensory motor function may be impaired with PbB levels as low as about 1.92 μmol/litre (40 μg/dl), and autonomic nervous system function (electrocardiographic R-R interval variability) may be affected at an average PbB level of approximately 1.68 μmol/litre (35 μg/dl). The risk of lead nephropathy is increased in workers with PbB levels above 2.88 μmol/litre (60 μg/dl). However, recent studies using more sensitive indicators of renal function suggest renal effects at lower levels of lead exposure.

d) Lead exposure is associated with a small increase in blood pressure. The likely order of magnitude is that for any two-fold increase in PbB level (e.g., from 0.8 to 1.6 μmol/litre, i.e. 16.6 to 33.3 μg/dl), there is a mean 1 mmHg increase in systolic blood pressure. The association with diastolic pressure is of a similar but smaller magnitude. However, there is doubt regarding whether these statistical associations are really due to an effect of lead exposure or are an artifact due to confounding factors.

e) Some but not all epidemiological studies show a dose-dependent association of pre-term delivery and some indices of fetal growth and maturation at PbB levels of 0.72 μmol/litre (15 μg/dl) or more.

f) The evidence for carcinogenicity of lead and several inorganic lead compounds in humans is inadequate.

g) Effects of lead on a number of enzyme systems and biochemical parameters have been demonstrated. The PbB levels, above which effects are demonstrable with current techniques for the parameters that may have clinical significance, are all greater than 0.96 μmol/litre (20 μg/dl). Some effects on enzymes are demonstrable at lower PbB levels, but the clinical significance is uncertain.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

2.1 Physical and chemical properties of lead and its compounds

Lead (atomic number, 82; relative atomic mass, 207.19; specific gravity, 11.34) is a bluish or silvery grey soft metal. The melting point is 327.5 °C and the boiling point at atmospheric pressure 1740 °C. It has four naturally occurring isotopes (208, 206, 207, and 204 in order of abundance), but the isotopic ratios for various mineral sources may differ. This property has been exploited in non-radioactive-tracer environmental and metabolic studies. The physical and chemical properties of elemental lead and some lead compounds are summarized in Table 1.

Although lead has four electrons in its valence shell, only two ionize readily. The usual oxidation state of lead in inorganic compounds is therefore +2 rather than +4. The inorganic salts of lead, such as lead sulfide and the oxides of lead, are generally poorly soluble in water. However, the nitrate, chlorate and, to a much lesser degree, the chloride are water soluble. Some of the salts formed with organic acids, e.g., lead oxalate, are also insoluble, but the acetate is relatively soluble, as shown in Table 1.

Under appropriate conditions of synthesis, stable compounds are formed in which lead is directly bound to a carbon atom. Industrially synthesized lead-carbon compounds include tetraethyllead and tetramethyllead, which are of importance as fuel additives and, hence, are sources of environmental lead.

2.2 Analytical procedures

In recent years substantial advances have been made in developing methods for the quantification of metals at low concentrations. In order to provide improved quality assurance of such measurements, various reference materials in different matrices have been produced (Muramatsu & Parr, 1985). To ensure adequate quality control, the analyst should choose a reference material that matches as closely as possible the experimental samples to be analysed. Choices are based upon matrix type and concentration of the element of interest. A summary of data on 60 biological and 40 environmental (non-biological) reference materials has been compiled by Muramatsu & Parr (1985).

Table 1. Physical and chemical data on lead and selected lead compounds[a]

Name	Synonym and formula	Relative atomic/ molecular mass	Melting point (°C)	Boiling point (°C)	Solubility in cold water (g/litre)	Soluble in
Lead	Pb	207.19	327.502	1740	insoluble	HNO_3; hot concentrated H_2SO_4; hot water; glycerine; alcohol (slightly)
Lead salts						
acetate	$Pb(C_2H_3O_2)_2$	325.28	280	-	443	
carbonate	cerrusite $PbCO_3$	267.20	315 (decomposes)		0.0011	acid; alkali; decomposes in hot water
chlorate	$Pb(ClO_3)_2$	374.09	230 (decomposes)		very soluble	alcohol
chloride	cotunite $PbCl_2$	278.10	501	950	919	NH_4 salts; slightly in dilute HCl and in NH_3; hot water (33.4 g/litre)

Table 1 (contd).

nitrate	$Pb(NO_3)_2$	331.20	470 (decomposes)	376.5	alcohol; alkali, NH_3; hot water (1270 g/litre)
ortho-phosphate	$Pb_3(PO_4)_2$	811.51	1014	0.00014	alkali; HNO_3
oxalate	PbC_2O_4	295.21	300 (decomposes)	0.0016	HNO_3
dioxide	plattnerite PbO_2	239.19	290 (decomposes)	insolubie	dilute HCl; acetic acid (slightly)
monoxide	litharge PbO	223.19	888	0.017	dilute HNO_3; acetic acid
sulfate	anglesite $PbSO_4$	303.25	1170	0.0425	NH_4 salts; concentrated H_2SO_4 (slightly)
sulfide	galena PbS	239.25	1114	0.00086	acid

[a] Data from Weast (1985)

With the increased interest in measuring lead in the low μg/kg and μg/m^3 range in both environmental and biological samples, there is need for particular attention to analytical sensitivity and reliability. As lower concentrations are measured, problems of laboratory contamination become more significant and quality control and quality assurance programmes are important. Because of these concerns, all analytical results for lead should report the laboratory performance for reference standards and for parallel blank measurements of sample contamination for the entire analytical process. Without these, the validity of the data should be questioned.

2.2.1 Sampling procedures

Particular attention should be paid to the cleanliness of equipment and glassware and the purity of the chemicals to prevent secondary contamination by lead.

For the collection of samples, standard trace element methods are generally required (Behne, 1980) with adequate quality control procedures (Friberg, 1988; Jorhem & Slorach, 1988, Vahter & Friberg, 1988). Quality control samples for blood, faeces, air filters and dust have been described (Lind et al., 1988).

2.2.1.1 Sampling of environmental media

In air sampling, both high-volume samplers and low-volume techniques have been used. It should be noted that the collection characteristics of high-volume samplers are strongly affected by particle size and the orientation of the sampler. For particles larger than 5 μm in diameter the high-volume sampler system is unlikely to collect representative samples (US EPA, 1986a). As in all sampling for suspended particulate matter, the accuracy of volume meters should be checked periodically. The size of the pores in filters for collecting lead-containing particles should be small, possibly less than 0.2 μm for glass-fibre filters (Lee & Goranson, 1972).

Depending on the purpose of sampling, care should be taken to select the appropriate site for sampling devices and to achieve the best possible sampling conditions by:

- estimating the amount of particulate required for analysis before deciding on the sample volume and the sampling procedure;

- placing the sampling devices in the appropriate position (e.g., in the breathing zone, level with inlet tubes of house ventilators, at window level in the case of a traffic-laden town street, at a reasonable distance from the highway in uninhabited zones, etc);

- taking the samples at appropriate rates and volumes (e.g., daily breathing volumes, daily ventilating capacities of installations) and for a sufficient time to make possible the estimation of the average concentration (e.g., during a work-shift, or a 24-h or longer period for general population exposure);

- taking into account the use of areas under study (cattle grazing, recreational zones, children's playgrounds, etc).

In addition, whenever possible a procedure should be used that makes it possible to evaluate particle-size distribution and the physicochemical properties of the lead compounds involved, including the shape of the particles and the state of their aggregation.

Lead may be found in water bound to particulate matter as soluble complexes or soluble compounds. Techniques for sampling water must take this into account. It is necessary to sample water without fractionation (filtration) when total lead levels are required. Because of the potential for metals from low ionic strength waters to be adsorbed onto the surfaces of some containers, samples should be acidified (US EPA, 1986a). Selection, cleaning, and conditioning of storage and sample containers deserve special attention (Moody, 1982).

The preparation of soil and dust samples for lead analyses usually involves drying (at 100 °C), homogenization by grinding, and sieving (Thornton & Webb 1975; Bolter et al., 1975). Brown & Black (1983) have discussed the issues related to quality assurance and quality control in the collection and analysis of soil samples. Most reports of lead in soil provide the total elemental abundance either by acid extraction or X-ray fluorescence. However, the leachable or bioavailable fraction is of special interest.

For the study of the dietary intake of lead from food, two general methods have been utilized. The advantages and disadvantages of the "duplicate portions" technique and the equivalent composite technique ("market basket") have been

reviewed by Pekkarinen (1970). Although the duplicate portions (duplicate diets) technique can define variability in consumption, it is expensive, and the sampling and analytical procedures involved are complicated and limit the number of individuals included in any study. With the equivalent composite technique, the economy and ease of collection must be considered in the light of the variability of results obtained due to uncertainties in knowledge of actual preparation techniques, including possible lead levels in water used for processing in individual homes.

The quantity of lead likely to be leached from ceramic surfaces by different foods and beverages may be assessed using dilute acetic acid solutions (1 to 4%) at temperatures in the range 20 to 100 °C for times ranging from 30 min to more than 24 h (Laurs, 1976; Merwin, 1976).

Colorimetric methods are suitable for screening inorganic materials such as pottery or paint for lead. Positive reactions require confirmation by established quantitative methods. Spot tests using dithizone, rhodizonate and iodide (Feigl et al., 1972) are available.

2.2.1.2 *Sampling of biological materials*

The main problem in the sampling of body fluids and tissues for lead analysis is potential secondary contamination with lead. The low general population blood lead (PbB) levels in many regions of the world are complicating screening efforts, requiring levels of analytical precision and sensitivity that can be achieved only through intensive QA/QC programmes. Issues related to such sampling have been examined in detail by US EPA (1986a).

Special precautions are needed to ensure that all venous blood-collecting and blood-storage materials are as free from lead as possible (IPCS, 1977). All glass equipment involved in blood collection and storage should be made of lead-free silicate glass, rinsed first in mineral acid, then with copious amounts of glass-distilled or deionized water. Polypropylene syringes have been recommended (NAS-NRC, 1972). Needles should be of stainless steel with polypropylene hubs. Blood is often drawn directly from the needle into vacuum tubes. It is wise to confirm periodically the absence of significant amounts of lead in the anticoagulant used in the blood container as well as monitoring the contamination level (blank) for the entire analytical process.

New analytical techniques make it possible to determine lead concentrations in microlitre quantities of blood. The trend towards the procurement of micro-samples of blood by skin prick increases the chance of secondary contamination of the blood. Systematic investigation on the significance of this problem has been reported (Mitchell et al., 1974; Mahaffey et al., 1979; DeSilva & Donnan, 1980). Mitchell et al. (1974) describe a procedure whereby sample contamination can be reduced by spraying collodion over the cleansed skin before lancing. The correlation between the concentration of lead in micro-samples and in macro-samples obtained by venepuncture was fairly good (r=0.92) over a wide range of PbB concentrations (0.48-4.41 μmol/litre or 10-92 μg/dl whole blood). Mahaffey et al., (1979b) found that capillary blood levels in a comparison test were systematically higher than corresponding venous blood levels; similar elevations have been reported by DeSilva & Donnan (1980). Since about 1980 the requirement for reliable and accurate micro procedures has resulted in the development of good protocols. Sinclair & Dohnt (1984) described a procedure which resulted in the ability to collect capillary samples with PbB levels only 3.3% higher than the presumably correct venous value. This procedure has been used in the Port Pirie Cohort Study (Baghurst et al., 1985, 1992) and for routine surveillance in the Port Pirie Lead Decontamination Program (Calder et al., 1990). Also, Lyngbye et al. (1990b) have shown that capillary sampling without lead contamination is possible. Routine validation by cross-comparison with venous blood samples should be undertaken on a regular basis.

The same general precautions to avoid contamination must be taken in the collection of urine samples as in the collection of blood samples. Additionally, special care must be taken to prevent precipitation during storage.

2.2.2 *Analytical methods for lead*

A number of analytical methods exist for determination of lead in environmental and biological samples. These methods differ enormously in their costs (e.g., sophisticated equipment, an adequate infrastructure to maintain laboratory conditions and chemical supplies) and personnel requirements (e.g., availability of skilled personnel in adequate numbers for the work to be undertaken). Both accuracy and precision of any of the methods can be affected greatly by contamination of samples within the laboratory. It is important to utilize the principles of a "clean"

laboratory described by Patterson & Settle (1976) and Everson & Patterson (1980).

It is not the purpose of this section to provide an exhaustive description of the analytical methods that could be available to detect and quantify lead levels in environmental and biological samples. However, an attempt will be made to identify well-established methods in current use and to provide information on their application to assist in the interpretation of experimental and epidemiological studies.

2.2.2.1 *Analysis of lead in environmental samples*

The most common methods used for the analysis of lead in samples from air, water, dust, sediment, soil and foodstuffs are flame atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS), anodic stripping voltametry (ASV), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and X-ray fluorescence spectroscopy (XRFS). The reference method for the determination of the absolute amounts of lead is by isotope dilution mass spectrometry (IDMS) (Settle & Patterson, 1980; Grandjean & Olsen, 1984; US EPA, 1986a), but due to equipment costs and required expertise, it is not widely used. Spectrophotometric methods, using diphenylthiocarbazone as the colorimetric reagent, were widely used in the past; they are less sensitive and are labour-intensive but are still appropriate. The advantages and disadvantages were described by Skogerboe et al. (1977).

Gould et al. (1988) utilized a citric acid solution on filter paper to leach lead from glazed ceramic and/or enamelled metal-ware. When treated with a lead-sensitive chromogen, there is a reaction indicating the presence of lead on the paper. The minimal amount of lead required to produce an observable reaction was 0.25 $\mu g/cm^2$; the maximum amount tested was 5 $\mu g/cm^2$. A colorimetric test based on the use of sodium sulfide in solution is used to estimate lead in paint films. It is possible to determine lead concentrations greater than 1 mg/cm^2 of dried paint 90% of the time when the method is used by a trained chemical laboratory technician.

Table 2 summarizes the utility of several representative methods for specific environmental media.

Table 2. Analytical methods for determining lead in environmental samples[a]

Sample type	Preparation method	Analytical method	Sample detection limit	Percentage recovery	Reference
Air (particulate lead)	collect particulate matter on membrane filter; wet ash with $HNO_3/HClO_4/H_2SO_4$; dissolve in acetate buffer	ASV with mercury-graphite electrode (NIOSH method P&CAM 191)	0.16 $\mu g/m^3$	90-110	NIOSH (1977b)
Air (particulate lead)	collect particulate matter on cellulose acetate filter; wet ash with $HNO_3/HClO_4$	ICP-AES (NIOSH method P&CAM 351)	0.34 $\mu g/m^3$	95-105	NIOSH (1981)
Air (particulate lead)	collect particulate matter on filter; dry ash; extract with HNO_3/HCl; dilute with HNO_3	AAS AES	0.1 $\mu g/m^3$ 0.15 $\mu g/m^3$	93 102	Scott et al. (1976)
Air (particulate lead)	sample on cellulose acetate filter; dissolve in HNO_3 with heat; add HCl/H_2O_2 and react in hydride generator with sodium borohydride to generate lead hydride	AAS	8 ng/litre	100-101	Nerin et al. (1989)
Air (particulate lead)	collect sample on filter; spike filter with ^{206}Pb; dissolve filter in NaOH; acidify; separate lead by electrodeposition; dissolve in acid	IDMS	0.1 ng/m^3	NR	Volkening et al. (1988)

Table 2 (contd).

Sample type	Preparation method	Analytical method	Sample detection limit	Percentage recovery	Reference
Water (total lead)	digest sample with acid; heat; dilute with water	AAS	1.0 ng/g	NR	Chau et al. (1979)
Soil	dry sample and sieve for XRF; digest sieved sample with HNO_3 and heat for AAS	XRF AAS	NR NR	65-98 63-68	Krueger & Duguay (1989)
Soil	dry sample, dry ash; digest with acid and dilute with water	AAS	2 µg/g	79-103	Beyer & Cromartie (1987)
Soil, waste, and ground water	digest sample with acid; dilute with water and filter	AAS (EPA method 7420) GFAAS (EPA method 7421)	0.1 mg/litre 1 µg/litre	NR NR	US EPA (1986b)
Soil, dust and paint	digest sample with hot acid; dry; redissolve in HNO_3	AAS	12 ng/g	> 80	Que Hee et al. (1985b)
Sediment, fish, vegetation (total lead)	digest sample with acid; heat; dilute with water	AAS	50 ng/g (sediment) 10 ng/g (fish and vegetation)	NR NR	Chau et al. (1980)

Table 2 (contd).

Milk	add 50 µl $(C_2H_5)_4NOH$ in ethanol to 25 µl milk; heat and dilute with water to 125 µl	GFAAS	NR	NR	Michaelson & Sauerhoff (1974)
Evaporated milk	dry ash sample; dissolve in HNO_3	ASV	0.005 µg/g	99	Capar & Rigsby (1989)
Agricultural crops	dry ash sample with H_2SO_4 and HNO_3, dilute with water	DPASV	0.4 ng/g	85-106	Satzger et al. (1982)
Grains, milk, mussels, fish	bomb digest sample with acid; heat or digest with acid and dry ash; dissolve in acid; dilute with water	GFAAS DPASV	20 µg/g (bomb) 5 µg/g (dry ash) NR	85-107 75-107 82-120	Ellen & Van Loon (1990)
Citrus leaves and paint	chop or pulverize sample; digest with hot acid; dry; redissolve in acid	ICP-AES	10-50 µg/litre	75-82 (citrus leaves) 89-96 (paint)	Que Hee & Boyle (1988)

[a] AAS = atomic absorption; AES = atomic emissions spectroscopy; ASV = anode stripping voltametry; $(C_2H_5)_4NOH$ = tetraethylammonium hydroxide; DPASV = differential pulse anodic stripping voltametry; EPA = US Environmental Protection Agency; GFAAS = graphite furnace atomic absorption spectrometry; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; H_2O_2 = hydrogen peroxide; H_2SO_4 = sulfuric acid; ICP-AES = inductively coupled plasma/atomic emission spectroscopy; IDMS = isotope dilution mass spectrometry; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; NR = not reported; XRF = X-ray fluorescence

2.2.2.2 Analysis of lead in biological materials

Biological samples present special problems for the analyst because of the low lead concentrations and matrix effects. Most analytical techniques developed to detect and quantify lead can be adapted to the analysis of such biological materials as blood, urine, serum, cerebrospinal fluid, solid tissues, hair, teeth and bone. However, certain techniques are more often used for specific matrices.

Currently, the most commonly used methods are AAS, GFAAS, ASV, and ICP-AES. Spectrophotometric methods were commonly used in the past and can be useful. Other specialized methods for lead analysis are XRFS, neutron activation analysis (NAA), inductively coupled plasma-mass spectrometry (ICP-MS), and IDMS. Table 3 summarizes the utility of several analytical procedures applied to various biological matrices. Included in this table are examples of the application of XRFS (Christoffersson et al., 1986; Wielopolski et al., 1986; Nilsson et al., 1991) for the determination *in situ* of the body burden of lead.

2.2.2.3 Analytical procedures for biomarkers of lead exposure and effect

Using standard clinical laboratory techniques, analytical procedures have been developed: δ-aminolaevulinic acid (ALA); δ-aminolaevulinic acid dehydratase (ALAD); urinary coproporphyrin (CPU) and erythrocyte protoporphyrin (EP). All of these assays are well established and reliable (Grandjean & Olsen 1984; US EPA, 1986a). These biochemical parameters are influenced by physiological factors other than lead. They lack the specificity and sensitivity of PbB measurements as an index of either current lead exposures or body stores of lead.

2.3 Conversion factors

1 μg/dl = 0.048 μmol/litre
1 μmol/litre = 20.7 μg/dl

Using the above conversion factor, blood lead concentrations are given as μmol/litre with the equivalent μg/dl in brackets. Calculated figures have not been rounded and added precision is not to be inferred from the number of significant figures.

Table 3. Analytical methods for determining lead in biological materials*

Sample type	Preparation method	Analytical method	Sample detection limit	Percentage recovery	Reference
Blood	wet ash sample with acid mixtures; dissolve residue in dilute $HClO_4$	ASV with mercury-graphite electrode (NIOSH method P&CAM 195)	0.192 µmol/litre (4 µg/dl)	95-105	NIOSH (1977c)
Blood	wet ash sample with HNO_3; dissolve residue in dilute HNO_3	GFAAS (NIOSH method P&CAM 214)	0.48 µmol/litre (10 µg/dl)	NR	NIOSH (1977e)
Blood	dilute sample with Triton X-100®; add nitric acid and diammonium phosphate	GFAAS	0.011 µmol/litre (0.24 µg/dl)	93-105	Aguilera de Benzo et al. (1989)
Blood	dilute sample with ammonia solution containing Triton X-100®; analyse	ICP-MS	0.072 µmol/litre (1.5 µg/dl)	96-111	Delves & Campbell (1988)
Blood	dilute sample in 0.2% Triton X-100® and water; analyse	GFAAS	≈ 0.072 µmol/litre (≈ 1.5 µg/dl)	97-150	Que Hee et al. (1985a)

Table 3 (contd).

Sample type	Preparation method	Analytical method	Sample detection limit	Percentage recovery	Reference
Blood and urine	wet ash sample with HNO_3, complex with dephenylthiocarbazone and extract with chloroform	Spectrophotometry (NIOSH method P&CAM 102)	0.144 µmol/litre (3.0 µg/dl) (blood); 0.0576 µmol/litre (12 µg/litre) (urine)	97 97	NIOSH (1977a)
Serum, blood and urine	filter sample if needed; dilute with acid or water	ICP-AES	0.048-0.240 µmol/litre (1.0-5.0 µg/dl)	85 (serum)	Que Hee & Boyle (1988)
Urine	wet ash sample with acid mixture and dissolve in dilute $HClO_4$	ASV with mercury-graphite electrode (NIOSH method P&CAM 200)	0.0192 µmol/litre (4 µg/litre)	90-110	NIOSH (1977d)
Liver, kidney, muscle	bomb digest sample with acid and heat, or digest with acid and dry ash; dissolve in acid; dilute with water	GFAAS	20 µg/g (bomb); 5 µg/g (dry ashing)	85-107 (bomb); 75-107 (dry ashing)	Ellen & Van Loon (1990)

Table 3 (contd).

Bone	direct partially polarized photons at second phalanx of left forefinger (non-invasive technique)	XRF	20 µg/g	NR	Christoffersson et al. (1986)
Bone	direct partially polarized photons at anteromedial skin surface of mid-tibia (non-invasive technique)	XRF	20 µg/g	NR	Wielopolski et al. (1986)
Teeth	clean and section tooth; digest with HNO_3; evaporate; redissolve in buffer solution	ASV	NR	83-114	Rabinowitz et al. (1989)
Teeth	dry ash sample; crush; dry ash again; dissolve in HNO_3	AAS	NR	90-110	Steenhout & Pourtois (1981)

[a] AAS = atomic absorption spectrometry; ASV = anode stripping voltametry; GFAAS = graphite furnace atomic absorption spectrometry; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; ICP-AES = inductively coupled plasma-atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; NIOSH = National Institute for Occupational Safety and Health; NR = not reported; XRF = X-ray fluorescence

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

Because lead is relatively abundant in the earth's crust it is found naturally throughout the world. The major natural sources of lead are volcanic emissions, geochemical weathering, and emissions from sea spray. A small amount of radioisotopic lead (^{207}Pb) is derived from the decay of radon gas released from geological sources. It has been estimated that the worldwide natural emission rates of lead are of the order of 19 000 tonnes/year (Nriagu & Pacyna, 1988), with volcanic sources accounting for 6400 tonnes/year (Nriagu, 1979).

Owing to centuries of human exploitation of lead resources, it is difficult to determine the natural content of lead in most ecosystems. Data on environmental levels, uses, and sources of lead have been summarized in a recent review (OECD, 1993).

3.1.1 Rocks and soils

The average concentration of lead in the earth's crust is between 10 and 20 mg/kg (IPCS, 1989). The major geological sources of lead are in igneous and metamorphic rocks.

The soil is the most important repository in terrestrial ecosystems for contaminants of anthropogenic origin (Nriagu & Pacyna, 1988; Nriagu, 1989). The lead content of soils (which are for discussion purposes distinguished here from surface dusts) is greatly influenced by anthropogenic activities and by long- and short-range airborne transport of lead from various sources. Both dry and wet deposition are important routes of input.

Lead in soil may be relatively insoluble (as a sulfate, carbonate or oxide), soluble, adsorbed onto clays, adsorbed and co-precipitated with sesquioxides, adsorbed onto colloidal organic matter, or complexed with organic moieties in soil (US EPA, 1986a; IPCS, 1989). Soil pH, content of humic and fulvic acids, and amount of organic matter influence the content and mobility of lead in soils. Since acidic conditions favour the solubilization and leaching of lead from the solid phase, acidic soils tend to have lower lead concentrations when analysed as dry soil. Humic and fulvic acids can also mobilize lead, and certain complex organic molecules can act as chelators of lead (IPCS, 1989).

Background levels of lead in soil are in the range of 10-70 mg/kg (GEMS, 1985). Similar results have been found in studies of mobile source contamination near highways; soil taken at distances of 50-100 m from highways (outside the range of immediate impact from traffic emissions) usually shows levels of lead below 40 mg/kg. In the 1985, GEMS survey of selected countries, lead concentrations in topsoil from Malta were found to have a mean of 54 mg/kg in areas at least 5 m from roadways; less than one metre from roadways the mean concentration was 138 mg/kg. A 1977 report from Sweden found a mean of 16 mg/kg in non-contaminated areas (GEMS, 1985).

3.1.2 Sediments

Sediments from freshwater and marine environments have been studied for lead content. This compartment provides a unique record of the history of changes in global lead fluxes (Patterson, 1983). Levels of lead in sediments dated before the onset of the industrial revolution in Western Europe show very low levels, less than 10% of current levels (Flegal et al., 1987). The average background level of lead in marine sediments off southern California was reported by Flegal et al. (1987) to be 1.3 mg/kg.

3.1.3 Water

Flegal et al. (1987) estimate that the natural concentration of lead in surface water is about 0.02 μg/litre. In general, lead is not found in ground or surface waters at concentrations above 10 μg/litre (IPCS, 1989).

Data from oceans indicate very low levels of lead in sea-water samples not affected directly by significant sources of lead. Water samples taken from an area of the Pacific, where annual windborne-input fluxes of lead are estimated to be 3 mg/cm^2, have lead concentrations of 3.5 ng/litre (0-100 m depth) and 0.9 ng/litre at depths greater than 2500 m. In contrast, water samples taken from the north Atlantic, where annual windborne-input fluxes of lead are 170 mg/cm^2, contain 34 ng lead/litre at the surface and 5 ng/litre in depths below 2500 m (Patterson, 1983). Settle & Patterson (1980) have estimated that prehistoric oceans contained 0.5 ng/litre lead. Flegal et al. (1987) have estimated that over 95% of the lead in off-shore surface waters is the result of windborne inputs. However, in coastal waters near Monterey

(California, USA), higher concentrations of lead were found in sea water, sediments and organisms; these elevations were related to specific sources by systematic isotope analyses (Flegal et al., 1987).

3.1.4 Air

Anthropogenic inputs of lead from a range of sources have resulted in global dispersion of both inorganic and organic species of lead into the air, of which 80-90% is derived from alkyllead fuel additives (WHO, 1987). Nriagu & Pacyna (1988) estimated that a total of 330 000 tonnes of lead is discharged directly into the atmosphere each year. Estimations of pre-industrial levels of lead in air from natural origins (volcanic emissions, crustal weathering, radon decay and sea-spray releases) are in the range of 0.01-0.1 $\mu g/m^3$ (US NRC, 1980). The lowest level reported since 1975 is 0.076 ng/m^3 measured at the South Pole (US EPA, 1986a).

3.1.5 Plants

Lead occurs naturally in plants and results from both deposition and uptake. There is a positive linear relationship between lead concentrations in plants and soil (Davies & Thornton, 1989). As with other environmental compartments, measurement of "background" levels of lead in plants is complicated by the general contamination of the globe from centuries of lead use, which has included direct application of lead-containing chemicals in agriculture (see below) and contamination of fertilizers with lead. Lead has been measured in superphosphate fertilizer at concentrations as high as 92 mg/kg (Lisk, 1972). Sewage sludge, used as a source of nutrients in agriculture, may contain even higher levels of lead. The concentration of lead in sewage sludge is typically < 1000 mg/kg. Levels as high as 26 g/kg have been measured in the USA (Chaney et al., 1984). Soil receiving heavy sludge applications over long periods of time (years) contained 425 mg lead/kg; the concentration in untreated soil was 47 mg/kg (Beckett, 1979).

3.1.6 Environmental contamination from natural sources

The contribution of natural sources of lead to human exposure is small. As a result of various breakdown processes, rocks yield lead which is transferred to the biosphere and the atmosphere, and, ultimately, back to the earth's crust in the form of sedimentary rocks. Soluble lead has for thousands of years entered the oceans with river discharges, and the rate has been estimated

by Patterson (1965) to be around 17 000 tonnes/year. Sources contributing to airborne lead are silicate dusts, volcanic halogen aerosols, forest fires, sea salts aerosols, meteoric and meteorite residues, and lead derived from the decay of radon. While the lead content of most coals is relatively low, coal fly ash is enriched in lead (Hutton et al., 1988) and is a source of environmental contamination.

3.2 Anthropogenic sources

World lead consumption has steadily increased over the period 1965-1990 and was about 5.6 x 10^6 tonnes in 1990 (OECD, 1993).

Further review of the data summarized by OECD (1993) indicates a change in consumption patterns worldwide. Although the consumption of lead within the 24 countries of the OECD increased only slightly over the decade from 1980 to 1990, consumption within less developed economies (Africa and Asia) increased from 315 000 tonnes in 1970 to 844 000 tonnes in 1990.

3.2.1 Lead mining

Lead occurs in a variety of minerals, the most important of which are galena (PbS), cerrusite ($PbCO_3$) and anglesite ($PbSO_4$). Galena is by far the most important source of primary lead. It occurs mostly in deposits associated with other minerals, particularly those containing zinc. Mixed lead and zinc ores account for about 70% of total primary lead supplies. Ores containing mainly lead account for about 20% and the remaining 10% is obtained as a by-product from other deposits, such as mixed copper-zinc deposits. The proportions of various metals may differ in the ores of different countries. Silver is the most important of the other metals frequently present in lead deposits, but copper may also be present in concentrations high enough to be commercially important. Other minor constituents of lead ores are gold, bismuth, antimony, arsenic, cadmium, tin, gallium, thallium, indium, germanium and tellurium.

The major countries producing lead from mining activity during 1987-1991 were the USA, Canada, Australia, Peru, the former USSR and Mexico, as shown in Table 4. Other countries producing lead from lead ores include China, the former Yugoslavia, Morocco, Spain, Sweden and Tunisia. In general, the level of world production of lead from mining activities has remained relatively constant at about 3.3 x 10^6 tonnes between

1988 and 1991 (ILZSG, 1992); this represents roughly 60% of the world demand for lead.

Table 4. Major countries producing lead from ore and ore concentrates[a]

Country	1987	1988	1989	1990	1991
Canada	423 200	366 600	276 100	241 300	278 100
USA	318 300	395 700	419 300	495 200	483 300
Ex-USSR	510 000	520 000	500 000	490 000	—
Australia	489 200	462 000	495 000	570 000	579 000
Mexico	177 200	178 100	163 000	174 100	158 800
Peru	204 000	149 000	192 200	187 800	199 100

[a] From: World Bureau of Metal Statistics (1992)

3.2.2 *Smelting and refining*

Smelting and refining are classified as either primary or secondary, the former producing refined lead products from ores or concentrates (primary lead) and the latter producing lead by recovering it from lead-bearing scrap and waste materials (secondary lead). Secondary lead is derived from processing what is termed new scrap arising during manufacturing processes and recycled old scrap arising from waste materials containing lead. Most scrap is from old sources, of which the most important are lead plates from batteries, solder, common babbitt, soft lead, lead solders, cable coverings, type metals, dross and other lead-containing products. There has been an increasing contribution of secondary lead sources to the total worldwide production of lead, as shown in Table 5 (World Bureau of Metal Statistics, 1992). Secondary sources of lead supplied between 35 and 40% of world production during the period from 1970 to 1990.

3.2.3 *Environmental pollution from production of lead*

Mining operations and the smelting and refining of both primary and secondary lead are known to cause contamination of the nearby environment. The nature and extent of contamination

depends on many factors, including the level of production, the effectiveness of emission controls, climate, topography and other local factors. Concentrations are usually highest within 3 km of the point source (US EPA, 1989). A report from China found that lead levels in ambient air, plants and soil increased proportionally with proximity to a large primary smelter; at 50 m from the source, the air lead level was 60 $\mu g/m^3$, the lead level in plants was 29.1 mg/kg, and soil lead level was 170 mg/kg (Wang, 1984). However, some earlier studies have shown air pollution and soil contamination as far as 10 km from smelters (Djurić et al., 1971; Kerin, 1973; Landrigan et al., 1975).

Table 5. Relative contribution of primary and secondary sources relative to world lead production (1987-1990)[a]

	1987	1988	1989	1990
Primary	422 100	3 414 200	3 286 500	3 324 500
Secondary	2 045 600	2 103 900	2 272 900	2 254 800

[a] From: World Bureau of Metal Statistics (1992)

The impacts of lead mining and smelting can persist for long periods of time. A study conducted in Wales, United Kingdom, in an area where lead mining began 2000 years ago and ended in the middle of the 20th century, found high concentrations of lead in soils (Davies et al., 1985). In Port Pirie, Australia, a community with one of the world's largest and oldest primary lead smelters, lead levels in soils were found to be grossly elevated, and the incidence of elevated blood lead levels in pregnant women and young children was also increased above that found in other communities in Australia (Wilson et al., 1986).

3.3 Consumption and uses of lead and its compounds

Lead has a combination of physical and chemical properties that have made it extremely useful industrially, i.e. high density, high opacity to gamma and X-ray energies, low sound conductance, a low melting point, exceptional malleability, high

corrosion resistance, and stability. In 1990, 5.627 x 10^6 tonnes of lead were consumed worldwide (ILZSG, 1992). The twenty-four industrialized countries of the OECD consumed approximately 65% of this amount, with eastern Europe and the former USSR using 21%. Asia now utilizes about 9% of the world's lead production.

The use patterns of refined lead vary from country to country. The situation in 1990 in Mexico is shown in Table 6, while end-use categories within OECD countries are summarized in Fig. 1, which indicates the changes between 1970 and 1990 (OECD, 1993).

Table 6. Principal uses of refined lead in Mexico[a]

Type of product	1988 (%)	1990 (%)
Oxides	69.7	56.7
Batteries	9.2	17.9
Tetraethyllead	7.9	11.9[b]
Cables	4.0	1.5
Others	9.2	11.9

[a] ILZSG (1992)
[b] This does not reflect the introduction of lead-free petrol in 1990.

From Fig. 1, it is evident that the largest use of lead within OECD countries is for battery production, whereas there has been a large drop in the demand for lead-containing gasoline additives. However, this pattern is not valid worldwide, e.g., concentrations in petrol range from zero in such countries as Japan and Thailand to 1.12 g/litre in the Virgin Islands (Octel, 1991).

In the past the use of lead in the chemical industry for the preparation of paints, pigments and coloured inks was widespread. Many countries have now restricted this use, and concentrations of lead greater than 0.06% (USA) and 0.5% (New Zealand) are not permitted in indoor paints (Albert & Badillo, 1991; OECD, 1993). In 1982, data from the United Kingdom (UK, 1982) indicated

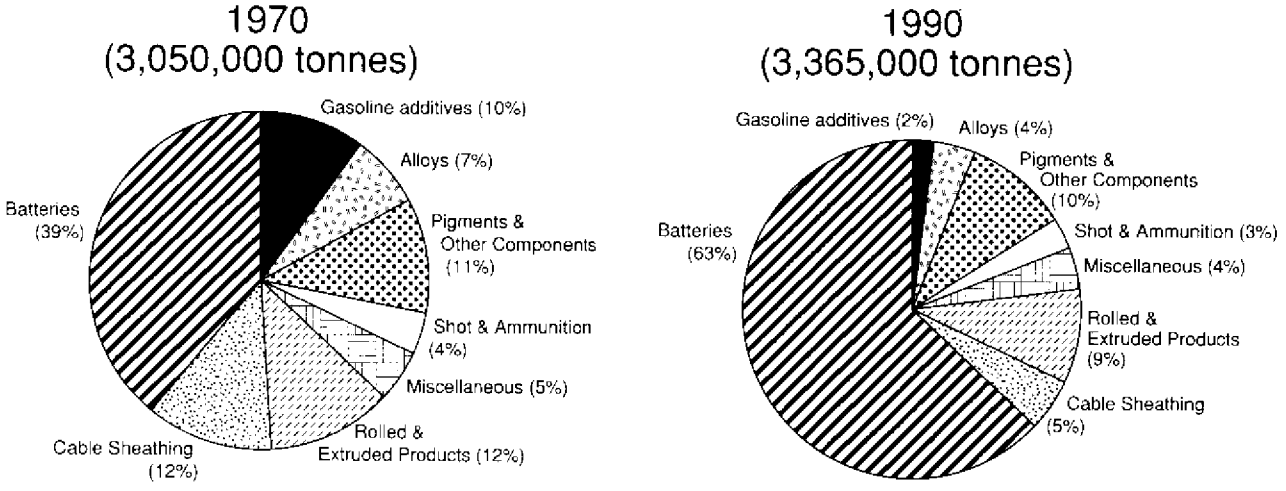

Fig. 1. Utilization of lead in OECD countries in 1970 and 1990 (From: OECD, 1993)

levels of lead between 2500 and 3000 mg/kg in decorative glass paints and up to 448 g/kg in white-lead primer. Red-lead-containing paints, still used widely to paint structural steel works, can contain up to 661 g lead/kg.

Other disperse uses of lead include lead solders (now banned in USA for use in drinking-water systems), ammunition (Novotny et al., 1987), foil on wine bottles (Wai et al., 1979) and cosmetics and folk-medicines (surma in Asia, Kohl in India, and Al Kohl in Saudi Arabia and Kuwait) (Fernando et al., 1981).

3.4 Sources of environmental exposure

As noted above, lead is a ubiquitous pollutant in the global ecosystem, as well as occurring naturally. Its uses have resulted in increases in soil, water and air lead levels to one to two orders of magnitude above those estimated to have prevailed prior to rapid industrialization in the 18th and 19th centuries (Patterson, 1983). Whereas in specific areas point sources may contribute significant amounts of lead to the environment, on a global scale, the combustion of alkyllead in petrol is the predominant source of increased lead in all compartments of the environment. This has been hypothesized based upon mass balance studies (Nriagu, 1979) and confirmed by the changes in environmental lead levels which have followed the significant reductions in worldwide use of alkyllead as a gasoline additive since the mid-1980s. For example, lead concentrations in Greenland snow decreased by a factor of 7.5 over a 20-year period from the late 1960s (Boutron et al., 1991).

Nriagu & Pacyna (1988) have estimated the global emissions of lead to the atmosphere resulting from anthropogenic uses (Table 7). Current estimates (OECD, 1993) of emissions from mobile sources would be about 30% of the 1983 amounts. Similarly estimates of emissions of lead to soil in 1983 were made by Nriagu & Pacyna (1988) (Table 8). Since lead is never degraded, all lead which is shifted from geological sources by human technology eventually enters the environment through disposal, although this can be slowed by recycling and recovery.

Municipal solid waste (MSW), solid waste, hazardous waste, sewage sludge, and industrial waste-water discharges all may contain lead at concentrations as high as 50 g/kg. Although few measurements of environmental lead concentrations in the vicinity of disposal sites have been conducted, analyses of fly and bottom ash from municipal incinerators show high concentrations (up to

50 g/kg) of lead (Wadge & Hutton, 1987), and land disposal sites which have received incinerator ash for a number of years show high levels of lead in soil (Hutton et al., 1988).

Table 7. Estimated worldwide anthropogenic emissions of lead to the atmosphere (1983)[a]

Source category	Emission rate (tonnes/year)
Coal combustion	
- electric utilities	780-4650
- industry and domestic	990-9900
Oil combustion	
- electric utilities	230-1740
- industry and domestic	720-2150
Pyrometallurgical non-ferrous metal production	
- mining	1700-3400
- lead production	11 700-31 200
- copper-nickel production	11 000-22 100
- zinc-cadmium production	5520-11 500
Secondary non-ferrous metal production	90-1440
Steel and iron manufacturing	1070-14 200
Refuse incineration	
- municipal	1400-2800
- sewage sludge	240-300
Phosphate fertilizers	60-270
Cement production	20-14 200
Wood combustion	1200-3000
Mobile sources[b]	248 030
Miscellaneous	3900-5100
Total	**289 000-376 000**
	(median 332 000)

[a] Adapted from: Nriagu & Pacyna (1988), as in OECD (1993).
[b] Current estimates (OECD, 1993) for mobile source emissions would be about 30% of the 1983 amounts.

Table 8. Worldwide emissions of lead into soils (1983)

Source category	Emission rate (tonnes/year)
Agricultural and food wastes	1500-27 000
Animal wastes, manure	3200-20 000
Logging and other wood wastes	6600-8200
Urban refuse	18 000-62 000
Municipal sewage sludge	2800-9700
Miscellaneous organic wastes, including excreta	20-1600
Solid wastes, metal manufacturing	4100-11 000
Coal fly ash, bottom fly ash	45 000-242 000
Fertilizer	420-2300
Peat (agricultural and fuel use)	450-2000
Wastage of commercial products	195 000-390 000
Atmospheric fall-out	202 000-263 000
Total yearly input to soils	**479 090-1 038 800**
Mine tailings	130 000-390 000
Smelter slags and wastes	194 000-390 000
Total yearly discharge on land	**803 090-1 818 800**

[a] From: Nriagu & Pacyna (1988), adapted from OECD (1993); many of these emissions remain localized due to the nature of the particulate matter

Dusting and flaking of lead paint from surfaces can be a source of lead contamination in surface dust and soil near houses or buildings as well as contributing to the concentrations of lead in household dust. This process is a function of the type of paint and the age and state of repair of the structure. When lead paint is present on structures, both interior and exterior dusts have higher concentrations than otherwise would be expected (Thornton et al., 1985). Abatement of lead paint may be a major local source of environmental contamination, as shown by studies near school

buildings in London (Rundle & Duggan, 1986). Removal of lead-based paints from bridges and water towers using improper techniques can also result in significant environmental contamination. Direct application of lead-contaminated sludge as fertilizers, and residues of lead arsenate from use in agriculture can lead to the contamination of soil, surface water and ground water. In local aquatic environments, pollution can result from leaching of lead from lead shot, shotgun cartridges and fishing weights (IPCS, 1989). Coal contains small amounts of lead, which can be concentrated in fly ash from coal combustion (Wadge & Hutton, 1987) or in stack emissions (Table 8).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

Over the last 10–15 years, a great many studies have been conducted on the complex interrelationships between environmental lead emissions and their deposition on such environmental surfaces as vegetation, soil, house dust and water. All are potential sources of lead exposure for humans. Transport between environmental compartments also takes place (see Fig. 2). A full discussion of the complex physical and chemical processes controlling these pathways is beyond the scope of this monograph and the reader is directed towards other reviews for more details (Elias, 1985; US EPA, 1986a; IPCS, 1989).

4.1 Transport and distribution between media

4.1.1 Atmospheric deposition

From the mass balance point of view, the transport and distribution of lead from major emission sources, both fixed and mobile, is mainly atmospheric. Most of the lead discharged to the atmosphere is deposited near the source. However, approximately 20% is widely dispersed (Nriagu, 1979; IPCS, 1989) and contaminates areas as remote as glacial strata in Greenland (Settle & Patterson, 1980). The extent of long-range transport of lead particles is dependent upon particle size, particles > 2 μm in diameter being deposited close to the source of emission. Between 20 and 60% of emissions from vehicles has been reported to remain within 25 m of the roadway (ATSDR, 1991). However, in view of the marked decrease in the concentration of lead in cores of ice from Greenland since the decreased use of leaded petrol (Boutron et al., 1991), it is apparent that vehicle emissions can contribute to the levels of lead in air far from the source. Long-range transport of lead particles was also noted by Evans & Rigler (1985).

Lead can be removed from the atmosphere and transferred to environmental surfaces and compartments by wet or dry deposition. Wet deposition appears to be more important than dry deposition for the removal of atmospheric lead. Depending upon geographical location and the level of emissions in the area, between 40 and 70% of atmospheric lead is removed by wet deposition (Nielsen, 1984). In most cases it is poorly soluble and either precipitates out in soils and sediments or is bound to organic

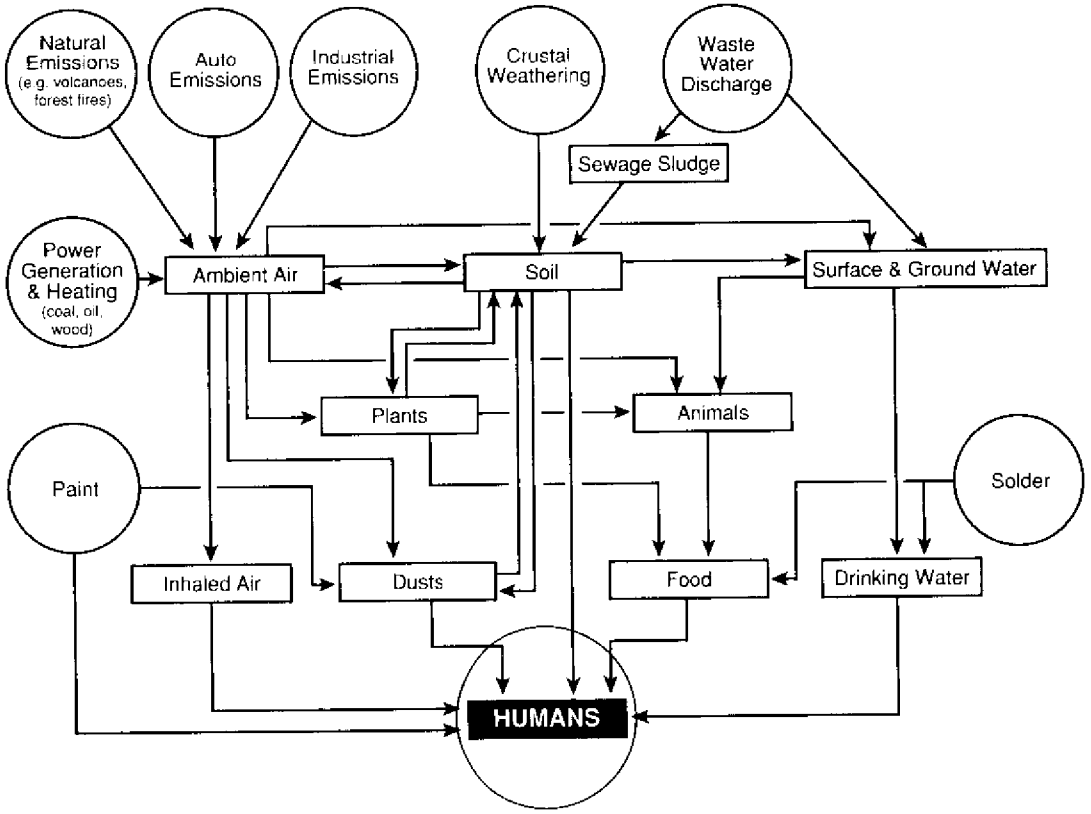

Fig. 2. Pathways of human exposure (OECD, 1993)

matter in these compartments. For these reasons lead is not readily removed and tends to accumulate in those ecosystems where it is deposited (IPCS, 1989). Chan et al. (1986) calculated the ratio of wet to dry deposition to be 1.63, 1.99 and 2.50 for sites in south, central, and northern Canada, respectively, while Talbot & Andren (1983) reported that wet deposition accounted for 80% of the total lead deposited in a semi-remote site in the USA.

Making several assumptions regarding global atmospheric lead concentrations, wind speed, surface area and texture, a global deposition of approximately 410 000 tonnes/year (combined wet and dry) was calculated by the US EPA (1986a).

4.1.2 Transport to water and soil

When deposited in water, whether from air or through run-off from soil, lead partitions rapidly between the sediment and aqueous phase, depending upon the salt content of the water as well as the presence of organic complexing agents. For example, at pH > 5.4 the total solubility of lead is about 30 μg/litre in hard water and 500 μg/litre in soft water (Davies & Everhart 1973). In addition, the presence of sulfate and carbonate ions can limit lead solubility, as described by Hem & Durum (1973) in a review of the aqueous chemistry of lead.

Water-borne lead has been found to exist as soluble lead or undissolved colloidal particles, either suspended in the aqueous phase or carried as surface coatings on other suspended solids (Lovering, 1976). The ratio of lead in suspended solids to lead in the dissolved form has been found to vary from 4:1 in rural areas to 27:1 in urban streams (Getz et al., 1977).

Both natural organic compounds (humic and fulvic acids) as well as those of anthropogenic origin (e.g., ethylenediaminotetraacetic and nitrilotriacetic acids) may complex lead found in surface waters (Steelink, 1977; Reuter & Perdue, 1977; Neubecker & Allen, 1983). The presence in water of such chelators can increase the rate of solution of lead compounds (e.g., lead sulfide) 10 to 60 times over that of water at the same pH without fulvates (Bondarenko, 1968; Lovering, 1976).

Lead accumulation in soils is primarily a function of the rate of wet and dry deposition from the atmosphere. Transport within soil and the bioavailability of lead from soil are dependent upon many factors, including pH, mineral composition of the soil, and

amount and type of organic material, with most of the lead being bound within the upper 5 cm of soil (Reaves & Berrow 1984; Garcia-Miragaya, 1984). This limits the amount which can be leached into water or be available for uptake into plants. It has been shown that only 0.2% of the total lead in soil can be released into solution by shaking (Dong et al., 1985). However, the release of lead from organic complexes to the soluble, and thus bioavailable, form is highly pH dependent. Within the usual pH range for soils (4 to 6), the organic-lead complexes become more soluble and the lead more available for plant uptake and leaching into water (US EPA, 1986a).

4.1.3 Transport to biota

The transfer of air lead to the biota may be direct or indirect (uptake from water, soil and vegetation). Examples of the accumulation of lead into aquatic (wet and dry deposition) and terrestrial organisms are given in Environmental Health Criteria 85: Lead - Environmental Aspects (IPCS, 1989). Relevant parts of that monograph are summarized here.

4.1.3.1 Aquatic organisms

In aquatic and aquatic/terrestrial model ecosystems, uptake by primary producers and consumers seems to be determined by the bioavailability of the lead. Bioavailability is generally much lower whenever organic material, sediment or mineral particles (e.g., clay) are present. In many organisms, it is unclear whether lead is adsorbed onto the organism or actually taken up. Consumers take up lead from their contaminated food, often to high concentrations but without biomagnification.

The uptake and accumulation of lead by aquatic organisms from water and sediment are influenced by various environmental factors such as temperature, salinity and pH, as well as humic and alginic acid content.

In contaminated aquatic systems, almost all of the lead is tightly bound to sediment. Only a minor fraction is dissolved in the water, even in the interstitial water.

The lead uptake by fish reaches equilibrium only after a number of weeks of exposure. Lead is accumulated mostly in gill, liver, kidney and bone.

Fish eggs show increasing lead levels with increased exposure concentration, and there are indications that lead is present on the egg surface but not accumulated in the embryo.

Fish accumulate lead from water as well as sediments; aquatic uptake is influenced by the presence of cations and the oxygen content of the water (IPCS, 1989).

4.1.3.2 *Terrestrial organisms*

In bacteria, the majority of lead is found in the cell wall. A similar phenomenon is also noted in higher plants. Some lead that passes into the plant root cell can be combined with new cell wall material and subsequently removed from the cytoplasm to the cell wall. Of the lead remaining in the root cell, there is evidence of very little translocation to other parts of the plant because the concentration of lead in shoot and leaf tissue is usually much lower than in root. Foliar uptake of lead occurs, but only to a very limited extent.

In animals, there is a positive correlation between tissue and dietary lead concentrations, although tissue concentrations are almost always lower. The distribution of lead within animals is closely associated with calcium metabolism.

Lead shot is typically trapped in the gizzard of birds where it is slowly ground down resulting in the release of lead.

The tetravalent organic form of lead is generally more toxic than the divalent inorganic form, and its distribution in organisms may not specifically follow calcium metabolism.

4.2 Environmental transformation

4.2.1 *Abiotic transformation*

Once released into the environment lead may be transformed from one inorganic species or particle size to another. However, as an element it is not subject to degradation. For example, lead-containing particles in automobile exhaust are usually lead halides or double salts with ammonium halides (Biggins & Harrison, 1979). Within 24 h, over 75% of lead particulate matter is transformed to lead carbonates and sulfates (Olson & Skogerboe, 1975).

4.2.2 Biotransformation

The transformation of inorganic lead to tetramethyllead (TML) has been observed in aquatic systems, particularly in sediments, and biomethylation was postulated by Wong et al. (1975) and Schmidt & Huber (1976). However, no biological methylation of inorganic lead was noted by Reisinger et al. (1981) in studies under many conditions using several bacterial species known to alkylate mercury and other heavy metals. The authors did find chemical methylation in the presence of methylcobalamin and sulfide or aluminium ions and it was independent of the presence of bacteria. The evidence for microbial methylation of various compounds of lead in aquatic systems has been reviewed by Beijer & Jernelöv (1984). It is still unclear whether the TML formed is produced abiotically or by biotransformation.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

This chapter describes the sources of lead to which people are exposed and quantifies that exposure. Depending on the source, the concentration of lead and its bioavailability, the relative contribution of each source may vary considerably. For example, men working in ship-breaking, children exposed to deteriorating lead paint, and people consuming soft water distributed in lead pipes have frequently been shown to have excessive absorption of lead, leading to clinically obvious lead poisoning.

In evaluating the exposure of the general population to lead, it is critical to consider the interrelationships among environmental pathways for lead and transfers across environmental media. The general population is exposed to lead simultaneously from many sources and through multiple pathways as shown in Fig. 2. Thus, while, for purposes of discussion, exposure via air, water, food, dusts and soils, and other sources are presented separately in this document, the total exposure of the general population from all sources must be considered. Those working in industries where lead is used or produced may be subject to additional exposure compared with the general population.

In addition, exposure of certain groups within the general population may vary because of physiological, behavioural or other factors. For example, the fetus is exposed to lead via maternal transfer of internal and external doses, nursing infants may be exposed to lead in breast milk, the young child is exposed more intensively to dusts and lead on non-food items (such as lead-painted toys), alcohol consumption and smoking increase lead exposure, differences in diet may influence lead exposure markedly, and some people may be exposed to lead through hobby or occupational activities in addition to their exposure as members of the general population.

5.1 Inhalation route of exposure

5.1.1 Ambient air

Ambient air can be a major pathway of lead distribution in the environment. Sources of lead in air include combustion products of lead additives in petrol, and point sources such as smelters, incinerators, and some industrial processes including the burning of fossil fuels.

Concentrations of lead in air range from 7.6×10^{-5} $\mu g/m^3$ in remote areas such as Antarctica (Maenhaut et al., 1979) to > 10 $\mu g/m^3$ near lead smelters (Elias, 1985).

Almost all lead in air is bound to fine particles of less than 1 μm diameter, although some may be solubilized in acid aerosol droplets. The size of these particles varies with the source and with the age of the particle from the time of emission (US EPA, 1986a; WHO, 1987). Most lead in air is inorganic lead, and the predominant source is from the combustion of tetraethyl- and tetramethyllead used as fuel additives (US EPA, 1986a; WHO, 1987). A summary of lead levels on fine airborne particles from some cities in the USA and France is given in Table 9.

Table 9. Concentrations of lead in fine airborne particles from some cities in the USA and France in 1984-1985[a]

City	Population	Mean lead concentration ($\mu g/m^3$)	No. of samples
Clemson (USA)	3000	0.33	15
Senonches (France)	3000	0.005	6
Orleans (France)	110 000	0.11	7
Clermont (France)	161 000	0.045	7
Akron (USA)	200 000	0.052	6
Strasbourg (France)	260 000	0.072	7
Norfolk (USA)	270 000	0.031	6
Chicago (USA)	10 000 000	0.064	5
Paris (France)	10 000 000	0.44	7

[a] From: Delumyea & Kalivretenos (1987)

5.1.1.1 *Emissions from motor vehicles*

In Europe, where leaded vehicle fuel is still used, airborne concentrations of lead in urban areas are likely to be in the range of 0.5-3 $\mu g/m^3$ (WHO, 1987). Concentrations of between 0.6 and 5.7 $\mu g/m^3$ were reported in Mexico in 1982 (GEMS, 1985). Where leaded vehicle fuel is no longer used, concentrations are likely to

fall to < 0.2 $\mu g/m^3$ (Elias, 1985). In 1990, concentrations of lead in air in urban areas of the USA had fallen to below 0.07 $\mu g/m^3$ (US EPA, 1991). This decrease in airborne lead levels in the USA is shown in Fig. 3. Reductions in lead in air have been reported from Canada, Germany, Norway and the United Kingdom (OECD, 1993).

5.1.1.2 *Stationary sources*

Where emissions are largely uncontrolled, concentrations of lead in air around stationary sources such as lead smelters range from over 10 $\mu g/m^3$ 50 m from the smelter to 1.5 $\mu g/m^3$ one km away (Wang et al., 1992). Where more stringent emission controls are used, concentrations of lead are much lower (US EPA, 1991). The Port Pirie smelter in South Australia is estimated to have lost 80 000 tonnes of lead to the environment in non-stack fugitive emissions from 1889 to 1982. It is also estimated that from 1969 to 1981 this smelter discharged 40 tonnes of lead per year into the environment. Ambient air concentrations near the smelter were between 0.5 and 10 $\mu g/m^3$ (Body et al., 1988).

5.1.2 *Indoor air*

Davies et al. (1987a) sampled indoor and ambient air lead levels and found that where there was no interior lead source, such as lead-painted surfaces, air lead concentrations inside dwellings were highly correlated with those outside and averaged approximately 60% of those in the external air immediately outside the house. A similar ratio was reported in the Arnhem lead study (Diemel et al., 1981). Indoor air lead levels are affected by the presence of smokers and lead-painted surfaces.

Levels of airborne lead in indoor shooting ranges have been shown to range from 2.7 to 90.5 $\mu g/m^3$ depending upon the location of sampling, which varied from the showroom to target area (Novotny et al., 1987).

5.1.3 *Air in the working environment*

The diversity and extent of the industrial applications of lead is such that it is impossible to make general statements about exposure levels. In many instances actual exposure levels have not been measured and often work is carried out in small enterprises which may not be subject to workplace controls or legislated requirements.

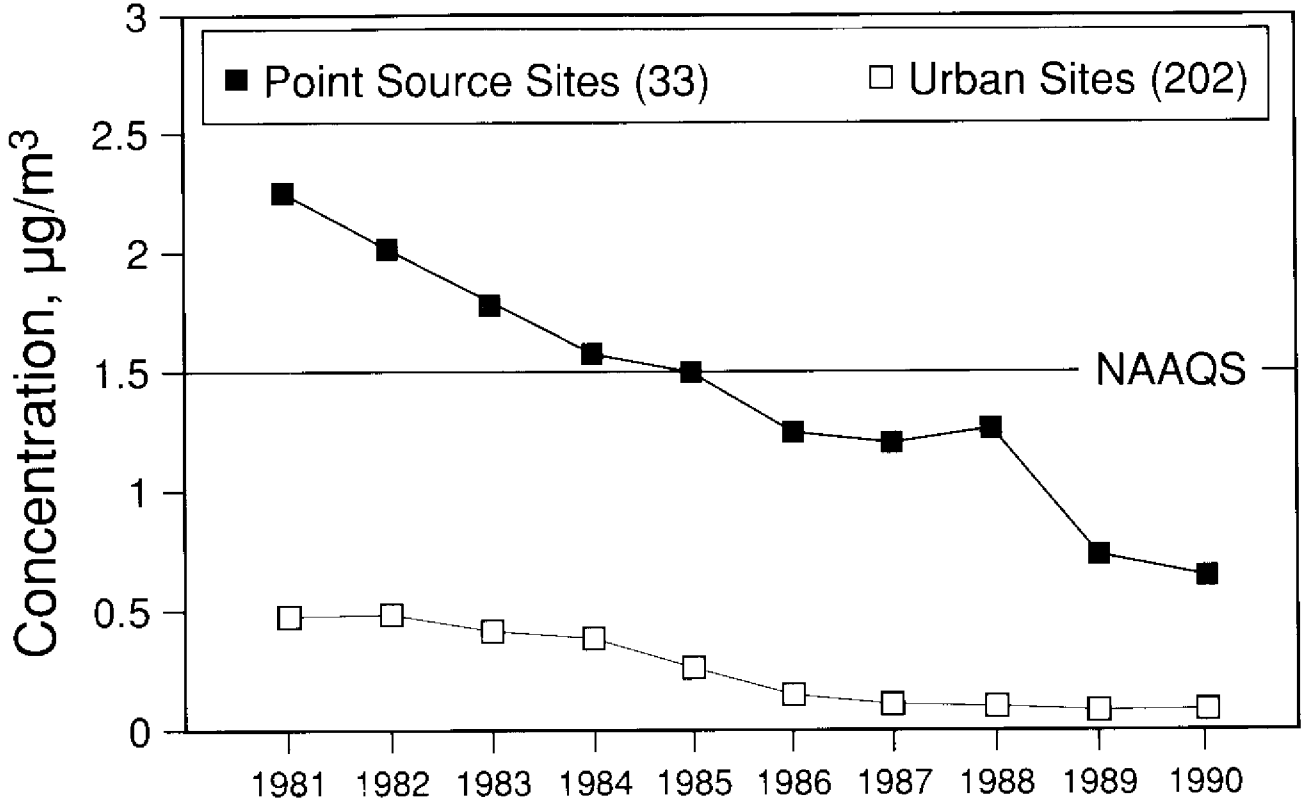

Fig. 3. Comparison of national trend (USA) in the composite average of the maximum quarterly lead concentrations at urban and point source oriented sites, 1981-1990 (NAAQS = National Ambient Air Quality Survey). (From: US EPA, 1991)

Airborne lead concentrations in the occupational setting vary considerably according to the type of industry and the level of industrial hygiene practised at each plant. Occupations and operations that may present lead hazards to workers are listed in Table 10. Recent monitoring data (1980–1985) from Finland are summarized in Fig. 4 (Jaakkola & Anttila, 1992).

Table 10. Occupations or operations which may present lead hazards for workers[a]

Primary and secondary lead smelting	Lead mining
Welding and cutting of lead-painted metal constructions	Plumbing
Welding of galvanized or zinc silicate coated sheets	Cable making
Shipbreaking	Wire patenting
Nonferrous foundries	Lead casting
Storage battery manufacture: pasting, assembling, welding of battery connectors	Type founding in printing shops
Production of lead paints	Stereotype setting
Spray painting	Assembling of cars
Mixing (by hand) of lead stabilizers into polyvinyl chloride	Automobile repair
Mixing (by hand) of crystal glass mass	Shot making
Sanding or scraping of lead paint	Welding (occasionally)
Burning of lead in enamelling workshops	Lead glass blowing
Repair of automobile radiators	Pottery/glass making

[a] Adapted from: Hernberg (1973)

5.1.4 Smoking of tobacco

Lead is present in tobacco. The mean content of lead in filter-tipped cigarettes produced between 1960 and 1980 was 2.4 μg/g.

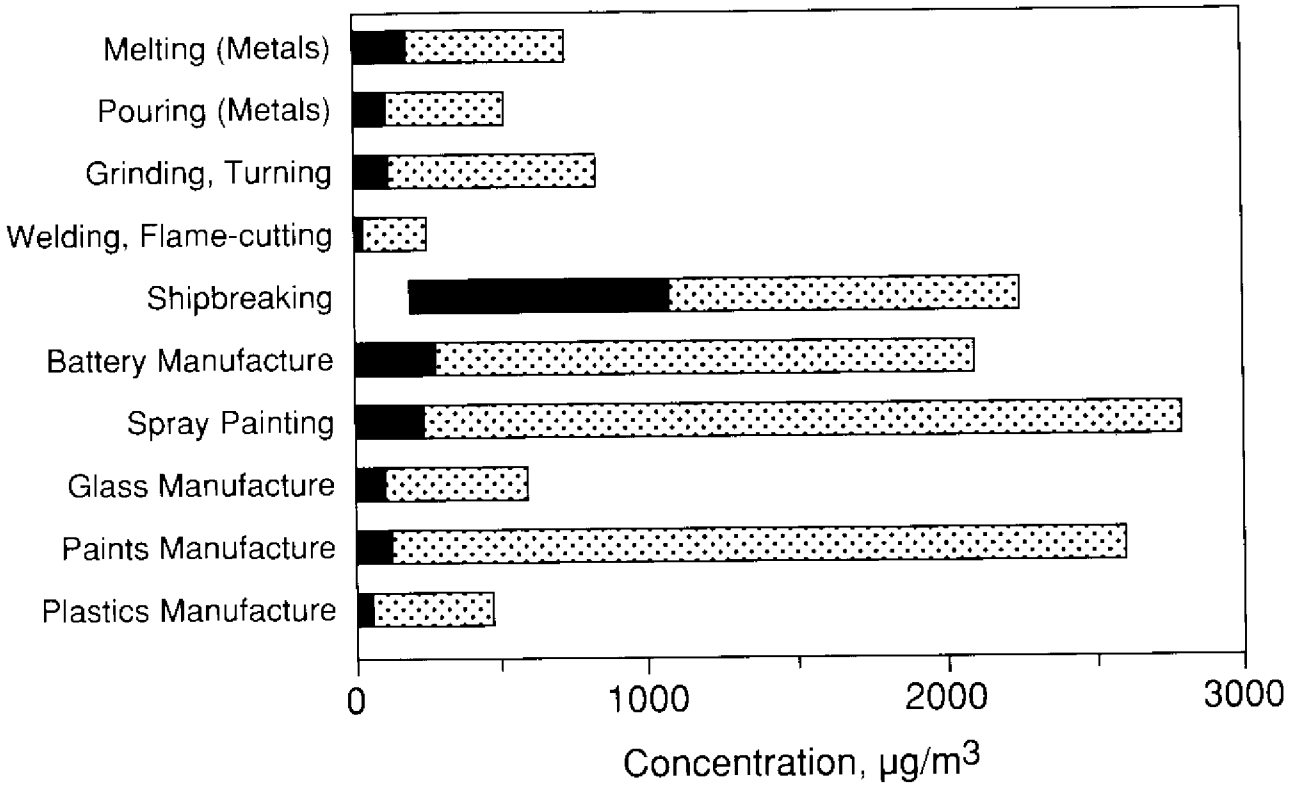

Fig. 4. The lead concentrations (minimum, mean, maximum, $\mu g/m^3$) in workplace air in selected work tasks in Finland. The figure is based on 503 airborne lead measurements during 1980-1985 at the Institute of Occupational Health (Jaakkola & Anttila, 1992)

Approximately 5% of this lead may be inhaled; the remainder occurs in the ash and side-stream smoke (Mussalo-Rauhamaa et al., 1986).

5.2 Exposure by ingestion

5.2.1 Water

Exposure of humans to lead from water has been underestimated in studies of total exposure. Due to the practice of sampling water systems at points before entry into the distribution piping and domestic plumbing (US EPA, 1986a; Dabeka et al., 1987), it had been widely assumed that exposure to lead in drinking-water was not significant.

Background or natural levels of lead in surface and ground water are generally low. However, water with low pH and only low concentrations of dissolved salts (referred to as aggressive) can leach substantial quantities of lead from pipes, solder and fixtures. Lead-lined reservoirs, cisterns and holding tanks for water (Mushak & Crocetti, 1989) can be a major source of lead contamination of drinking-water. For example, Wiebe et al. (1991) reported the analysis of over 2000 water samples in Hawaii, USA, following increased volcanic activity that resulted in the release of acid aerosols. The lead concentration of drinking-water collected in catchment systems ranged from < 20 to 7000 μg/litre. Sampling programmes conducted at the tap in the USA during 1985-1988 revealed widespread elevation of lead in drinking-water, often above the WHO guidance value of 50 μg/litre (WHO, 1984), which has now been revised to 10 μg/litre (WHO, 1993).

The combination of acid or aggressive water and lead in plumbing results in very high concentrations of lead in drinking-water, particularly after it has been standing for several hours (Worth et al., 1981; Sherlock et al., 1982; Kaminsky et al., 1988).

Surveys in Canada and the USA showed that drinking-water supplies leaving treatment plants contain 2-3 μg lead/litre (US EPA, 1986a; Dabeka et al., 1987). In the case of plumbosolvent water, up to 40% of household samples may exceed 100 μg lead/litre. This has been observed in Scotland (Sherlock et al., 1986), and reflects the contribution of plumbing and plumbing fixtures to lead levels of drinking-water.

5.2.2 Food and alcoholic beverages

5.2.2.1 Food

The major source of lead for non-occupationally exposed adults is food and drink. The proportion of total intake derived from food is dependent on the concentration of lead in air, water and other sources. Detailed data are available from several countries, including Australia (NFA, 1991), USA (Bolger et al., 1991), Sweden (Vahter et al., 1990) and Canada (Dabeka et al., 1987). Foods have been surveyed from several other industrialized and developing countries (Galal-Gorchev, 1991b). Children are exposed to additional lead from dust and soil, and so lead from foods and beverages may not be the predominant sources of lead for all age groups.

Lead is present in soils and is transferred to food crops growing on the soil. Roots usually contain more lead than stems and leaves, while seeds and fruits have the lowest concentrations.

Particulate lead present in air may adhere tenaciously to leafy vegetables. Leaves collected in or very near urban areas have been shown to contain substantially elevated concentrations of lead. Quantities of lead ingested from the diet vary widely from country to country.

Data on the lead levels of specific foodstuffs or groups of food materials, from which one can estimate a daily dietary lead intake, are available from several countries. In a few studies, foodstuffs specific to infants and children have also been analysed (Kolbye et al., 1974; Dabeka & McKenzie, 1987; Vahter et al., 1990; Bolger et al., 1991; Albert & Badillo, 1991). Data are available for canned foods typically consumed by young children (Capar & Rigsby, 1989). The utilization of such data in the calculation of total intake of lead from food is discussed in section 5.2.2.2.

An overview of the foods contributing to the dietary lead levels in Australia is shown in Fig. 5. Similar data from other countries are shown in Table 11 (Galal-Gorchev, 1991b). A summary of the data on lead levels in foodstuffs from the USA is given in Table 12 and from Canada in Table 13. More recent data from the USA have shown that there has been a substantial reduction of lead levels in food consumed by all age groups during the past two decades (Bolger et al., 1991) (Fig. 6). A similar decrease in lead intake has been found in the United Kingdom (OECD, 1993).

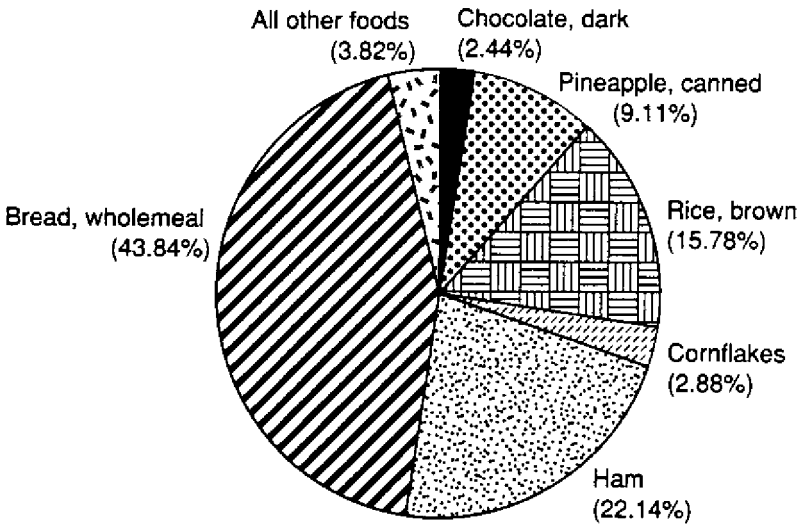

Fig. 5. Foods contributing to dietary lead levels in Australia (NFA, 1991)

These data should be considered as representative of specific areas and such values can be expected to vary elsewhere according to local agricultural and food-processing practices, particularly in areas where lead-soldered cans are still used. Support for this is indicated by a comparison on the one hand of the decreased use of lead-soldered food and beverage cans in the USA (Fig. 7) and the increased use of cans produced by alternative technology, and on the other hand the marked decrease in food-borne lead shown in Fig. 6. Food may represent a pathway for human lead exposure from other media such as air and water. The use of leaded gasoline or the proximity of industries that may produce ambient emissions of lead can greatly influence dietary lead intake. Therefore further caution is required when extrapolating between countries with regards to levels of food-borne lead.

Representative levels of lead in foodstuffs from some 20 countries are given in Table 14 (Galal-Gorchev, 1991a). These results from the GEMS/FOOD data can be compared with the levels of lead in specific foodstuffs in the USA and Canada (Tables 12 and 13).

Table 11. Foods contributing to dietary lead levels in Canada, Finland, Netherlands and the United Kingdom[a]

Country	Food	Percentage of total intake
Canada	vegetables	17
	meat/fish/poultry	17
	beverages	15
	cereals and products	15
	fruits and juices	10
Finland	cereals and products	24
	fruits	22
	beverages, sweets, etc.	20
	milk and products	17
	vegetables	9
Netherlands	drinking-water	30
	cereals and products	17
	vegetables	12
	wines and spirits	9
	fruits	6
United Kingdom	bread and cereals	15
	beverages	14
	potatoes	10
	milk	9
	canned vegetables	8

[a] From: Galal-Gorchev (1991b)

Table 12. Concentrations of lead in various foods in the USA[a]

Food group	Concentration of lead[b] (μg/g)
Dairy products	0.003-0.083
Meat, fish and poultry	0.002-0.159
Grain and cereal products	0.002-0.136
Vegetables	0.005-0.649
Fruit and fruit juices	0.005-0.223
Oils, fats and shortenings	0.006-0.073
Sugar and adjuncts	0.006-0.073
Beverages	0.002-0.041

[a] From: US EPA (1986a)

[b] Range of concentrations shown are the lowest and highest mean values for items within the food group and listed in Appendix 7-D of US EPA (1986a).

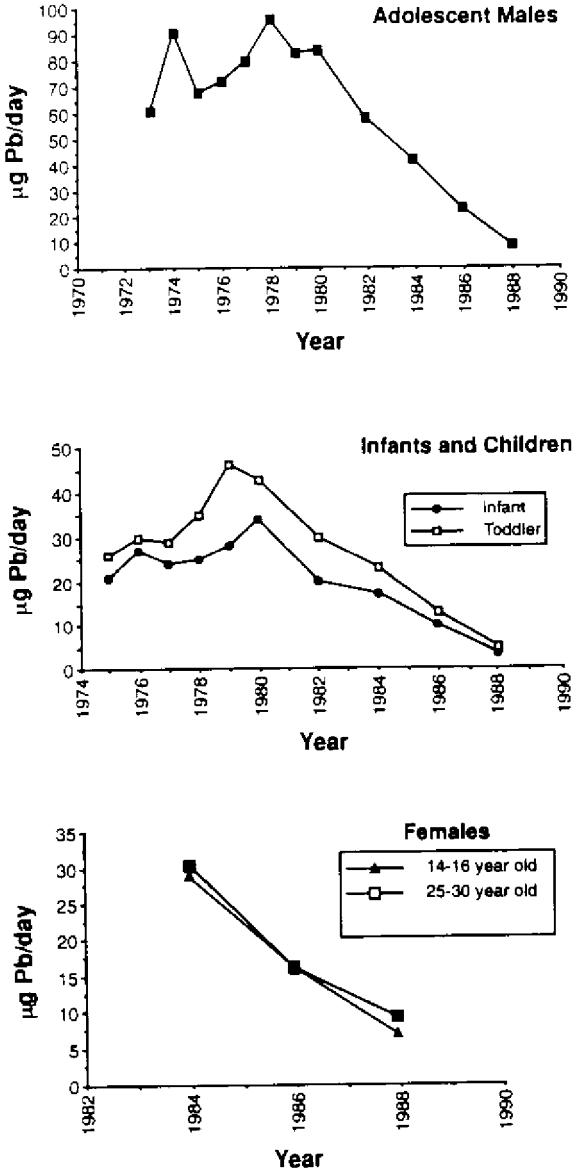

Fig. 6. Time trends in dietary lead intake for adolescent males, infants and children, and females from US FDA total diet study (Adapted from: Bolger et al., 1991)

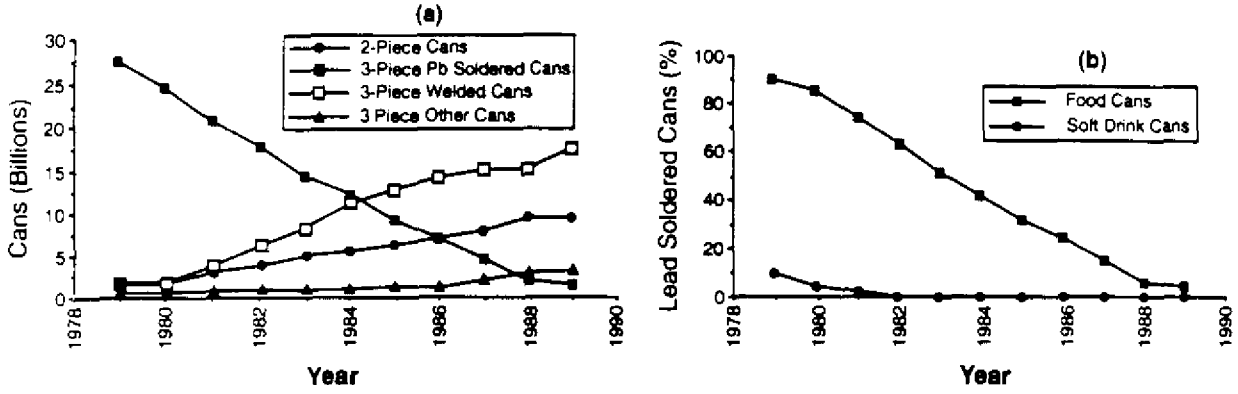

Fig. 7. (a) Percentage of lead soldered cans as a proportion of total cans shipped. (b) Percentage of lead soldered cans used for food and beverages in the USA (Adapted from: Bolger et al., 1991)

Table 13. Levels of lead in various Canadian food categories[a]

	Description of food category	Median concentration of lead (μg/kg)[b]
I	Cereals (as prepared with milk, sugar, etc.), bread and toast	32.4 (11.5-78.3)
II	Water consumed directly	2.0 (0.25-71.2)
III	Coffee, tea, beer, liquor, sodas, etc. (as prepared)	8.8 (< 0.05-28.9)
IV	Fruit juices, fruits (canned and fresh)	7.9 (1.5-109)
V	Dairy products and eggs	3.3 (1.21-81.9)
VI	Starch vegetables, e.g. potatoes, rice	16.9 (5.5-83.7)
VII	Other vegetables, vegetable juices and soups	31.7 (0.62-254)
VIII	Meat, fish, poultry, meat-based soups	31.3 (11-121)
IX	Miscellaneous (pies, puddings, nuts, snack foods)	33.1 (13.6-1381)
X	Cheese (other than cottage cheese)	33.8 (27.7-6775)

[a] From: Dabeka et al. (1987)
[b] Values in parentheses are the ranges.

The lead levels in infant foods in Canada, Mexico and USA are shown in Table 15. In 1987, Dabeka et al. (1987) found the intake of lead by infants fed evaporated milk stored in lead-soldered cans exceeded the Provisional Tolerable Weekly Intake of 25 μg lead/kg body weight, set in 1993 (FAO/WHO, 1993). These values do not include lead in water used to prepare formulae. It has been reported that infants fed formulae prepared with water containing high levels of lead (> 100 μg/litre) have lead intakes exceeding 25 μg/kg body weight per week (Galal-Gorchev, 1991b).

5.2.2.2 *Total intake from food*

Guidelines for the determination of dietary intake of chemical contaminants have been published (WHO, 1985). Three basic approaches were described, namely: (i) total diet (i.e. market or shopping basket) studies; (ii) selective studies of individual foodstuffs, and (iii) duplicate portion (duplicate diet) studies. It is essential to have food consumption data for the first two methods in order to estimate a total intake. For all methods, well-designed quality assurance and quality control programmes are

Table 14. Representative levels of lead in foods from GEMS/FOOD data[a]

Commodity	Typical lead levels (μg/kg)
Cereals	60
Roots and tubers	50
Fruit	50
Vegetables	50
Meat	50
Vegetable oils and fats	20
Fish	100
Pulses	40
Eggs	20
Nuts and oilseeds	40
Shellfish	20
Offal	20
Spices and herbs	30
Other foods	not assessed
Drinking-water	20
Canned beverages	200
Canned food[b]	200

[a] From: Galal-Gorchev (1991a)
[b] It is assumed that canned food consumption is 2% of total.

essential and these have been described by Vahter & Slorach (1990) and Vahter et al. (1991a).

Given the differences between countries with respect to dietary composition, the amount of specific foodstuffs consumed, the processing technologies employed, whether consumption of water and alcoholic beverages are included in the estimates of dietary lead, and the number of samples taken, caution must be exercised in making comparisons between countries.

During the late 1970s and 1980s the quantity of lead ingested as part of diet decreased markedly in many countries. For adults not occupationally exposed to lead, the diet remains the largest

Table 15. Lead levels (μg/kg food) in cow's milk and infant formula

Product	Canada median (range)[a]	Mexico average[b]	USA average[c]
Fluid milk	1.19 (0.01-2.5)	5	
Evaporated milk (canned)	71.9 (27-106)	88	10
(cardboard)	—	9	
Infant formula			
Ready to use lead-solder can	30.1 (1.1-122)	13	10
Ready to use lead-free can	1.6 (1.5-2)		1
Formula powder (1985)	96.6 (3.7-19)		
Powdered milk[d]	—	21	

[a] From: Dabeka & McKenzie (1987)
[b] From: Albert & Badillo (1991). Data were obtained in 1982.
[c] From: Bolger et al. (1991). Data were obtained in the late 1980s.
[d] The concentration of lead in milk consumed by the infant will be highly dependent on the concentration of lead in water used to dilute the powdered milk.

contributor to lead intake. However, the quantities ingested are far lower than in previous decades. In the USA, typical levels of intake declined as shown in Fig. 6.

An overall summary of the GEMS/FOOD data for adults is given in Fig. 8 (Galal-Gorchev, 1991a). The trends for lead intake for the period 1980-1988 in the USA, Japan, Hungary and the United Kingdom are shown in Fig. 9 (Galal-Gorchev, 1991b). Data for intake of lead by infants and children in eight countries are shown in Fig. 10 (Galal-Gorchev, 1991a). Additional data are available from other countries. Although collection methods vary, these data illustrate the wide variations in ingestion of lead from food. Brunekreef (1986) noted that the market basket studies tended to overestimate lead intake when compared with duplicate diet analysis. Examples cited included reports from the United Kingdom by Fouassin & Fondu (1980), Buchet et al. (1983) and Sherlock et al. (1982), where market basket surveys overestimated this intake by 2- to 3-fold.

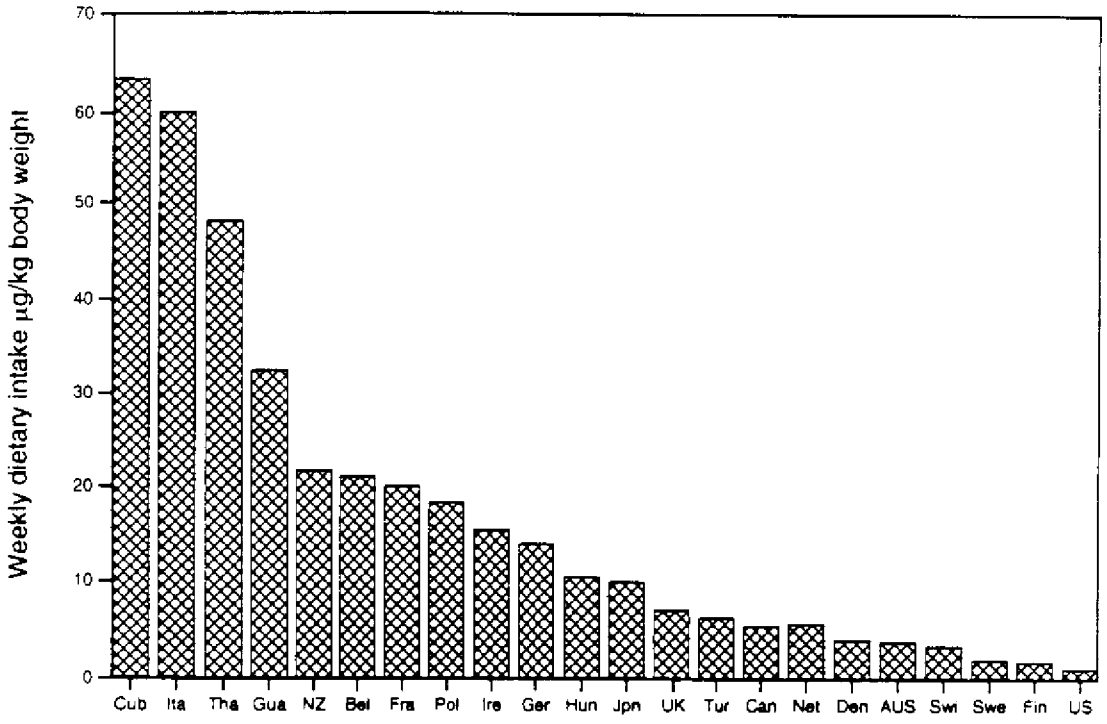

Fig. 8. Average intake of lead in adults, 1981-1988 (Galal-Gorchev, 1991a)

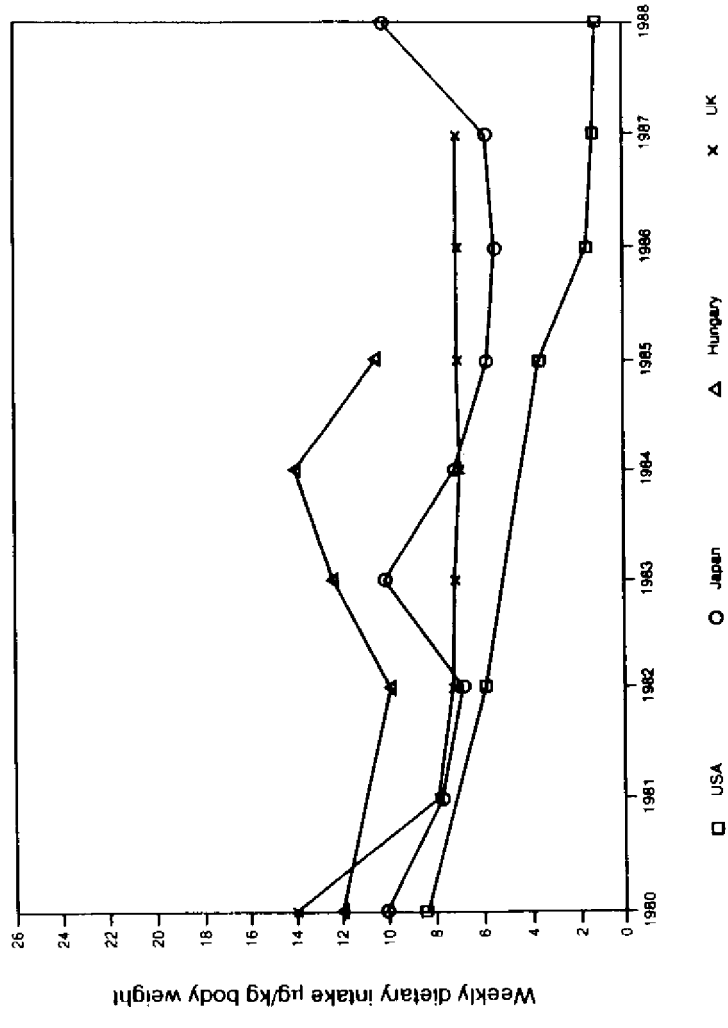

Fig. 9. Trends in lead intake by adults (Galal-Gorchev, 1991b)

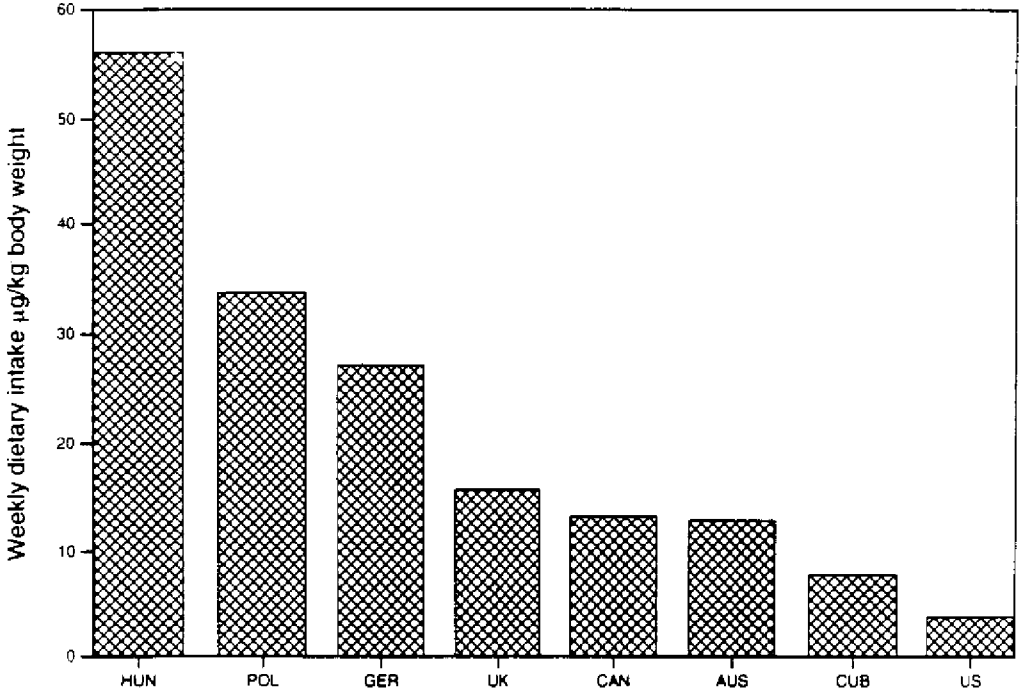

Fig. 10. Average intake of lead in infants and children, 1980-1988 (Galal-Gorchev, 1991a)

Other studies from various countries on total lead intakes by children and adults are summarized in Table 16. Lead contaminated water has been shown to be a contributor to food-borne lead where large volumes of water are used in food preparation and cooking, e.g., in foods prepared in boiling water.

The relative intake of lead from various sources in 1986 and 1990 in 2-year-old infants and women of child-bearing age in the USA is shown in Fig. 11. These data illustrate the marked decrease in lead intake from food over a 4-year period in which there were marked reductions in the use of lead-soldered cans and lead-containing petrol additives in the USA (Bolger et al., 1991). Similar decreases in other countries would no doubt occur after similar actions by public health officials.

5.2.2.3 *Alcoholic beverages*

Contamination of alcoholic beverages with lead may occur in several way. For example, lead solder used to repair casks or keg and tap lines from lead capsules used as seals or from residues of lead arsenate pesticides in soils now used to grow grapes. Alcoholic beverages tend to be acidic and there is the possibility that large amounts of lead can be dissolved during preparation, storage or serving (Wai et al., 1979). Published reports on lead levels in wine show that important variations occur from sample to sample (Jorhem et al., 1988). The US Department of the Treasury (1991) analysed 432 table wines sold within the USA. The results are summarized in Table 17.

Sherlock et al. (1986) found that the majority of canned and bottled beer (90 and 86% respectively) contained less than 10 μg lead/litre. Draught beers typically contained higher lead concentrations with 55% having lead concentrations greater than 10 μg/litre, 16% with concentrations over 20 μg/litre, and 4% with concentrations over 100 μg/litre. The higher lead concentrations in draught beers are considered most likely due to the draught-dispensing equipment which sometimes contains brass or gun-metal, both of which contain low but significant amounts of lead (Sherlock et al., 1986).

In general, alcoholic beverages do not appear to be a significant source of lead intake for the average person.

Table 16. Daily lead intake via food in adults and children

Population studied	Daily intake (μg/day)[a]		Reference
Adults, United Kingdom	110	M	Brunekreef (1986)
Adults, United Kingdom	71	D	Brunekreef (1986)
Adults, Belgium[b]	282	M	Fouassin & Fondu (1980)
Adults, Belgium[b]	96	D	Buchet et al. (1983)
Adults, Sweden	27	M	Slorach et al. (1983)
Adults, Finland	66	M	Varo & Kovistoinen (1983)
Adults, Canada	43	D	Dabeka et al. (1987)
Adults, USA	82	M	Gartrell et al. (1985a)
Adults (female), Japan	31	D	Vahter et al. (1991b)
Adults, Germany	61		Kampe (1983)
Adults (female), Croatia	15	D	Vahter et al. (1991b)
Adults, Italy	140		IAEA (1987)
Adults (female), China	46	D	Vahter et al. (1991b)
Adults, Turkey	70		IAEA (1987)
Adults (female), Sweden	26	D	Vahter et al. (1991b)
Children, Poland			
0-1 year	225		Olejnik et al. (1985)
1-3 years	259		
7-18 years	316		
Adults, New Zealand	316	M	Pickston et al. (1985)
Children (infant), UK	2-3	breast milk	Kovar et al. (1984)
Children (< 1 year), USA	16-17	infant formula & milk	Ryu et al. (1983)
Children, USA			
6 months	33.5	M	Gartrell et al. (1985b)
2 years	43.4		

[a] M = Market basket survey; D = Duplicate diet study
[b] Populations studied from the same region.

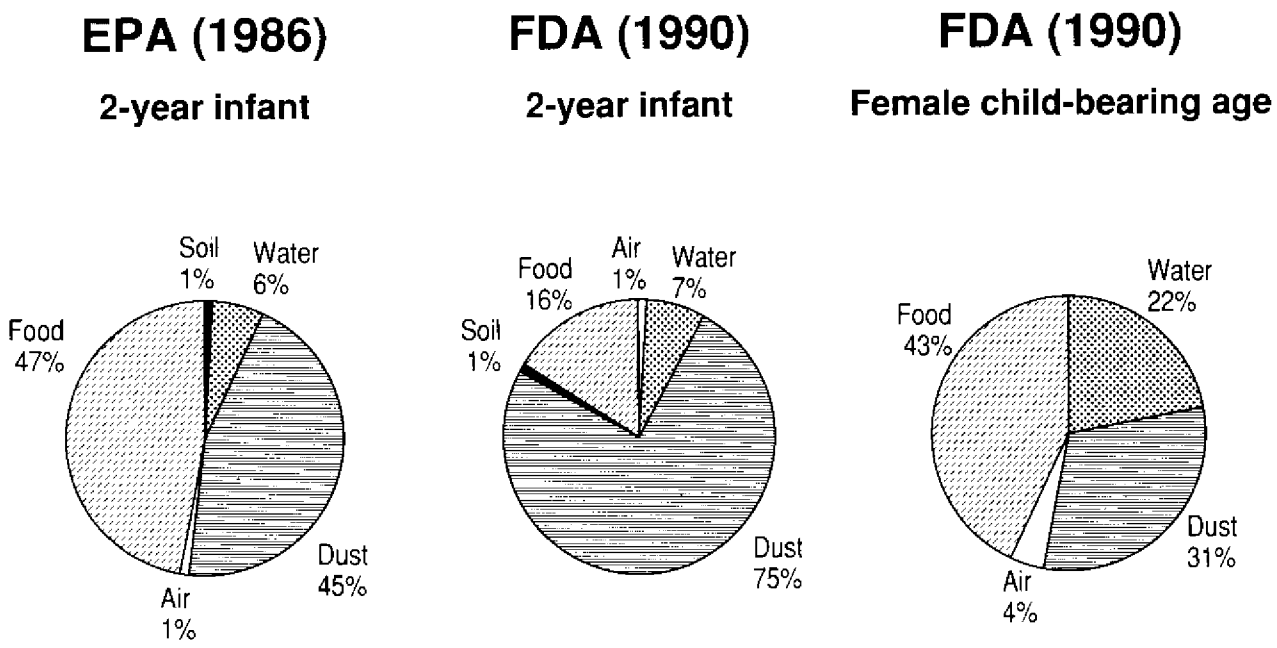

Fig. 11. Percentage of lead intake from food and other sources in two-year-old infants and women of child-bearing age in the USA (Adapted from: Bolger et al., 1991)

Table 17. Distribution of lead in table wines in USA[a]

Range (μg/litre)	Number of samples	Percentage of total samples analysed[b]
0-10	36	8.3
11-25	62	14.4
26-50	105	24.3
51-100	144	33.3
101-250	64	14.8
251-500	12	2.8
501-673	9	2.1

[a] From: US Department of the Treasury (1991)
[b] In all, 432 samples were analysed.

5.2.3 *Dust and surface soils*

5.2.3.1 *Dust*

Dust is a significant source of exposure to lead, particularly for young children (see Fig. 11), as has been demonstrated in several studies correlating children's blood lead concentrations with dust lead levels (Rabinowitz et al., 1985; Bornschein et al., 1987; Davies et al., 1987a; Laxen et al., 1987; Steenhout, 1987).

The major contributions to lead levels in soil and outdoor dust are from the combustion of fossil fuels (principally leaded petrol), stationary sources such as smelters, and peeling and flaking of lead-based paint. Typical lead levels in road dust in the USA are 800-1300 mg/kg in rural areas to 100-5000 mg/kg in urban areas (US EPA, 1989c).

Concentrations of lead in household dust vary greatly between different dwellings and areas of the world. Mean concentrations of 300-2500 mg/kg have been found in the United Kingdom and USA, but individual samples may be in the range of 10 000 to 30 000 mg/kg (Que Hee et al., 1985b; Clark et al., 1985; Bornschein et al., 1986; Raab et al., 1987).

Flaking lead-based paint, paint chips, and weathered powdered paint markedly increase intake of lead from surface dust, particularly for urban children with pica (US EPA, 1986a; Bornschein et al., 1986). Lead-based paint chips have been found to contain 1000-5000 μg lead/cm^2 (Billick & Gray, 1978). When lead-based paint is present, interior renovation activities greatly increase household dust lead concentrations (Laxen et al., 1987). Improved control of dust and surface clean-up after lead-based paint removal have been shown to reduce lead exposure of children reoccupying affected houses (Charney et al., 1983).

5.2.3.2 *Soil*

In rural and remote areas, lead in soil is derived mainly from natural geological sources. These natural sources account for 1-30 mg lead/kg, but where soils are derived from lead-mineralized rocks, natural concentrations may range from several hundred to several thousand mg/kg.

Typical values for lead in rural soils in the United Kingdom are 15-106 mg/kg with a geometric mean of 42 mg/kg (Davies, 1983). A geometric mean of 48 mg/kg for 2780 samples has also been reported (McGrath, 1986).

Concentrations of lead in urban soil vary greatly. In the USA, a study of city parks recorded concentrations of 200 to 3300 mg/kg (US EPA, 1989). Concentrations of up to 10 960 mg/kg have been reported for urban garden soils in the USA (Mielke et al., 1984), and up to 14 100 mg/kg in the United Kingdom (Culbard et al., 1988). Concentrations can exceed 20 000 mg/kg around lead mining and processing operations (Culbard et al., 1988). In areas where lead-based paint has been used, soil samples taken near building foundations have been reported to be as high as 20 000 mg/kg (Schmitt et al., 1988; Krueger & Duguay, 1989).

In general, lead concentrations in soils near roads are high where road traffic density is high. Concentrations decrease exponentially with distance from the road (IPCS, 1989).

Continuous application of sewage sludge results in an accumulation of lead in soil. For example, soil receiving heavy applications over a long period was found to contain 425 mg/kg, compared with 47 mg/kg in an untreated soil (Beckett et al., 1979).

5.2.3.3 Migration of lead from food containers

The available data on the daily intake of lead by adults and children indicate a general decrease in those areas where the level of lead in petrol has decreased and a concerted effort made to avoid lead-soldered cans for food storage (OECD, 1993). However, in many regions of the world, lead can migrate from food storage and serving vessels such as lead-soldered cans (see section 5.2.2.2), ceramic dishes, pottery vessels, crystal glassware and decals on food wrap and/or dishes. Acidic foods tend to leach more lead. However, certain foods such as corn and beans are associated with greater release of lead than would be predicted from their acidity alone (Bolger et al., 1991). Oxygen appears to accelerate the release of lead from food containers.

If foods are stored in ceramic or pottery dinnerware that was lead-glazed and fired in a low temperature kiln, lead can migrate from the pottery glaze into the food. The glazing process uses a flux, which is a material that, at high temperatures, reacts with and helps dissolve the components of the glaze. Lead oxide is a commonly used flux. Factors that determine whether and to what extent lead will migrate include the temperature and extent of firing of the pottery in the manufacturing process, temperature and duration of food storage, and the acidity of the food. It is extremely difficult to quantify the extent of such exposures in view of the variations in the manufacturing processes and the quality control practised in the country of origin. However, the extent of exposure can be quite significant, particularly among infants. Cases of lead intoxication from this source have been reported (Wallace et al., 1985).

Lead has been found to migrate from lead crystal glass into beverages. This problem is especially severe if beverages are stored in lead-crystal containers, e.g., decanters or liquor bottles (de Leacy, 1987; Graziano & Blum, 1991). This phenomenon was not observed with borosilicate glass containers (de Leacy, 1987).

Several studies have been made of lead contamination of foods and beverages from lead used in the manufacture or repair of metal vessels. Recoating the inner surface of brass utensils with a mixture of lead and tin, described as "tinning", is widely practised by artisans in India (Vatsala & Ramakrishna, 1985). The tin-lead alloy contains 55 to 70% lead. Water containing tamarind contained 400-500 μg lead/litre after 5 min of boiling. The practice is considered to be widely prevalent in at least the three

southern states of India. Zhu (1984) described 344 cases of chronic lead poisoning in Jiansu Province, China, involving people who had drunk rain water boiled in tin kettles. Analysis of the lead content of water showed that after boiling the water contained 0.79 to 5.34 mg lead/litre.

5.3 Miscellaneous exposure

5.3.1 Cosmetics and medicines

Some traditional medicines and customs have been found to result in exposure to high levels of lead, most of which cannot be quantified with any degree of accuracy. Rather than occurring as trace ingredients or trace contaminants, various lead compounds are used as major ingredients in traditional medicines in numerous parts of the world (Table 18). Clinically overt lead poisoning due to traditional cosmetics and medicines has been identified among infants (Shaltout et al., 1981; Fernando et al., 1981; Sharma et al., 1990), children and adults (Pontifax & Garg, 1985; Cueto et al., 1989; Mitchell-Heggs et al., 1990; Gupta et al., 1990). There are case reports of lead toxicity secondary to inhalation of lead from traditional remedies (Aslam et al., 1979; Shaltout, 1981; Cueto et al., 1989; Sharma et al., 1990; Mitchell-Heggs et al., 1990).

Often the use is not limited to adults; these may be used on infants and young children, as well as on women. In Kuwait, the leaded "kohl", also called "Al kohl", is traditionally applied to the raw umbilical stump of the newborn in the erroneous belief of a beneficial astringent action (Fernando et al., 1981). An additional use of lead metal and lead sulfide is for inhalation of the fumes ("Bokhoor") produced from heating on hot coals, in the mistaken belief that this will calm irritable infants and children (Fernando et al., 1981; Shaltout et al., 1981).

Latin-American countries also report the use of traditional medicines with high lead concentrations. For example, the Mexican traditional remedy "azarcon" (lead chromate) and/or "greta" (mixed lead oxides), distributed as finely ground powders, may contain more than 70% lead. They are used in the treatment of "empacho", a gastrointestinal disorder considered to be due to a blockage of the intestine (Trotter, 1990).

In addition to the potential risks of lead exposure from the use of traditional medicines, clinical lead poisoning can result from the lodging of lead shot *in vivo* (Manton & Thal, 1986).

Table 18. Sources of lead exposure in traditional medicines and cosmetics

Source of lead (product)	Comments	Reference
Summa/Kohl	used in Indo-Pakistan and other Muslim cultures as eyes preparation; placed on conjunctival surface or as astringent on umbilical cord stump. Antimony originally used but lead cheaper.	Aslam et al. (1979); Fernando et al. (1981); Shaltout et al. (1981); Sharma et al. (1990)
Hindu folk medicine	ground seeds and roots as treatment for diabetes (8 mg lead/g)	Pontifax & Garg (1985)
Bokhoor	tribal custom to produce lead fumes to ward off evil	Shaltout et al. (1981)
Azarcon	lead chromate and mixed lead oxides as treatment for gastrointestinal disorders in Mexico and southwestern USA	Trotter (1990)
Skin ointments and cosmetics	cosmetics used by Chinese actors; skin ointment in Europe	Lai (1977)

5.4 General population exposure

The total intake of lead by adults and children in the general population varies greatly as to the relative contributions from individual sources (air, water, food, soil/dust and others) and is partly dependent on life-style and socioeconomic status. It is beyond the scope of this review to provide comprehensive information covering a wide range of circumstances. However, a few simplified calculations will be given as guidance for carrying out such determinations.

Table 19 gives a summary of the total lead intake and uptake from the general environment in adults and in children aged 1 to 5. The assumptions made are shown and are taken from WHO (1987). Additional intake of lead will take place in certain groups from the use of tobacco and alcoholic beverages. The estimates given are probably on the high side with respect to the contribution from air and dust, since indoor and outdoor lead contributions were considered equal.

Table 19. Estimates of lead (μg/day) absorbed by adults and children from air, dust, food and water[a]

Mean air lead concentration (μg/m^3)	Dust intake (mg/day)[b]	Source of lead (μg/day)				Total absorbed (μg/day)
		Air	Dust	Food	Water	
Adults						
0.3	N.S.	2.4	–	10	2	14.4
0.5	N.S.	4.0	–	10	2	16.0
1.0	N.S.	8.0	–	10	2	20
2.0	N.S.	16.0	–	10	2	28
Children 1-5 years						
0.3	–	0.6	–	25	5	30.6
0.5	–	1.0	–	25	5	31.0
1.0	–	2.0	–	25	5	32.0
2.0	–	4.0	–	25	5	34.0
1.0	25	2	12.5	25	5	44.3
1.0	50	2	25.0	25	5	57.0
1.0	100	2	50.0	25	5	82.0
1.0	200	2	100.0	25	5	132.0

[a] Adapted from WHO (1987); Dust is not considered a significant source of lead in adults, but is a significant source for workers where hygiene practices are poor

The above estimates are based on the following assumptions:

Air: Respiratory volume in adults is 20 m^3/day, and in children 5 m^3/day, and the respiratory absorption is 40%.

Food: Intake of lead by adults 100 μg/day with 10% absorption and 50 μg/day for children with 50% absorption.

Water: A lead concentration of 20 μg/litre, with adult consumption of 1 litre/day and 10% absorption and for children 0.5 litre/day with 50% absorption.

Dust: Dust concentration of lead was 1000 μg/g and absorption was 50%.

[b] N.S. = Not significant

Additional intake of lead is possible due to ciliary clearance of particles 1-5 μm in diameter with subsequent swallowing and gastrointestinal absorption.

5.5 Blood lead concentrations of various populations

Under certain conditions, blood lead (PbB) levels are a useful indicator of exposure and are therefore discussed here, as well as in section 6.1.4. In general, PbB levels correlate better with recent exposure levels (Lyngbye et al., 1990b). As is discussed in sections 5.5.1 and 5.5.2, the general trend observed in all blood lead surveys carried out in countries engaged in risk reduction programmes over the last 15 to 20 years is a fall in the measured levels (OECD, 1993).

PbB concentrations are the most often used estimate of general exposure to lead. The USA, Commission of European Communities (CEC), Australia and the WHO have carried out epidemiological surveys to determine lead exposures in various populations. The designs of these studies differed; some provided estimates for the country as a whole, others compared PbB levels of people working in the same occupation in various countries, and others surveyed general populations but were not designed to be extrapolated as national estimates. What these studies have in common is that they did not emphasize groups with high lead exposures, but concentrated on typical PbB concentrations of non-occupationally-exposed groups in the regions or countries studied. These surveys also offer the possibility of examining the data as distributions, especially at the high end of the distribution profile. Such examination may identify unusual exposures and thus populations at risk. Average PbB concentrations may disguise the risk to various segments of the population.

In the USA, national estimates of the extent and severity of recent human exposures to lead in the general population were based on PbB measurements from the second National Health and Nutrition Examination Survey of 1976-1980 (NHANES II) (Annest & Mahaffey, 1984). The design of this study permitted extrapolation to the USA population as a whole.

The CEC study was directed toward biological screening of the extent of exposure to lead outside the workplace using PbB level as the index of exposure (CEC, 1981). The object of the study was to assess non-occupational exposure of the population to lead in the member states; it was implemented by member states and coordinated by the CEC. Specific populations studied were selected by member states and 168 separate areas and population groups were investigated in 1977.

Two other major international studies were limited to urban populations. A pilot study of human lead exposure (Friberg & Vahter, 1983), organized by the United Nations Environment Programme and WHO, was a collaborative effort under the Global Environmental Monitoring System (GEMS). The following countries participated in at least part of the study: Belgium, China, India, Islamic Republic of Iran, Israel, Japan, Mexico, Peru, USA and the former Yugoslavia. The subjects of the study were teachers, since they comprise an occupational group not extensively exposed to lead. An Australian study was based on urban residents only, and included 651 subjects between 6 and 91 years of age (Hopper et al., 1982).

Based on demographic, economic and individual variables found in the USA study to be associated with PbB levels (Mahaffey et al., 1982), it is clear that results from these major studies cannot be directly compared. However, a comparison of such studies can provide information on the exposure to lead of segments of the various populations in various countries worldwide.

5.5.1 Adult populations

In a large health screening programme within the USA during 1976-1980 (NHANES II), over 27 000 residents aged 6 months to 74 years were examined (Annest & Mahaffey, 1984). PbB concentrations were determined in a subsample (9933 individuals) and yielded an arithmetic mean value of 0.67 μmol/litre (13.9 μg/dl). In 5841 individuals aged 18-74 years, the overall mean was 0.68 μmol/litre (14.1 μg/dl) (Roberts et al., 1985). A sex difference was noted: 0.77 μmol/litre (16.1 μg/dl) was found in males and 0.57 μmol/litre (11.9 μg/dl) in females. Residents in the centre of large urban areas were found to have a PbB level of 0.72 μmol/litre (14.9 μg/dl), while rural residents it was 0.62 μmol/litre (13.0 μg/dl). Because of the design of the study, information on PbB levels, in relation to smoking, alcohol consumption, and occupational status, were available. Male workers in occupations with a high potential for lead exposure had mean PbB levels of 0.78 μmol/litre (16.2 μg/dl) for non-drinkers/non-smokers, 0.92 μmol/litre (19.2 μg/dl) for non-drinkers/non-smokers and 0.95 μmol/litre (19.7 μg/dl) for drinkers/smokers. It was noted that a true decrease of 37% in PbB level occurred during the period of the survey (Annest et al., 1983).

Rabinowitz & Needleman (1982) reported an arithmetic mean umbilical cord PbB concentration of 0.32 μmol/litre (6.6 μg/dl) (range 0-1.78 μmol/litre; 0-37 μg/dl) in over 11 000 samples collected between 1979 and 1981. A decrease in PbB level of approximately 11% was noted during the period of collection.

Friberg & Vahter (1983) reported the PbB levels of 200 teachers from nine countries (see section 5.5). The median PbB level in this study ranged from 0.29 μmol/litre (6 μg/dl) in Beijing and Tokyo to 1.06 μmol/litre (22 μg/dl) in Mexico City. Smokers generally had higher PbB levels than non-smokers.

During the period 1978-1988 marked decreases (approximately 30 to 40%) in the average PbB levels of adults were noted in Belgium, Germany, New Zealand, Sweden, the United Kingdom, and the USA (OECD, 1993).

5.5.2 Children

Results from the NHANES II survey in the USA indicated a mean PbB level for children (6 months to 2 years old) of 0.78 μmol/litre (16.3 μg/dl). It was noted that 18.6% of black inner city children had PbB levels > 1.44 μmol/litre (30 μg/dl) whereas only 4.5% of white children had such PbB concentrations. The percentage of children with high PbB level decreased with increasing family income (Roberts et al., 1985). The NHANES II data were analysed in detail for information on the demographic correlates of children's PbB concentrations (Mahaffey et al., 1982; Annest et al., 1983). The racial differences in these proportions were significant among both boys and girls. The proportion with elevated PbB concentrations was slightly higher among boys than girls for both races. Among both black and white children, the percentage with elevated PbB concentrations decreased with increasing family income. Proportionately more young children in urban than rural areas and in the central cities of large urban areas had elevated blood lead concentrations.

PbB concentrations were measured in 286 Finnish children living in the three largest cities of Finland (number of subjects = 172), in rural areas (54 subjects) and in a lead smelter area (60 subjects) (Taskinen et al., 1981). The mean PbB levels in urban, rural and lead-smelter areas varied between 0.29 μmol/litre and 0.32 μmol/litre, range 0.14-0.82 μmol/litre (6.0 and 6.7 μg/dl, range 3-17 μg/dl). There were no significant differences between the areas of residence. The five children who lived within

500 metres of the lead smelter had a mean PbB concentration of 0.44 μmol/litre, range 0.24-0.62 μmol/litre (9.2 μg/dl, range 5-13 μg/dl), which was significantly higher than the mean blood lead concentration among children living in the rest of the country.

In a study carried out in Sweden, which included 1781 samples obtained from children during 1978-1988, the mean PbB level decreased from 0.29 μmol/litre (59.6 μg/litre), range 0.09-1.20 μmol/litre (18-250 μg/litre) in 1978 to 0.16 μmol/litre (32.9 μg/litre), range 0.07-0.34 μmol/litre (15-71 μg/litre) in 1988 (Schutz et al., 1989). In Finland, a remarkably similar decrease has been reported; the mean PbB value was 0.14 μmol/litre (30 μg/litre), range 0.1-0.40 μmol/litre (21-41 μg/litre) among 35 children in the Helsinki area in 1988 (Ponka et al., 1991).

As in the USA (Annest et al., 1983), children's PbB concentrations in Sweden have decreased in recent years. Levels were determined each summer during the period 1978-1984 in children from Scania in Southern Sweden (Skerfving et al., 1986). The average PbB concentration was 0.26 μmol/litre, range 0.07-1.20 μmol/litre (5.5 μg/dl, range 1.4-25.0 μg/dl). There was a statistically significant decrease over time in both the rural and urban areas, averaging about 0.019 μmol/litre (0.4 μg/dl) per year.

Decreases of 25-45% in average PbB levels in children between 1978 and 1988 have been reported in Belgium, Canada, Germany, New Zealand, Sweden and the United Kingdom (OECD, 1993).

5.5.3 Remote populations

In contrast, a much higher mean value of 0.16 μmol/litre (3.4 μg/dl) was obtained in Nepal upon examination of 103 children living in the Manang District, which is also very remote and thought to be free of anthropogenic sources of lead (Piomelli et al., 1982). However, these people are exposed to significant amounts of natural lead from living in dusty smoke-filled houses, and from burning pine and yak dung. The lead level in the houses was about 0.15 μg/m^3 (Davidson et al., 1981). For comparison outdoor air in Woods Hole, Massachusetts, USA, contains 0.004 and Boston, Massachusetts, 0.01 to 0.05 μg lead/m^3.

Another remote population studied was from Okapa, Eastern Highlands, Papua New Guinea (Poole et al., 1980). Extreme care was taken in sampling and analysis, and the precision was

acceptable at PbB levels as low as 0.24 μmol/litre (5 μg/dl). The children subsisted on root crops and a small amount of tinned fish and meat. Villages were typically hazy with wood smoke, natural mineral pigments were used extensively, and tobacco smoking was common. This survey of 100 children yielded a mean PbB level of 0.25 μmol/litre (5.2 μg/dl), well above the detection limit, and, as reported by Poole et al. (1980), far less than the mean of 1.10 μmol/litre (23 μg/dl) for Sydney, Australia, in 1974.

5.6 Occupational exposure

Occupational exposure to lead which results in poisoning, both moderate and clinically symptomatic, still occurs in many countries of the world. Although adults are mainly involved, in many countries, especially in those with developing industries and small home-based industries, the distinction between home and workplace is non-existent (Verrula & Noah, 1990) and children are exposed to workplace lead. Until recently, in the occupational setting, there was only concern for the identification of late stage, highly symptomatic cases of lead poisoning resulting in crippling neurological manifestations of lead poisoning such as palsy and encephalopathy (Chakravorti & Bhar, 1978; Wang, 1984; Davies, 1984; Lin-Fu, 1985). However, there is now concern for lower exposures to lead.

In many countries occupational lead exposure is entirely unregulated and no monitoring of exposures exists. Automobile battery manufacture and repair, radiator repair, secondary smelters (including scrap metal refiners) are found in most countries. The industries where there is a potential for lead exposure are listed in Table 10 (section 5.1.3). Significant lead exposures are not limited to traditional heavy industries. For example, Kaye et al. (1987) identified exposures from lead-borosilicate dust used in a capacitor and resistor plant in the USA.

Because of transfer of lead to the fetus (*in utero*) and the transport to the home of lead on clothing, etc., thereby exposing the young child in the home, the problems of occupational exposures to lead are not limited to the workplace *per se*. Cases of poisoning among the children of lead workers have been reported (Baker et al., 1979; Wang, 1984; Ryu et al., 1985).

Although most occupational standards are based on airborne lead only, this route of exposure does not fully reflect the total daily exposure of workers, also exposed to lead in food, water, alcoholic beverages and dusts.

The potential for hazardous exposures to lead during lead smelting and refining are well recognized, particularly where molten lead and alloys are poured, resulting in the vaporization of metal. This is true for both primary new metal and secondary (lead scrap) smelters and refineries.

Small domestic versions of secondary smelters exist in a large number of countries. These are typically located within or in close proximity to homes. For example, in Jamaica there has been a rapid proliferation of lead smelters, particularly illegal backyard smelters (Rodney & Lee, 1985). The lead fumes and dust generated in such operations pose an exceptional health hazard to children and adults living near these operations. Rodney & Lee (1985) reported that 51% of 116 children (aged 2 to 12 years, mean 5.9 years) and 60% of 235 adults working in or living near lead smelting factories had PbB concentrations of 1.92 μmol/litre (40 μg/dl) or more.

Other occupations where workers have been shown to be at risk from airborne lead include electric storage battery manufacturing, particularly where industrial hygiene is poor (Barrio & Badia, 1985); demolition, welding and shipbreaking where lead-based paint is present (Holness & Nethercott, 1988; Nosal & Wilhelm, 1990); pottery and ceramic-ware production, which is often a home-based operation involving women and children (Molina-Ballesteros et al., 1983; Katagiri et al., 1983; Kaye et al., 1987); small businesses repairing automobile radiators (Matte et al., 1989a,b; Verrula & Noah, 1990), and artisans producing jewellery and decorative wares. This latter industry is of particular concern since it is predominantly carried out at home or in non-regulated shops, often by women and children (Behari et al., 1982). Indian silver jewellery makers were found to have a PbB level of 5.8 μmol/litre (121 μg/dl) compared to non-exposed controls with a PbB level of 1.3 μmol/litre (27 μg/dl) (Behari et al., 1982).

6. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

6.1 Absorption

The absorption of lead from environmental sources is not dependent solely on the amount of lead presented to the portals of entry. It is also dependent on the physical and chemical state in which the metal is presented, and it is influenced by host factors such as age, physiological status, nutritional condition and, possibly, genetic factors. Men engaged in heavy work breathe more air and eat more food than sedentary individuals of the same weight, and on a body weight basis children eat almost as much food and breathe almost as much air as middle-aged adults.

Considerable data from human subjects are available. Therefore, discussion of animal studies will be limited to areas where the information on humans is inadequate. Various models used to predict body burden or distribution of lead have been developed (Bernard, 1977; Marcus, 1985a,b,c; Bert et al., 1989; Arnetz & Nicolich, 1990). A full review of these models has been judged to be beyond the scope of this document. However, some of them were used in section 6.1.4 when correlating intake and body burdens.

6.1.1 Absorption after inhalation

The absorption of lead from air to blood involves two processes: the deposition of airborne lead particles in the respiratory tract; and the absorption and clearance from the respiratory tract into the circulation. Using the International Radiological Protection Commission (IRPC) document on lung dynamics (Task Group on Lung Dynamics, 1966), a model was developed which predicted that 35 to 50% of inhaled lead is deposited in the respiratory tract (40-50% of particles with a mean mass median aerodynamic diameter (MMAD) of 0.5 μm, such as are typically generated by automobiles). These are deposited primarily in the alveolar sacs of the lung. Lead fumes and vapours, such as those generated in operations where metals are cut or heated, are of very small size and are respirable. Absorption after deposition will vary according to the solubility of the lead species (e.g., lead carbonate or lead chloride aerosols) and the inherent toxicity to lung macrophages and cilia.

6.1.1.1 Animal studies

Limited animal studies confirm that there is almost complete absorption of lead particles (0.1 to 0.5 μm in diameter) deposited in the lower respiratory tract. In rats the clearance half-time from lung is short (less than one hour) and 90 to 98% of the administered dose is absorbed within about 48 h (US EPA, 1986a).

6.1.1.2 Human studies

The respiratory deposition of airborne lead is in the range of 30-50% and varies with particle size and ventilation rate (US EPA., 1986a). Higher deposition rates may occur with larger particles, but this deposition takes place in the upper respiratory tract, with eventual displacement to the gastrointestinal tract and absorption via the ingestion route. This probably explains the observation of Kehoe (1961) that faecal excretion of lead increased after a subject breathed for many weeks aerosols of lead oxide (150 $\mu g/m^3$) with an MMAD of approximately 2.9 μm. In contrast, smaller particles of inhaled lead, such as those generated by automobile exhaust, regardless of physicochemical form, are almost (> 90%) completely absorbed after deposition in the lower respiratory tract (Rabinowitz, et al., 1977a; Chamberlain et al., 1978; US EPA, 1986a).

There are no quantitative data on the absorption of lead in children after inhalation exposure. It is known that young children weighing only one sixth of an adult inhale 40% of the daily volume of an adult and a proportionately higher daily air volume per unit measure (weight, body area) than do adults (Barltrop, 1972). After controlling for weight and taking into account differences in the anatomy of the respiratory tract between adults and children, James (1978) calculated a rate of deposition of lead particles in children which was 1.6 to 2.7 times that of adults.

6.1.2 Absorption of lead from the gastrointestinal tract

In the case of older children and adults without occupational exposure, lead absorbed by the gastrointestinal tract comes from the intake of lead in foods, beverages and soil/dust. In pre-school children, there is concern over the intake of both food and non-food items (e.g., toys, soil/dust). Young children may take in lead from non-food items, via normal mouthing activity, which in the extreme, is the behavioural trait pica, which refers to the ingestion

of such materials as soil, ash, paint chips and plaster (US EPA, 1986a). For infants and young children, the extent of absorption of the lead in dust/soils from the gastrointestinal tract is extremely important, particularly for children living in urban environments.

6.1.2.1 *Animal studies*

The absorption of lead from the gastrointestinal tract in experimental animals is age dependent and is modified by the level of food intake. In 1-week-old suckling rats, an absorption rate of about 52% was reported after a single oral dose of lead chloride, compared to 0.4% in 6-week-old animals (Kostial et al., 1978). Furthermore, Aungst et al. (1981) reported that rat pups had higher tissue levels of lead than adults after a single gavage dose of 1 or 10 mg lead (as lead acetate) per kg body weight. Fasting markedly enhanced the uptake of lead in the gastrointestinal tract of experimental animals (Garber & Wei, 1974; Pounds et al., 1978).

In experimental animals, absorption of lead from the gastrointestinal tract appears to be a saturable process. With increasing doses (1 to 100 mg lead (as lead acetate) per kg body weight), lead absorption as a percentage of dose was found to decrease from 42% to 2% (Aungst et al., 1981; Bushnell & DeLuca, 1983) in dietary studies. Such data are consistent with a saturable active transport process across the gastrointestinal tract.

The low rate of absorption of lead from soluble lead salts noted in adult rats may reflect a dietary effect. Kostial & Kello (1979) reported less than 1% absorption in adult rats given chow diets, whereas the absorption rate was 3-20% when rats consumed diets similar to that of humans (milk, bread, baby foods, etc). This range more closely resembles the human absorption rates.

The chemical form of lead can influence its bioavailability. Stone et al. (1981) determined the biological availability of lead intrinsically incorporated into the soft tissues of oysters. The bioavailability to the rat was 10-30% lower than that of lead acetate added to the basal chow diet. Henning & Cooper (1988) compared the absorption of lead from rat milk labelled *in vitro* with lead-203 and lead chloride or lead acetate solutions. Lead from soluble salts accumulated primarily in the duodenum, to some extent in the jejunum and minimally in the more distal small intestine. Lead from milk accumulated only in the upper ileum. After 20 h negligible lead-203 was found in any region following

administration of soluble salts, but there was substantial retention of lead in the ileum after dosing with milk.

Data obtained from a feeding study in rats (Dieter et al., 1993) showed that lead uptake into rat femurs was highly dependent on the chemical form of lead administered. Bioavailability was highest for lead acetate, intermediate for lead oxide, and lowest for lead sulfide and Alaskan mixed ore concentrate. This uptake was linearly related to dose over the range studied. However, the slopes of the linear regression equations differed according to the form of lead. They were 0.10 μg lead/g femur per kg diet for lead sulfide and 2.64 for lead acetate.

However, results of an investigation in young swine of the absorption of lead from mining and/or milling operation waste (LaVelle et al., 1991) differ from those reported by Dieter et al. (1993). The chemical species (predominantly lead sulfide) and particle size (i.e. larger than 100 μm) were expected to result in these sources being less bioavailable than soluble lead salts such as lead nitrate. However, experimental data indicate that the lead in mine tailings may be about 2-3 times more available than reagent grade lead sulfide under the conditions of the study. Additionally, Freeman et al. (1992) reported that the lead in mining waste soil was between 8 and 20% as bioavailable as lead acetate. No detailed comparisons were made of the physicochemical properties of these two mine wastes. An additional study involving the absorption of lead from lead sulfide ores and their oxidation products in rabbits and *in vitro* showed that lead from minerals was absorbed less well than from lead acetate by a factor of 5 (Davis et al., 1990a). The significance of these phenomena is not clear.

6.1.2.2 *Human studies*

Gastrointestinal absorption of lead in humans, as in experimental animals, is influenced by dietary factors, nutritional status and the chemical form of the metal. Overall patterns of food intake may also influence lead absorption. For example, lead ingested during periods of fasting is absorbed to a much greater extent than lead ingested with food. Chamberlain et al. (1978) reported 45% absorption of lead chloride in fasting subjects and only 6% in feeding subjects. Using a similar procedure, Heard & Chamberlain (1982) reported absorption of 63.3% in fasting subjects. Using multiple stable isotope lead tracers, it was found that in adult men the gastrointestinal absorption rate with food containing lead nitrate or lead cysteine was 6-12%. However,

when consumed under fasting conditions, lead nitrate, lead sulfide and lead cysteine were absorbed at 16-53% (Rabinowitz et al., 1977b).

Kehoe (1961) estimated only 10% net absorption of dietary lead by adults in long-term metabolic studies. However, with appropriate calculation of biliary clearance as well as of urinary excretion, a figure of 15% was estimated by Chamberlain et al. (1978). In several studies on adult humans, absorption of lead was reported to be 14% when it was administered with food (Chamberlain et al., 1978; Moore et al., 1979; Rabinowitz et al., 1980).

Ziegler et al. (1978) reported that young children, aged two weeks to two years, absorbed 42% of ingested lead at levels of intake greater than 5 μg/kg body weight. Drill et al. (1979) estimated an absorption rate of 17% for lead in paint chips in children aged 2 to 3 years. These authors also estimated a 30% gastrointestinal absorption rate for lead in soil and dirt.

The amount of lead ingested by children from non-food items such as soil, dust and paint chips through normal mouthing activity, particularly for children with pica, is a major concern in calculating paediatric lead exposures. Using data from Day et al. (1975) and Lepow et al. (1974), it has been estimated that children 2 to 3 years of age ingest about 100 mg soil per day. Using aluminium and titanium as tracers, Clausing et al. (1987) estimated that children aged 2 to 4 years ingest between 50 and 100 mg of soil daily. The average amount of soil ingested by young children has recently been estimated to be between 12.5 and 21 mg/day (SAHC, 1993).

6.1.2.3 *Nutritional status and lead absorption via gastrointestinal tract*

It has been known for some time that the absorption and distribution of lead are affected by nutritional status in both experimental animals and humans (Sobel et al., 1940). Nutritional inadequacies can also affect the toxic response to lead (see sections 7 and 8). In view of documented nutritional inadequacies in many parts of the world, such interrelationships become crucial in assessing the full risk from lead exposures.

Vitamin D, calcium and phosphorus have complex and interrelated effects on lead absorption (Fullmer, 1990). Increasing the concentration of 1,25-dihydroxycholecalciferol, the active

metabolite of vitamin D, either exogenously or endogenously, increases gastrointestinal absorption of lead (Fullmer, 1990). However, this effect is dependent upon the duration of lead exposure and the magnitude of body lead stores. This homoeostatic mechanism for calcium and its dependence on nutritional status, as well as body burden of lead, is complex. This may explain the divergent results of the observed interaction in children (Rosen et al., 1980) or the lack of association (Koo et al., 1991) of lead with vitamin D metabolism.

In experimental animals, chronic ingestion of diets with less than adequate amounts of calcium (Quarterman & Morrison, 1975), phosphorus (Quarterman & Morrison, 1975), iron (Mahaffey-Six & Goyer, 1972; Ragan, 1977), selenium (Stone & Soares, 1976) or zinc (Cerklewski & Forbes, 1976) increases the fractional absorption of lead in the gastrointestinal tract. From the work of Fullmer & Rosen (1990), it appears that lead alters the transport of calcium and other trace minerals by affecting carrier proteins, rather than by competing at the mucosal surface.

The influence of iron on lead absorption in humans was assessed in double-labelling experiments conducted by Watson et al. (1980). Lead-203 and iron-59 were given to 28 subjects in their diet. There were significant positive correlations between iron levels in food and lead absorption. However, the association was not strong because 50% of those absorbing excess lead also absorbed excess iron.

Rats fed iron-deficient diets have increased concentrations of lead in kidney and bone when compared to rats ingesting equivalent quantities of lead (as lead acetate) in drinking-water while being fed an iron-adequate diet (Mahaffey-Six & Goyer, 1972). In contrast with calcium deficiency, iron deficiency does not result in a redistribution of lead to non-osseous tissue (Mahaffey-Six & Goyer, 1972). The degree of iron deficiency does not need to be severe to increase retention of lead. For example, Ragan (1977) demonstrated six-fold increases in tissue lead in rats when body iron stores were reduced, but before frank iron deficiency developed. High levels of dietary iron resulted in decreased kidney, femur and blood lead concentrations in rats (Mahaffey, 1985). Iron appears to increase absorption rather than decrease lead excretion (Barton et al., 1978). Lead interferes with normal transferrin transport of iron, and inhibits transferrin endocytosis and iron transport across the cell membrane of the reticulocyte (Qian & Morgan, 1990).

6.1.3 Dermal absorption

6.1.3.1 Human dermal absorption

Moore et al. (1980) examined the uptake of lead acetate from two hair-darkening cosmetics through the skin of eight human volunteers. Only minute quantities of lead (0-0.3% of the applied dose) were detectable in blood, and there was only a slight increase in absorption when the skin was damaged. Lilley et al. (1988) and Florence et al. (1988) have reported the dermal absorption of inorganic lead compound leading to elevated levels of lead in human saliva and sweat.

Dermal absorption of inorganic lead through unabraded human skin is considered to be minimal.

6.1.4 The relationship of external lead exposure to blood lead concentration

There are numerous environmental media that provide routes by which humans are exposed to lead: food, water, air, soil, dust. External exposures are the sum of the quantities of lead consumed from all sources.

Historically there have been two lines of approach in understanding the lead exposure and blood lead relationship. Most have been empirical and have measured environmental lead and PbB levels either at one time or repeatedly. With these observed correlations and with no assumptions about how lead moves inside the body, many reasonable predictions can be made. The validity of these predictions is optimum when only one environmental source dominates. Some of these rely on linear functions, while others have specified non-linearities, especially over very wide ranges (more than a factor of 10) of lead exposures. However, when multiple sources are considered these predictive models have been less satisfactory.

Internal lead levels in human populations have been estimated by analyses of a variety of biological tissues (e.g., blood, teeth, bone and hair). Lead concentrations in each of these have particular biological meanings with regard to external exposure to lead. Blood is the compartment in which lead is most often measured as a marker of exposure. However, it typically represents relatively recent exposures, since the half-life of lead in blood is short (US EPA, 1986a) and has been estimated to be in the order of 36 days from tracer studies (Rabinowitz et al., 1975). Lead in

blood is derived from levels in the current environment and from lead stored in tissues (particularly bone) that re-enters the blood during tissue mobilization (Manton, 1985). Although PbB concentration reflects recent exposure and bears a consistent relationship to levels of lead in the external environment, when bone mobilization is accelerated a greater fraction of PbB will be derived from tissue stores.

To date only a few studies have utilized a multimedia approach relating lead intake to PbB levels. The majority of studies have attempted to correlate PbB levels and lead concentrations in specific media.

6.1.4.1 Ambient air

a) Occupational exposure

Several studies have examined the blood lead: air lead relationship for workers exposed to levels of airborne lead between 9 and 450 $\mu g/m^3$ (King & Conchie, 1979; Gartside & Buncher, 1982; Bishop & Hill, 1983). The results of all three studies are in general agreement over the wide range of airborne lead studied and for PbB levels between 0.96 and 4.32 μmol/litre (20-90 $\mu g/dl$). The blood lead: air lead relationship in occupational settings is best described by a curvilinear relationship having slopes between 0.00096 and 0.0038 μmol/litre (0.02 and 0.08 $\mu g/dl$) per $\mu g/m^3$ air.

b) Non-occupational exposure

Both population and experimental studies have been used to estimate the PbB: ambient air lead relationship in adults and children. Under ambient conditions (air lead concentrations of 0.1-2.0 $\mu g/m^3$) and PbB levels less than 1.44 μmol/litre (< 30 $\mu g/dl$), the relationship has been described as linear (Colombo, 1985). The various slope estimates reported are based on the assumption that an equilibrium level of lead in blood is achieved. Based on three major studies (Yankel et al., 1977; Angle & McIntire, 1979; Roels et al., 1980), the median slope for children is about 0.091 μmol/litre (1.9 $\mu g/dl$) blood per $\mu g/m^3$. In adult males a slope estimate of 0.076 μmol/litre (1.6 $\mu g/dl$) blood per $\mu g/m^3$ was calculated. When one calculates the relationship between PbB and the total contribution from air (direct inhalation plus indirect through dust/soil), a value of about 0.14-0.24 μmol/litre (3-5 $\mu g/dl$) blood per $\mu g/m^3$ is obtained (Brunekreef, 1984; US EPA, 1986a). Also on the basis of a linear model, Snee

(1981) reported that the best estimate of the blood lead: air lead relationship was 0.048 μmol/litre (1 μg/dl) per μg/m³. After examining available epidemiological and experimental data, Chamberlain (1983) concluded that most published estimates of the slope were between 0.072 and 0.144 μmol/litre per μg/m³. From these results, it can be concluded that airborne lead will only be a major contributor to PbB levels in areas of high air lead levels.

6.1.4.2 Food

The relationship of PbB to dietary intake has been estimated from experimental (Stuik, 1974; Cools et al., 1976; Schlegel & Kufner, 1979) as well as population studies (Sherlock et al., 1982; UK, 1982; Ryu et al., 1983). In adults, the results from both types of studies using both linear and cube root models indicated a relationship of between 0.0019 and 0.0028 μmol lead/litre (0.04 and 0.06 μg/dl) per μg lead intake per day. From the study of Ryu et al. (1983) a slope of 0.0096 μmol/litre (0.2 μg/dl) per μg lead/day was obtained for infants aged 8 to 196 days.

Currently, data are available for adults and children from studies with careful control of important variables such as: intake of dietary lead and of other dietary constituents, minimal exposure to sources other than diet in the studies of infants, and intake/blood lead measurements that can be used to estimate intake from all sources. For infants these are studies reported by Sherlock et al. (1982), UK (1982), Ryu et al. (1983), and Lacey et al. (1985). Studies by the UK (1982) and by Sherlock et al. (1982) were conducted at higher levels of lead exposure than were the studies conducted with infants by Ryu et al. (1983). The latter studies were at exposure levels associated with PbB concentrations under 0.96 μmol/litre (20 μg/dl); the ratio of blood lead to ingested lead was 0.0076 μmol/litre (0.16 μg/dl) per μg lead ingested per day. Exposure levels were low: average dietary lead intake was 17 μg/day. After four months, the average PbB concentration was 0.29 μmol/litre (6.1 μg/dl) whole blood. Between the ages of 4 and 6 months, 10 children remained at a dietary lead intake of 0.76 μmol/litre (16 μg/dl). Their PbB concentrations were quite constant at 0.35 μmol/litre (7.2 μg/dl) at the end of the study period. The remaining seven children received canned infant formula and/or milk during this period and their average dietary lead intake was 61 μg/day. At the end of the study period, their PbB concentration was 0.69 μmol/litre (14.4 μg/dl). Based on these data, a curvilinear relationship between blood lead and total lead intake was suggested, a 4-fold increase

in lead intake resulting in a doubling of PbB concentration. Sherlock et al. (1982) conducted a duplicate diet study of 31 mothers and their children from Ayr, Scotland. The slope for adults was substantially lower than for children.

6.1.4.3 Drinking-water

There is still debate over the most appropriate model (i.e. cube root, polynomial or logarithmic) to describe the curvilinear relationship of waterborne lead to blood lead. The highest estimates for the contribution of water lead to blood lead come from the cube root and logarithmic models. Much lower estimates are obtained from a linear model (Pocock et al., 1983; US EPA, 1986a). In a study by Sherlock et al. (1982), a cube root relationship between lead levels in drinking-water and blood fitted the data more closely than a linear relationship. The curvilinear model implies that as abatement processes lower water lead concentrations, there will be an increasing benefit in lowering of population PbB levels (Moore, 1983).

6.1.4.4 Soil and dust

It is extremely difficult to choose the most appropriate model to describe the soil/dust to blood lead relationship, given the many variables involved in determining the exposure patterns of children and the kinetics involved between the levels in the environment and the child. A review of the available studies shows the extreme variability in slopes obtained (0.028-0.36 μmol lead/litre (0.6-7.6 μg/dl) blood for each 1000 μg/g soil and 0.00096-0.35 μmol lead/litre (0.02-7.2 μg/dl) blood for each 1000 μg/g dust consumed by children) (US EPA, 1986a). Detailed consideration has been given to the process for the assessment of lead contamination in soil and the derivation of soil clean-up criteria by Wixon (1991). The guideline model uses a PbB target and slope for the soil:blood lead relationship in the particular community in order to derive a PbB guideline. For house dust a median value of 0.086 μmol lead/litre (1.8 μg/dl) blood per 1000 μg lead/g dust in children appears to be based on data of reasonable quality, as does the 0.105 μmol lead/litre (2.2 μg/dl) blood per 1000 μg lead/g soil from the same authors.

According to Elwood (1986), studies of the association between lead in house dust and PbB have given inconsistent results and, in general, the only studies in which statistically significant association has been found are those where lead levels in dust are

quite high. Landrigan et al. (1975) found a highly significant association between PbB and dust lead in an area with a mean level of 4022 μg lead/g dust, but not in two areas with means of 922 and 816 μg lead/g dust. The US EPA (1986a) summarized a series of studies from which the overall relationship was judged to be 0.86 μmol/litre (18 μg/dl) blood per 1000 μg lead/g dust. Duggan (1980) reviewed the literature and determined that a slope of 0.24 μmol/litre (5 μg/dl) per 1000 μg lead/g dust is reasonable.

The overall relationship between PbB and dust/soil lead depends on the lead concentrations and bioavailability as well as on the proximity and linkage between humans and their environment. This relationship varies among locales.

6.1.4.5 *Total lead intake*

The non-linear relationship between PbB and total lead intake (see section 5.5) is curvilinear across a broad range of PbB values, such that the slope decreases with increasing lead levels. A number of biological factors may explain the curvilinear relationships, such as increased renal clearance with high PbB (Chamberlain, 1983, 1985), distributional non-linearities due to differences in lead binding sites in different tissues (Hammond et al., 1981; Manton, 1985; Marcus, 1985b), or a sizeable pool of mobile lead in bone maintained more or less independently of uptake (Rabinowitz et al., 1976; Chamberlain, 1983).

6.2 Distribution

The initial distribution of lead in the body may depend upon the rate of delivery of blood to various organs. However, it would appear that distribution occurs in a similar manner regardless of the route of absorption (Kehoe, 1987). The distribution of lead in humans under environmental exposure conditions reflects the fact that almost all exposures are chronic rather than acute.

6.2.1 *Animal studies*

Studies in rats have shown that lead is rapidly distributed into soft tissues and subsequently redistributed into soft and mineralizing tissues after acute and chronic exposures. After acute inhalation (Morgan & Holmes, 1978) or oral (Aungst et al., 1981) exposure, lead levels in rats were highest in liver, kidneys and lung, with levels increasing in bone as those in soft tissues declined and stabilized. Similar distribution patterns were

reported for mice exposed for 12 months to 21.5 μg lead/m^3, the highest levels being found in bone and the lowest in lung (Keller & Doherty, 1980a).

Age-related differences in the distribution of lead in experimental animals have been reported. Kostial et al. (1978) noted a greater retention of lead in suckling rats than in adults; the levels in the brain were also higher in the pups. A 2- to 3-fold increase in brain lead concentration (highest in hippocampus) was noted after a 10-fold (0.1 to 1 mg/kg body weight administered by gavage) increase in the dose given to 4- to 8-week-old rat pups (Collins et al., 1992).

Ageing has been shown to alter the pattern of distribution of lead in rats administered lead acetate in drinking-water. Juvenile (21 days old), adult (8 months old) and elderly (16 months old) rats received 0, 1.27 and 6.37 mg lead/kg bodyweight for 9.5 months. The pattern of distribution, namely femur > liver > brain was similar in all age groups. However, age-related increases in brain lead levels were noted, along with decreases in femur lead content (Cory-Slechta, 1990a).

6.2.2 Human studies

Lead is distributed to both soft tissues (blood, liver, kidney, etc.) and mineralizing systems (bone and teeth). Bone may be affected adversely by lead but also serves as the body's major storage site. Bone accumulates lead over much of the human life span, and a study of the kinetics of distribution is important since bone can, under appropriate conditions, pose a risk as a potential endogenous source of lead.

Once absorbed, lead is not distributed homogeneously throughout the body but rather into several distinct compartments. Such biokinetic movements have been explained by Rabinowitz et al. (1976) using a three-compartment model. This model was based on tracer and balance data from five healthy men and has been refined by Marcus (1985a,b,c). Three pools (blood, bone and soft tissues) were identified, with lead having distinct half-lives in each. Blood lead was considered the most labile compartment with a half-life of about 36 days, and bone lead the most stable with a half-life of about 27 years. Lead in soft tissue had a half-life of approximately 40 days.

The specific physiological foundations for these biokinetic models have received much attention and are currently being refined (O'Flaherty, 1991, 1993). A more thorough understanding of bone growth, for example, expressed as a series of allometric equations, should help improve models, especially when they must be applied to growing and maturing humans.

Under steady-state conditions, about 96% of PbB is in the erythrocyte. At PbB concentrations of < 1.92 μmol/litre (40 μg/dl), whole blood and serum lead levels increase linearly in a positive manner. At higher PbB concentrations a curvilinear relationship is apparent and the serum to blood ratio increases dramatically (Manton & Cook, 1984). Such kinetic relationships may be altered during pregnancy. From *in vitro* data (Ong & Lee, 1980), fetal haemoglobin appears to have a greater affinity for lead than adult haemoglobin.

In adults, approximately 94% of the body burden of lead is in the bones, whereas only 73% of the body burden in children is located in this compartment (Barry, 1975, 1981). In view of the extremely long half-life for lead in bone, this compartment can serve as an endogenous source of lead to other compartments long after exposure ceases (O'Flaherty et al., 1982; Kehoe, 1987). This is due to the labile lead compartment in bone (Rabinowitz et al., 1976) and the ongoing bone redistribution which is subject to alteration by *in vivo* metabolic processes (Parfitt, 1990). Although lead in bone generally increases continuously with age, there is evidence that lead levels in some bones (e.g., mid-femur and pelvic bone) plateau at middle age and decrease with further ageing (Drasch et al., 1987). It is difficult, however, to determine the role ageing plays in this process compared to other biological reactions. Ageing may account in part for the 20–25% increase in PbB levels in menopausal women noted by Silbergeld et al. (1988).

The metabolism of lead in bone has been summarized in reports by Barry (1975, 1981), Drasch et al. (1987), Silbergeld et al. (1988), Skerfving (1988) and Rabinowitz (1991).

Until recently, it was widely held that the human skeletal system provided a metabolically inert depository for lead and was of little consequence in health-risk assessment. It had been assumed that bone lead is metabolically inert, with a half-life long enough to forestall the risk of ready transfer back to blood. Current evidence is that bone comprises a set of kinetically variable subcompartments for lead deposition and is a target for

toxicity. These factors complicate bone lead kinetics as applied to long-term modelling; the mobility of bone lead to blood is important (Rabinowitz, 1991).

Bone lead is readily mobilized to blood and the effect is most apparent in people with a history of occupational exposure; bone lead also appears to be a major source of blood lead in older people with previous ambient exposures to lead. Of particular importance is mobilization of lead from bone in pregnant women and nursing mothers (Silbergeld, 1991). The mobilization of lead from bone to the more bioavailable maternal blood compartment poses a risk to the fetus and mother.

Human bone appears to have at least two, possibly three, kinetically distinct lead compartments. Lead in trabecular (spongy) bone appears to be more mobile than lead lodged in cortical (compact) bone, and there appears also to be a fraction of bone lead in equilibrium with the lead in blood (Skerfving, 1988). Trabecular bone seems to be an important source of resorbed lead when high exposure is reduced, e.g., through removal of medical reasons by retirement of lead workers, or in response to chelation in adults (Shutz et al., 1987).

6.2.3 *Transplacental transfer*

Lead is readily transferred from the mother to the developing infant during pregnancy and accumulates in bone during gestation (Barltrop, 1969). The lead concentration in cord blood is 85-90% that of maternal blood. Moore et al. (1982) reported a geometric mean level of 0.67 μmol/litre (14 μg/dl) in 236 pregnant women and 0.58 μmol/litre (12 μg/dl) for lead in umbilical cord blood. The mean concentration of lead in umbilical cord blood from a sample of over 11 000 women was 0.298 μmol/litre (6.6 ± 3.2 μg/dl) (Bellinger et al., 1987).

6.3 Elimination and excretion

In both humans and experimental animals lead is eliminated from the body in both urine and faeces. Any dietary (including waterborne) lead not absorbed in the gastrointestinal tract is excreted in faeces. Airborne lead that has been swallowed and not absorbed is also eliminated in this manner. Blood lead not retained in the body is excreted in urine or faeces, the latter by biliary excretion. Adults ingesting daily 0.3 to 3.0 mg lead (as lead acetate) in drinking-water for 16 to 208 weeks excreted more than

85% of the ingested lead, 90% of the excreted lead being in the faeces. The amount excreted through any route is affected by age and exposure characteristics and is species dependent (US EPA, 1986a). This section reviews only studies of lead excretion in humans; a discussion of the results of work on experimental animals can be found in reviews by US EPA (1986a) and ATSDR (1993).

The age dependency of lead excretion in humans has not been studied extensively. However, the studies of Rabinowitz et al. (1977b) and Chamberlain et al. (1978) in adults and Ziegler et al. (1978) in infants can be used to assess this phenomenon. Data from Ziegler et al. (1978) and Rabinowitz et al. (1977a) are given in Table 20. Ziegler et al. (1978) calculated a total daily retention by infants of 40 μg, which is about twice the amount calculated by Alexander et al. (1973).

Table 20. Comparison of daily lead intake and excretion in children and adults[a]

Parameter	Children[b]	Adults[c]
Dietary intake (μg/kg)	10.76	3.63
Fraction absorbed	0.55[d]	0.15
Dietary lead absorbed (μg/kg)	5.92	0.54
Air lead absorbed (μg/kg)	0.20	0.21
Total absorbed lead (μg/kg)	6.12	0.75
Urinary lead excreted (μg/kg)	1.00	0.47
Endogenous faecal lead (μg/kg)	1.56	0.24
Total excreted lead (μg/kg)	2.56	0.71
Excreted/absorbed lead	0.42	0.92
Fraction of intake retained	0.33	0.01

[a] Adapted from: US EPA (1986a)
[b] From: Ziegler et al. (1978)
[c] From: Rabinowitz et al. (1977a)
[d] Corrected for calculated endogenous faecal lead

Under conditions of relatively constant exposure to low concentrations of lead, approximately 140 to 215 μg/day, a steady state condition evolves in which excretion approximates intake (Rabinowitz et al., 1976). Under these conditions urinary lead

excretion is approximately 70% of absorbed lead. Chamberlain (1985) reported that approximately 60% of absorbed lead is retained by the body and 40% excreted.

Chamberlain (1983, 1985) also examined the relationship between the level of exposure and rate of lead excretion. Renal clearance at PbB levels of between 1.2 and 3.84 μmol/litre (25 and 80 μg/dl) was found to increase at a rate approximating the increase in plasma lead.

Chamberlain (1985) estimated endogenous faecal lead loss into the gastrointestinal tract following administration of lead-203 via the inhalation and parenteral routes. These estimates suggested a clearance of approximately 0.5% of administered dose per day when PbB concentrations were under 1.2 μmol/litre (25 μg/dl). A special form of excretion of endogenous lead is through breast milk. Studies of breast milk indicate that lead concentrations correlate with maternal PbB concentrations, most studies reporting that lead secreted from breast milk varies in concentration between 10 and 30% of the maternal PbB concentration (Ong et al., 1985).

6.4 Biological indices of lead exposure and body burden

6.4.1 Blood lead

The relationship between levels of exposure from various environmental media and PbB has been discussed briefly in section 6.1.4.

Due to the ease of sampling and homogeneity of the sample, blood has been the most widely used specimen to assess the human body burden of lead. However, in view of the relatively short half-life for lead in blood (28-36 days) (see section 6.2.2), PbB measurements in general reflect only recent exposures. Also, in view of the kinetics of distribution within the body (cycling between blood, bone and soft tissues), differentiation of low-level chronic exposure from a short high-level exposure is not possible on the basis of a single PbB measurement. Interpretation of PbB levels over a wide range of values must take account of the curvilinear relationship between total intake of lead and PbB concentrations, as well as the proportion of lead in plasma (Manton & Cook, 1984; see also section 8.1).

A number of cohort studies have collected serial PbB measurements for children from birth up to 7 or 10 years. For

children who have not had major changes in their environment, there is good correlation between consecutive PbB measurements (McMichael et al., 1988; Bellinger et al., 1992; Baghurst et al., 1992; Dietrich et al., 1993a,b). In these extended studies it has become apparent that for most of the children a single PbB analysis at 6 years of age gives a reasonable assessment of the lifetime lead exposure status of the child. However, random PbB levels in samples taken before 6 years of age can markedly underestimate the peak exposure usually seen at 2 years of age (SAHC, 1993).

A new exposure index, namely "lifetime average blood lead" or "lifetime average integrated blood lead" has been introduced in studies using serial blood data. It has been clearly explained in the proceedings of a recent Workshop and this explanation is quoted directly here. This measure, which is a reflection of the area under the "blood lead by age curve", has been occasionally misunderstood. Due to the shape of the longitudinal blood lead profile, the peak blood lead level, usually observed during the second year of life is considerably greater than the average lifetime blood lead. For example, a five-year-old child with a lifetime average blood lead of 0.96 μmol/litre (20 μg/dl) is likely to experience blood lead levels above 1.92 μmol/litre (40 μg/dl) during the second year of life and may spend 3 years of life, from 12 months to 48 months, above 0.96 μmol/litre (20 μg/dl). Due to the shape of the curve, with declining PbB beginning about 24-39 months of age, the average lifetime blood lead for a given child decreases with increasing age. This does not mean that the index is inappropriate but rather that developmental blood lead profiles change over time. For example, a lifetime average blood lead of 0.72 μmol/litre (15 μg/dl) should not be interpreted as being equivalent to a single blood lead determination of 0.72 μmol/litre (15 μg/dl) obtained at a single point in life (Dietrich et al., 1991).

6.4.2 *Tooth lead*

Unlike blood samples, teeth are composed of several anatomically distinct pools which form over several years. Thus, in contrast to blood, teeth are useful tissues for assessing long-term lead accumulation from prenatal exposures to the time of shedding of the tooth.

The accumulation of lead in teeth (PbT) has been used as a measure of exposure of children to lead in several epidemiological studies (Needleman et al., 1972; Winneke et al., 1982a; Rabinowitz

et al., 1989; Fergusson et al., 1989; Hansen et al., 1989). Studies measuring PbT and PbB, however, are few. Preliminary data from Australia (Baghurst et al., 1992) indicate a correlation of 0.8 between whole PbT and PbB prior to tooth exfoliation, but the only report relating lead in circumpulpal dentine and longitudinal PbB (by Greene et al., 1992) found a correlation of only 0.5. PbT concentrations can vary as a function of location of the tooth within the mouth, age, and whether total PbT or dentine PbT were reported. Therefore, the age of the tooth in the mouth and its location, the sample (whole tooth or dentine) analysed must be considered in any estimation of a corresponding PbB in the published studies (SAHC, 1993).

Because of the complex structure and development of teeth, concentrations of PbT will depend on the method of sampling and analysis, tooth type, and resorption and tooth age at exfoliation. As a result of varying procedures used by different investigators, there may be substantial variation in absolute values and possibly the biological meaning of PbT levels between different studies.

Different parts of a tooth sequester lead during different stages of development. This is especially of concern in tooth sampling because lead is not uniformly distributed within a tooth on a submillimeter scale. A pilot study of teeth from children with differing histories of exposure to lead and using high precision lead isotopic methods has shown that analyses of slices of the incisal part of deciduous teeth give the clearest indications of the *in utero* environment, and the cervical sections, the exposure from birth to exfoliation (Gulson & Wilson, 1994).

For more detailed discussions on the measurement of PbT the reader is referred to Grandjean et al. (1984), Purchase & Fergusson (1986) and Fergusson et al. (1989).

6.4.3 Bone lead

The human skeleton begins to accumulate lead during fetal development and continues to abut 60 years of age (Pounds et al., 1991). Interest in bone lead and its measurement *in vivo* stems from concern that skeletal lead is not metabolically inert (see section 6.2.2), but can be mobilized by physiological and pathological states, for example, during pregnancy and lactation (Silbergeld, 1991) and osteoporosis (Silbergeld et al., 1988), with possible adverse effects in other tissues, including the fetus, as well as the desire to develop a meaningful measure of cumulative

lead exposure as a tool in public health protection. Section 8.13 includes a brief discussion of the skeleton as a target organ for lead toxicity.

Procedures are available to analyse bone samples for lead levels in humans not occupationally exposed to lead (Drasch et al., 1987; Drasch & Ott, 1988). These studies have shown a decrease in levels of lead in bones from autopsy specimens in Germany after removal of lead from petrol. However, full utilization of bone lead stores as dosimeters of lead exposure in a prospective sense requires the utilization of technologies for *in vivo* measurement of lead in bone such as X-ray fluorescence analysis (Chettle et al., 1991; Rosen et al., 1991; Todd et al., 1992).

6.4.4 Lead in urine

Although urinary lead level has been used to measure current exposure (Robinson, 1974), its use as a biomarker of lead exposure is questionable in view of the relatively low and variable level of lead excreted in the urine (Jensen, 1984; Ibels & Pollock, 1986). For this reason, and in view of technical difficulties in analysing low levels of lead in urine, urinary lead appears to be of limited use for general screening. However, where an elevated body burden of lead has been estimated using PbB or other indices of lead exposure, urinary levels of lead after administration of the chelating agent $CaNa_2$-EDTA is considered an excellent measure of the potentially toxic fraction of the total body burden of lead (CDC, 1985). The chelatable lead excreted is assumed to represent lead removal from soft tissues and blood, as well as sub-compartments of bone (Ibels & Pollock, 1986; Mushak, 1989). In contrast, the urinary lead excretion associated with lead mobilization provides what is considered the best measure of the potentially toxic fraction of the total body burden (see CDC, 1985; US EPA, 1986a). On the basis of various *in vitro* experimental and epidemiological studies (CDC, 1985; US EPA, 1986a; Mushak, 1989), chelatable lead is assumed to be a chemical sample of both mobile body compartments (i.e. blood and soft tissues) as well as of sub-compartments of bone.

6.4.5 Lead in hair

Hair lead has been used as an indicator of exposure in children (Marlowe & Errera, 1982; Wilhelm et al., 1989). However, there are severe limitations on its use from both the methodological as well as the metabolic perspective. Systemic variations in lead level

have been reported according to hair colour, texture, location on the body and growth phase (Wilhelm et al., 1989). Also, it is almost impossible to avoid external contamination, and to date no validated methods are available for cleaning. Methods which are sufficiently vigorous to remove superficial lead also remove lead from the hair shaft.

7. EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Lead can affect various organ systems depending upon the level and duration of exposure. In all species studied, adverse effects on the nervous system have been noted at PbB concentrations lower than for other target organs. There is particular concern for the effects of lead on fetal development. Since the appearance of Environmental Health Criteria 3: Lead (IPCS, 1977), there have been very many reports on the effects of lead on *in vitro* and animal models. No attempt will be made in this chapter to summarize all such studies. Rather, emphasis has been given to those studies that relate most directly to the understanding of the effects of lead on humans and thus provide additional scientific support for the use of such human studies in the assessment of risk from lead exposures.

7.1 Biochemical effects

7.1.1 Haem synthesis and haematopoiesis

The principal clinical manifestation of the effect of lead on the haematopoietic system is anaemia but this occurs only with high levels of exposure that are rarely seen today. Lead affects the haematopoietic system at several levels. These include effects on haem and globin synthesis and on erythrocyte formation and function.

Most haem synthesis is directed toward formation of haemoglobin and the rest is used in cellular oxidative metabolism. Lead inhibits several steps in the biosynthesis of haem. More detail can be found in IPCS (1977), US EPA (1986a) and section 8.1.1 of this monograph.

Lead acts on steps in the synthetic pathway both inside and outside the mitochondrion. It inhibits certain enzymes (ALA dehydratase, ferrochelatase, coproporphyrinogen oxidase) and increases the activity of ALA synthase (ALAS) activity as a consequence of feed-back regulation by haem (Moore et al., 1980). The activity of ALAS is the rate-limiting step in the haem biosynthetic pathway.

Lead affects erythrocyte formation by impairment of globin and haem synthesis. Globin synthesis is inhibited by lead in rat

bone marrow cells at concentrations as low as 1 μmol/litre (Dresner et al., 1982). This is thought to be secondary to decreased protein synthesis in erythroid cells as a consequence of lead-induced inhibition of haem synthesis. Lead also decreases erythrocyte survival through its inhibition of membrane bound Na-K ATPase (Rhagavan et al., 1981).

It has been shown in *in vitro* cultures of cells from liver, bone marrow and the nervous system that ALAS activity may be increased by addition of only 50 μmol lead/litre and ALAD activity is decreased by 60% at a concentration of 0.5 μmol/litre (Kusell et al., 1978; Dresner et al., 1982). Lead (5 μmol/litre) also inhibits (20%) porphobilinogen deaminase in red blood cell haemolysates at 5 μmol/litre (Piper & Tephly, 1974). Fowler et al. (1980) have shown that disruption of haem synthesis results in reduction of tissue haem levels. Increased exposure to lead decreases the content and function of haem-dependent enzymes of the P-450 mono-oxygenase system (Meredith & Moore, 1979). More recently it has been shown that lead induces haem oxygenase activity thereby increasing the degradation of haemoproteins which may adversely affect a number of cell functions such as respiration and energy production (Maines, 1992). It has been suggested that delay in the accumulation of haemoproteins of the respiratory chain in brain tissue during development may result in decreased synthesis of haem enzymes in the brain (Bull, 1980; Moore et al., 1987). Holtzman et al. (1981), on the other hand, found no effect of lead on brain cytochromes in rat pups with impairment of growth due to exposure to lead.

7.2 Nervous system effects

7.2.1 Higher order behavioural toxicity

Experimental studies using animal models have demonstrated that lead impairs learning and memory functions at virtually all stages of the life cycle. The most significant studies have focused on behavioural and learning impairments in experimental animals with PbB levels below 1.44 μmol/litre (30 μg/dl). Bushnell & Levin (1983) fed post-weaning rats drinking-water containing 10 or 100 mg lead (as lead acetate) per litre for up to 7 weeks. PbB was not determined but has been estimated from comparisons with similar lead exposure models to have been less than 0.96 μmol/litre (20 μg/dl) (Davis et al., 1990b). Brain lead averaged about 0.05 μg/g wet weight. The rats exhibited impaired learning ability when tested for their ability to choose between alternate arms of

a radial maze. Cory-Slechta et al. (1985) demonstrated a significant learning impairment in rats given lead acetate in drinking-water (25 mg/litre) from weaning. The observed outcome was a significantly higher response rate in lead-exposed rats working under a fixed interval schedule of food reinforcement. PbB values of lead-treated rats in that study averaged 0.72-0.96 μmol/litre (15-20 μg/dl) and brain lead levels averaged 0.07 μg/g wet weight. Similar effects have been described in older rats (16 months of age) at steady-state PbB levels of 0.62-0.86 μmol/litre (13-18 μg/dl) (Cory-Slechta & Pokora, 1991). More recently, Cohn et al. (1993) demonstrated selective effects of lead on learning processes, as distinct from non-specific effects such as motivational levels, and sensory or motor impairment using a multiple schedule of repeated learning and performance. Exposure to lead acetate in drinking-water (50 mg/litre) produced a PbB of 1.2 μmol/litre (25 μg/dl).

Winneke et al. (1977) exposed rats to lead while *in utero*, through mother's milk and directly in drinking-water. Their learning ability was then tested by requiring the animals to discriminate between stimuli of either different orientation (stripes as an easy task) or different size (discs as a difficult task). Adult rats tested between 90 and 170 days of age with PbB levels of less than 1.44 μmol/litre (< 30 μg/dl) were slower to learn the difficult task of size discrimination (but not the easy discrimination problem) and tended to repeat more errors than control subjects.

Altmann et al. (1993) demonstrated deficits of both active avoidance learning (AAL) and *in vitro* hippocampal long-term potentiation (LTP) in adult rats that had received pre-weaning or pre- and post-weaning dietary lead exposure to achieve PbB levels of approximately 0.72 μmol/litre (15 μg/dl) and brain lead concentrations of 0.09-0.16 μg/g wet weight. Deficit in animals with only post-weaning exposure and blood lead levels was about 0.77 μmol/litre (16 μg/dl) but brain lead concentrations of only 0.09 μg/g was either absent (in the case of LTP) or markedly reduced (in the case of AAL).

Similar types of effects have been noted in studies using non-human primates. For example, Rice (1985) reported deficits of discrimination reversal performance in monkeys dosed orally with 0, 50 or 100 μg lead/kg body weight per day for the first 200 days of life. At the cessation of dosing, PbB concentrations were 0.144 μmol/litre (3 μg/dl), 0.72 μmol/litre (15 μg/dl) and

1.2 μmol/litre (25 μg/dl), respectively. Prior to behavioural testing (3 years of age), PbB levels were 0.144 μmol/litre (3 μg/dl), 0.528 μmol/litre (11 μg/dl) and 0.624 μmol/litre (13 μg/dl). Additional evidence for lead-induced changes in learning in non-human primates is provided by the study of Lilienthal et al. (1990), which showed a dose-related increase in the percentage of errors in a learning set formation task (discrimination) with PbB levels in the low exposure group (350 μg lead acetate/g diet) averaging 1.68 μmol/litre (35 μg/dl). Also, an impairment of reversal learning was found by Bushnell & Bowman (1979b) to persist in monkeys up to their fifth year, at which time the PbB level in treated animals averaged 0.24 μmol/litre (5 μg/dl) compared to 0.192 μmol/litre (4 μg/dl) in controls. In the study by Bushnell & Bowman (1979a), the period of lead exposure was limited to the first year of life and resulted in PbB levels averaging as high as 3.12 μmol/litre (65 μg/dl). No description was given of quality control procedures to ensure accuracy of PbB determinations at the lower levels reported.

Several studies on experimental animals have shown perseverative effects (the tendency to respond repetitively and inappropriately even though environmental conditions have changed) which may underlie many of the lead-induced changes in learning and other higher order behavioural processes noted in such studies. This has been clearly demonstrated in rodents by Cohn et al. (1993) in the context of learning impairments. In the study by Bushnell & Levin (1983) described above, the accuracy impairment derived from a tendency of lead-exposed rats to re-enter a previously explored arm of the maze. Similar perseverative tendencies have been described in non-human primate studies, e.g., on delayed matching to sample (Rice, 1984a) and delayed alteration tasks (Levin & Bowman, 1986; Rice & Karpinski, 1988).

Experimental animal studies also reveal the importance of task complexity in detecting lead-induced changes in behaviour, both in non-human primates (Levin & Bowman, 1983, 1986; Gilbert & Rice, 1987) and rodents (Winneke et al., 1977, 1982b).

Persistence of lead-induced changes in some higher order behavioural processes is also suggested by a number of experimental animal studies. Several reports from the longitudinal studies of non-human primates by Bowman and his colleagues (e.g., Bushnell & Bowman, 1979a,b; Levin & Bowman, 1983, 1986, 1989) have demonstrated persistent neurobehavioural deficits extending up to 8 years after the termination of exposure and long

after PbB levels had declined to the control level. In rats, Cory-Slechta & Thompson (1979) showed that the levels of lead exposure determine the persistence of lead effects, while Cory-Slechta (1990a,b) revealed that apparently transient effects of lead on behaviour could re-emerge with changes in the reward contingencies of the environment. Munoz et al. (1986) found deficits in both spatial and visual discrimination performance of rats at several months of age resulting from pre-weaning exposure via the dams. The same outcome was noted by Altmann et al. (1993) in a study where deficits in adult rats were noted following pre-weaning exposure.

7.2.2 *Mechanisms of lead-induced behavioural toxicity*

While the mechanisms underlying lead-induced behavioural toxicity have yet to be adequately determined, the experimental animal literature provides suggestive leads. The early experimental studies of Pentschew (1965) and Pentschew & Garro (1966) demonstrated in the rodent model that the pathogenesis of acute high-dose encephalopathy was secondary to increased permeability of capillaries in the brain, leading to leakage of fluid and red blood cells. These changes are similar to those occurring in children with acute lead encephalopathy characterized clinically by coma, convulsions and death, and identify the brain microvasculature as the primary target for lead in the central nervous system following high level exposure to lead.

Changes in microvascular morphology are not evident with low level lead exposure, but it is the vulnerability of the blood-brain barrier that permits exposure of the brain to lead. Exposure of the developing fetus to lead results in higher uptake of lead in the brain than from later exposures (Rossouw et al., 1987). The development of resistance to acute encephalopathy in rat pups during the first few days of life is thought by Holtzman et al. (1984) to be related to maturation of the blood-brain barrier and possibly to the ability of the older animals to sequester lead in protein complexes. Thus neuropathological changes may relate more to the issue of exposure than to mechanism of effect.

More recently, the focus of mechanistic studies has involved biochemical and neurochemical changes. Biochemical changes in synaptic transmission are likely to be related to problems in dendrite-nerve organization and function (Goldstein, 1990). There is continuing reorganization of dendrite and nerve terminal connections throughout early months of neural development. A

number of biochemical and functional studies concerning possible mechanisms of lead effect suggest lead may disrupt this process and its function through early childhood (e.g., Cookman et al., 1987, 1988).

Other biochemical effects from lead exposure which may be the basis of important neurobiological mechanisms of lead-induced behavioural toxicity include changes in protein kinases, with implications for neurotransmitter system disturbances. At least three protein kinases present in nerve terminals involved in modulating the release of neurotransmitters have been shown to be affected by lead. However, the relevance of these findings to cognitive function has not been established (Goldstein, 1990).

From both *in vivo* and *in vitro* studies, lead exposure has been reported to have effects on virtually all neurotransmitter systems (US EPA, 1986a). Depending on the stage of development, these include dopaminergic, cholinergic, serotonergic, GABAnergic, glutamatergic and opiate systems. Probably the most extensively investigated system has been the dopaminergic system where a number of changes at the biochemical and receptor level have been described. One of the difficulties, however, is determining the relationship of the reported changes at the biochemical/receptor level to changes in behavioural function. McIntosh et al. (1989) noted lead-induced changes in tetrahydrobiopterin metabolism which may be related to changes in IQ scores (Blair et al., 1982; McIntosh et al., 1985). In further support of a functional role for lead-induced changes in dopaminergic systems, Cory-Slechta & Widzowski (1991) reported alterations in both D1 and D2 dopaminergic sensitivity in rats with PbB levels of 1.2-1.44 μmol/litre (25-30 μg/dl).

More recently, studies by Altmann et al. (1993) and Cohn & Cory-Slechta (1993) suggest a role for changes in the N-methyl-D-aspartate (NMDA) receptor complex in lead-induced behavioural toxicity. The NMDA receptor complex has been implicated in the learning and memory processes.

Effects of lead on mitochondrial energy metabolism may also be important in the pathogenesis of neurological effects. Impairment of respiration in brain mitochondria has been observed in *in vitro* preparations (Holtzman et al., 1978) and in mitochondria isolated from brains of lead-exposed rats (Gmerek et al., 1981).

7.2.2.1 Conclusions

Given their ability to establish causal relationships between lead exposure and biological effects, experimental animal studies can provide evidence supportive of human epidemiological findings. Many experimental animal studies have been carried out to characterize the nature of lead's effects on various target organ systems as well as to establish the underlying mechanisms of effect. Furthermore, these studies, by their very nature, are not confounded by such co-variates of children's IQ as parental IQ, socioeconomic status and quality of the home environment, or complicated by nutritional inadequacies of the study population. Earlier experimental animal studies tended to utilize relatively high lead exposure levels, but over the past ten years, exposure levels and protocols have been more relevant to the human situation.

There are, of course, some limitations of experimental animal studies that must be considered. For example, there may be differences in species sensitivity as well as differences in pharmacokinetic and pharmacodynamic behaviour of lead in rodents, primates and humans. Higher external exposure levels of lead are required to produce PbB levels corresponding to levels experienced in human populations, and higher PbBs are necessary to induce encephalopathy in rodents than are associated with such effects in humans. Such differences in sensitivity obviously reflect, at least in part, differences in kinetics of lead across species. Despite these differences, it should be noted that corresponding levels of PbB have been associated with neurobehavioural toxicity in both animal models (rodents as well as non-human primates) and human populations. This comparability of effect levels, despite the relative insensitivity of the animal models, suggests that the levels of concern in humans might be even lower, although quantitative extrapolation is difficult. Although one cannot presume that the neurotoxic effects of lead in experimental animals necessarily predict specific effects in humans, the similarities in neurobehavioural end-points in humans and animals are sufficient to conclude that neurobehavioural deficits in animals are at least qualitatively predictive of effects in humans.

7.2.3 Sensory organ toxicity

Visual and auditory functions have been shown to be affected by lead; other sensory modalities have largely been neglected.

Bushnell et al. (1977b) studied visual acuity in infant rhesus monkeys using different degrees of illumination. Four control animals and three animals each in a low and a high lead group were tested. The animals were orally dosed between postnatal days 5 and 365. Although the dosing regimen of this group was intended to produce blood lead levels around 4.08 μmol/litre (85 μg/dl), peak levels of between 6.58 and 14.4 μmol/litre (137 and 300 μg/dl) occurred between the fifth and the ninth weeks of dosing. Significant impairment of scotopic vision was observed only in the animals of the high lead group.

Using flash-evoked visual potentials (VEP), Lilienthal et al. (1986) studied visual function in 7- to 7½-year-old rhesus monkeys pre- and postnatally exposed to lead acetate (0, 350 and 600 mg/kg) in their diets. Seventeen animals were tested altogether: six controls, and five or six in each of the exposed groups. PbB levels fluctuated around 1.92 μmol/litre (40 μg/dl) in the group fed 350 mg/kg diet during the seven postnatal years, whereas in the group fed 600 mg/kg they had declined from the initial average of 5.28 μmol/litre (110 μg/dl) at age 9 months to about 2.88 μmol/litre (60 μg/dl) at 7 years of age. PbB levels in the mothers of both these groups had been between 1.15 and 1.78 μmol/litre (24 to 37 μg/dl) during pregnancy. A dose-related decrease of amplitudes and a similar increase of latencies for the main VEP component were found; these were, in most instances, significant in both the high and low lead groups.

These findings are supported by the results of studies on rodents by Fox et al. (1977). Prolonged VEP latencies were observed following chronic developmental lead exposure. Lower VEP amplitudes have also been observed in rats at PbB levels exceeding 1.44 μmol/litre (30 μg/dl) (Winneke, 1979). *In vitro* studies suggest that rods are more sensitive to the effects of lead than are cones (Fox & Sillman, 1979).

Information on the impairment of auditory function by lead comes from electrophysiological studies using brainstem auditory evoked potentials (BAEP) in rhesus monkeys (Lilienthal et al., 1990). PbB levels in the various groups at the time of testing averaged 0.432 μmol/litre (9 μg/dl; controls), 1.92 μmol/litre (40 μg/dl; low lead), and 2.688 μmol/litre (56 μg/dl; high lead). Of the four peaks discernible in the monkey, BAEP peaks II and IV exhibited significantly prolonged latencies, which were observed only in the animals of the high lead group.

7.3 Renal system

The renal effects of lead in animal models occur as a result of both acute and chronic exposures. Acute lead nephrotoxicity is characterized by decreased reabsorption of small molecular weight compounds by the renal tubule, particularly amino acids, glucose and phosphate (Fanconi Syndrome).

Morphological changes of chronic lead exposure include cytomegaly, development of nuclear inclusion bodies and ultrastructural changes in mitochondria. The basis for the cytomegaly is not understood but it is known that there is altered homoeostasis of water and electrolytes and cellular swelling. Inclusion bodies are lead-protein complexes composed of acidic non-histone proteins. As much as 90% of lead in the kidney has been shown to be contained in the inclusion bodies, suggesting that they provide a detoxification function. The origin of the protein is not known but Egle & Shelton (1986) have identified the most abundant component of isolated inclusion bodies to be a constitutive protein of the adult central nervous system primarily in the cerebral cortex. The lead in the inclusion bodies is chelatable with EDTA (Goyer & Wilson, 1975).

Mitochondria isolated from kidneys of lead-intoxicated rats have impaired respiration and oxidative phosphorylation capacity, (Goyer & Rhyne, 1973).

Kholil-Manesh et al. (1992) studied the evaluations of renal histological and functional changes in rats continuously dosed with high dose lead. Glomerular filtration rate (GFR) was significantly increased at 3 months, but significantly decreased at 12 months. Lead inclusion bodies were noted throughout the duration of the study. Tubular atrophy and intestinal fibrosis appeared at 6 months. The brush border of proximal tubular cells was disrupted at 1 and 3 months, but recovered later.

With continued exposure to lead, acute nephropathy may progress to chronic interstitial nephritis that does not have any unique or distinguishing features. There is progressive increase in interstitial fibrosis, dilatation of tubules and formation of microcysts with hyperplasia of tubular epithelial cells. In the rat, inclusion bodies are reduced in number and may be entirely absent in later stages of the nephropathy. Glomerular sclerosis occurs with onset of proteinuria and renal failure (Goyer & Rhyne, 1973).

The sequence of morphological changes observed in experimental models is thought to be generally true for humans. Experimental studies in rats suggest that there may be a threshold for lead renal toxicity in the rat at PbB levels similar to those observed for humans. In rats exposed to different doses of lead for up to 12 weeks, a PbB level of 2.88 μmol/litre (60 μg/dl) appears to be the threshold for proximal renal tubular cell injury by lead (Goyer et al., 1989). This PbB level is equivalent to kidney lead levels of about 45 mg/kg wet weight and is the level of lead at which excretion of renal calcium increases and ultrastructural changes occur in proximal tubular cell mitochondria. This finding is consistent with the observation in humans by Buchet et al. (1980) and Gennart et al. (1992) of a threshold value of 2.88 μmol/litre (60 μg/dl) of PbB which leads to adverse renal effects by lead.

7.4 Cardiovascular system

Early studies concerning the production of hypertension in experimental animals, summarized in Environmental Health Criteria 3: Lead (IPCS, 1977), were conflicting. Among rats given 70 mg of lead acetate per day orally, only a few survived 40 days and all were hypertensive (Griffith & Landaver, 1944). On the other hand, other studies did not reveal a blood pressure effect from high-level lead exposure in rats (Padilla et al., 1969) or in dogs (Fouts & Page, 1942). More recently, several experimental studies have confirmed that lead can produce hypertension, and evidence for several plausible mechanisms has been provided. Rats, both normotensive and spontaneously hypertensive, exposed to lead in water supplies for up to a year, resulting in PbB levels of up to 0.6 μmol/litre (12.5 μg/dl), exhibited ventricular tachycardia and ventricular fibrillation (Evis et al., 1985). Subsequent studies (Evis et al., 1987) showed that adrenaline had a significant arrhythmogenic effect in hypertensive animals. It was concluded that chronic exposure to lead, when combined with high blood pressure, slightly enhances the susceptibility of the heart to arrhythmias induced by myocardial ischaemia. Overviews of the experimental evidence related to hypertension and lead exposure have been published by Victery (1988) and US EPA (1986a, 1989). Taken as a whole, these studies demonstrate that increase in blood pressure does occur secondary to renal failure in rats with continuous high-level exposure to lead. More recent studies on effects of chronic low-level exposure to lead on blood pressure in rats have shown alterations in cardiovascular parameters in the PbB range of 0.24-1.92 μmol/litre (5-40 μg/dl),

and provide some insights as to mechanisms involved in the pathogenesis of lead-related cardiovascular effects.

Victery et al. (1982a) exposed rats to lead *in utero* by giving dams drinking-water containing 0, 5, and 25 μg lead/ml and continued this regimen to the pups for 5 to 6 months. Although no change in blood pressure was noted at these levels of exposure, significant changes in the renin-angiotensin system were reported in animals given water containing 25 μg lead/ml with a PbB level of 0.864 μmol/litre (18 μg/dl). In a similar study (Victery et al., 1982b), exposure to 100 μg lead/ml in drinking-water (but not 500 μg/ml) produced a significant (17 mmHg) elevation in blood pressure beginning at 3½ months of age and continuing until 6 months of age. Chai & Webb (1988) found an elevation of 15 to 20 mmHg in the systolic blood pressure of rats given drinking-water containing 100 μg lead/ml. These authors suggest that alterations in the cellular mechanisms that regulate intracellular calcium concentration may enhance pressor responsiveness to catacholamines. Boscolo & Carmignani (1988) found raised blood pressure in rats with exposure to drinking-water containing 0, 30 or 60 μg lead/ml for 18 months. Cardiovascular responses to blood pressure agonists indicated that lead exposure affects the renin-angiotensin system and induces sympathetic hyperactivity by acting on central and peripheral sympathetic junctions, increasing the responsiveness to stimulation of alpha-2-adrenergic receptors, and by increasing sensitivity to stimulation of cardiac and vascular beta-adrenergic and dopaminergic receptors.

From the experimental evidence summarized by Victery (1988), it appears that low-level exposure to lead produces an elevation in blood pressure. The failure to demonstrate increased blood pressure in some studies with high-level exposure to lead suggests that the effect of lead on blood pressure may be biphasic, i.e. a consistent effect with low-level exposure but inconsistent effects with high-level exposure.

7.5 Reproductive system

Experimental studies on the effects of lead on the reproductive system most often concern toxicity to either the male or female but have addressed results of exposure to both parents. Environmental Health Criteria 3: Lead (IPCS, 1977) identified effects on spermatogenesis in rats exposed to lead and showed that high maternal exposure to lead in rats can reduce numbers and size of

offspring. There may also be paternally transmitted effects resulting in reductions of litter size, weights of offspring and in survival rate.

Few studies into the effects of lead on male sexual function have reported PbB levels. Ivanova-Chemishanska et al. (1980) reported changes in levels of enzymatic activity and ATP in testicular homogenates from rats given 0.0001 or 0.01% solutions of lead acetate as drinking-water over a 4-month period. Chowdhury et al. (1984) found testicular atrophy along with cellular degeneration in rats with PbB levels over 3.36 μmol/litre (70 μg/dl), but not in rats with levels of 2.59 μmol/litre (54 μg/dl). Donovan et al. (1980) found that lead inhibited androgen binding by cytosolic receptors in mouse prostate. Testicular homogenates from 2- to 3-week-old male offspring (PbB levels 0.30 μmol/litre, 6.3 μg/dl) of lead-exposed female rats showed a decreased ability to metabolize progesterone (Wiebe et al., 1982). In an *in vitro* study, Wiebe et al. (1983) found a 10 to 20% decrease in FSH binding and in the production of cyclic AMP by Sertoli cells isolated from prepubertal rats and cultured in the presence of lead acetate (2.64×10^{-4} mol/litre). In addition, the activity of cellular 3β-hydroxysteroid dehydrogenase was decreased. It was shown by Sokol et al. (1985) that there is a dose-related suppression of serum testosterone levels and spermatogens in adult rats (100 day of age) given a solution of 0.3% sodium acetate as drinking-water for up to 60 days. PbB concentrations were between 1.44 and 2.40 μmol/litre (30 and 50 μg/dl), depending on the length of treatment. Further studies (Sokol, 1987) supported the hypothesis that lead disrupts the hypothalamic control of pituitary hormone secretion. However, other evidence indicates that lead may directly or indirectly affect testicular enzymes or may act indirectly by a reduction in testicular binding of FSH and production of cyclic AMP (US EPA, 1986a).

Dosing mature female rats with lead in order to produce PbB concentrations of 1.44 μmol/litre (30 μg/dl) resulted in irregular estrous cycles. At a PbB level of 2.54 μmol/litre (53 μg/dl), animals developed follicular cysts and there was a reduction in the number of corpora lutea (Hilderbrand et al., 1973). Grant et al. (1980) reported delayed vaginal opening in rats whose mothers were given drinking-water containing 25, 50 and 250 μg lead/ml. The vaginal opening delays in the group given 25 μg lead/ml of drinking-water occurred in the absence of any growth retardation or other developmental delays and were associated with median PbB levels of 0.86-1.39 μmol/litre (18-29 μg/dl). Studies on

female monkeys have shown that pre- and/or postnatal exposure to lead can affect pubertal progression and hypothalamic-pituitary-ovarian-uterine functions. Chronic exposure of nulliparous female monkeys to lead (PbB levels of approximately 1.68 μmol/litre, 35 μg/dl) resulted in subclinical suppression of circulating luteinizing and follicle stimulating hormone and estradiol without producing overt effects on general health or menstruation (Foster, 1992).

7.6 Effects on bone

There is growing interest in lead in bone for several reasons. Bone is a store for lead accumulated from past exposure. It has a long biological half-life but may be mobilized and contribute to blood lead during pregnancy. With the development of X-ray fluorescence techniques to measure lead in bone *in vivo*, there is a need to improve our understanding of bone lead metabolism and of factors that influence lead retention and release. In addition, lead may adversely affect bone metabolism, particularly in post-menopausal women, and contribute to the development of osteoporosis. There has only been limited experimental study of these concerns to date, but there are some relevant reports in the literature.

A summary of much of the currently available literature on the potential toxicological implications of lead in bone during pregnancy and lactation is contained in a review by Silbergeld (1991). Toward the latter half of pregnancy in mice, there seems to be a preferential transfer of lead across the placenta to the fetus (Danielson et al., 1983). In rats exposed to lead for 150 days and then not exposed for 50 days prior to mating, Buchet et al. (1977) found that there was a substantial mobilization of lead from mother to fetus. Keller & Doherty (1980b) found using radiotracer lead (^{210}Pb) in female mice that there was also a major transfer of lead to the pup during lactation. The concomitant decrease in maternal bone lead supports the hypothesis that bone resorption of lead occurs during lactation.

It has been shown that lead may directly and indirectly affect various aspects of bone metabolism (Pounds et al., 1991). Lead inhibits the renal enzyme 1-hydroxylase, reducing plasma levels of 1,2-dihydroxychole-calciferol (activated vitamin D). Lead impairs the Haversian remodelling system in beagle dogs chronically exposed to lead (Anderson & Danylchuk, 1977).

7.7 Immunological effects

The effects of lead on the immune system are diverse but not well documented. Lead reduces resistance and increases mortality of experimental animals when they are infected by a broad range of bacterial and viral agents (Koller, 1984). Lead impairs antibody production in animals and generally decreases immunoglobin plaque-forming cells (Koller & Roan, 1980).

7.8 Mutagenicity

Lead is thought to have genotoxic properties. However, lead-induced gene mutations in cultures of mammalian cells have only been observed at concentrations toxic to the cells. Studies for point mutations in bacterial systems have also yielded negative results (US EPA, 1986a). Zelikoff et al. (1988) found that both insoluble lead sulfide and more soluble lead nitrate were mutagenic when added to Chinese hamster V79 cells. A 6-fold increase in mutation frequency was noted at a lead nitrate level of 500 μmol/litre medium. These authors also found that lead acetate induced morphological transformation of Syrian hamster cells. However, they concluded that these effects may not have been the result of direct damage to DNA but may have occurred via indirect mechanisms including disturbances in enzyme functions important in DNA synthesis and/or repair.

Studies on the production of chromosome aberrations, sister-chromatid exchanges and micronuclei by lead, whether in *in vitro* cultures or *in vivo*, have given mixed results, and summaries are available (US EPA, 1986a; IARC, 1987a,b; ATSDR, 1991).

7.9 Carcinogenicity

There have been several experimental studies in rats and mice in which long-term administration of a lead compound in food or drinking-water or parental administration has produced tumours of the kidney (Van Esch & Kroes, 1969; Moore & Meredith, 1979). These and other studies have been discussed in detail in IARC (1980) and summarized in US EPA (1986a). In general, methodological problems, including dose levels, number of animals, and doses, and lack of toxicity monitoring, make many of the studies difficult to interpret in a quantitative manner. One study (Azar et al., 1973) addressed some of these problems and reported an increase in the numbers of renal tumours in rats fed diets containing 500 mg lead/kg for 2 years. PbB levels were

3.84 μmol/litre (80 μg/dl). In all studies renal carcinogenicity occurred against a background of proximal tubular cell hyperplasia, cytomegaly and cellular dysplasia in response to the high doses of lead and long exposure times (Goyer, 1985). Renal adenocarcinoma occurred in a high percentage of lead-exposed animals and the incidence of tumours was related to the length and severity of exposure (Mao & Molnar, 1967). Males appear to be more susceptible to tumours than females. The maximum dose of lead in drinking-water, not associated with any morphological or functional evidence of renal toxicity in rats fed a diet containing adequate levels of trace minerals, particularly calcium, is 200 mg lead/litre (Goyer et al., 1970). No evidence of renal tumours at doses below this value has been reported (Azar et al., 1973; US NCI, 1979).

Several hypotheses have been proposed for the mechanism of lead carcinogenicity in experimental animals. These include mutagenicity, cellular proliferation, nuclear protein (inclusion bodies), promoter activity, activation of protein kinase C, and cystic hyperplasia (Goyer, 1993). Lead is a weak mutagen in mammalian cell systems, but is a strong mitogen. Exposure to a single intraperitoneal injection of lead acetate in rats stimulates a 40-fold increase in cell proliferation as measured by autoradiography, and this is further increased by unilateral nephrectomy (Choie & Richter, 1972). DNA synthesis in kidneys, as measured by ^{3}H-thymidine incorporation, is increased 15-fold and the mitotic index 45-fold following a single intracardiac injection of lead acetate in mice (Choie & Richter, 1974). Cell proliferation and hyperplasia are seen in the liver of rats given a single intravenous injection of lead nitrate (Columbano et al., 1984). In both of these studies, increases in cell proliferation occurred in the absence of cellular necrosis, suggesting that this was a mitogenic rather than regenerative response.

Activation of protein kinase C and formation of nuclear inclusion bodies or lead protein complexes are additional events that may influence regulation of cell growth and development and play a role in the carcinogenic response in experimental animals resulting from administration of lead (Goyer, 1993). Cystic hyperplasia, a late morphological manifestation of chronic lead nephropathy, is a risk factor for renal cancer (Bernstein et al., 1987). Prior to adenoma formation in animals treated with renal carcinogens, cystic hyperplasia was reported (Dees et al., 1980; Goyer et al., 1981).

8. EFFECTS ON HUMANS

Despite the long recognition of lead poisoning, new clinical cases continue to be the subject of published reports. Although important, they affect a comparatively small proportion of the population at risk from the potential effects of exposure to environmental lead.

Over the last 10–15 years, particular attention has been directed towards epidemiological studies designed to evaluate the possible neurotoxic effects of lead on the developing child, especially delayed or impaired neurobehavioural development and performance.

In the adult population, considerable attention has been directed towards evaluating cardiovascular effects and the implication of lead in hypertension.

New studies have contributed to our understanding of the biochemical effects of lead, and may facilitate early recognition of significant change and mitigation of potentially adverse outcomes.

The effects of lead have been studied widely in both the general population and in those exposed occupationally. Since these effects are the same in both settings, no distinction has generally been made in the discussion. However, it is often important to distinguish between adults and children because of different susceptibility.

8.1 Biochemical effects of lead

Lead is known to affect a number of enzymes and physiological systems which result in a wide variety of changes in humans. While those affecting the haematopoietic system are well known, there are others which need to be considered in the risk assessment process and are considered in this section.

In considering the effects of lead on biochemical systems, it is appropriate to discuss the form of the lead in the various body compartments.

Blood lead (PbB) is distributed between the plasma and the erythrocyte. There is less than 1% in the plasma for PbB levels of

up to 4.8 μmol/litre (100 μg/dl) (Manton & Cook, 1984). The curvilinear relationship of serum lead to blood lead is shown in Fig. 12. The data show that the erythrocytes have a capacity to bind lead up to PbB levels of about 2.4 μmol/litre (50 μg/dl). Above this level a fairly rapid increase in the serum levels occurs.

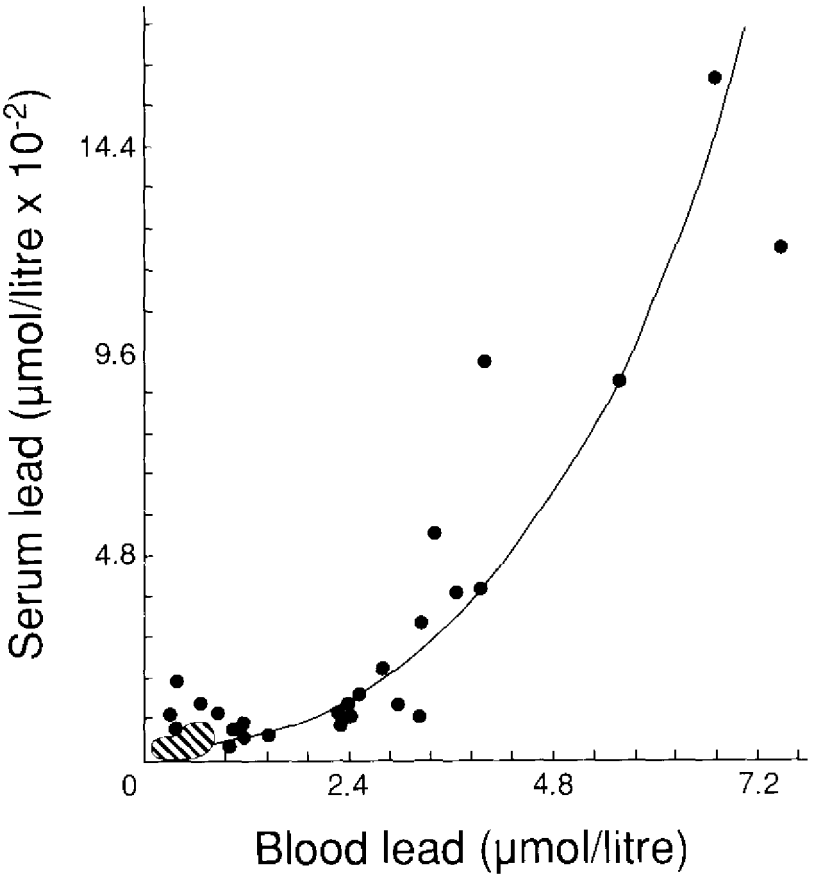

Fig. 12. The curvilinear relationship of serum lead to blood lead levels (the hatched area contains 23 points) (adapted from: Manton & Cook, 1984)

It should be noted that the proportion of "free" (i.e. unbound) lead in blood is important in relation to biological activity. Lead is bound to haemoglobin in blood and has a greater affinity for fetal than adult haemoglobin (Ong & Lee, 1980). It may, therefore, be important to consider the proportion of fetal haemoglobin present in blood samples from mothers and infants in assessing PbB concentrations in relation to biological effects. Also, increased fetal haemoglobin has been found in cases of human and experimental animal poisoning (Albahary, 1972).

8.1.1 Haem synthesis

Lead is known to affect several enzymatic reactions critical in haem synthesis, causing abnormal concentrations of haem precursors in blood and urine. These effects of lead on haem synthesis are shown in Fig. 13.

As shown in Fig. 13, lead inhibits the activity of three enzymes of the biosynthetic pathway, 5-aminolaevulinate dehydratase (ALA-D), coproporphyrinogen oxidase (COPRO-O) and ferrochelatase (FERRO-C). This depletes haem synthesis and depresses the synthesis of the initial and rate-limiting enzyme 5-aminolaevulinate (ALA) synthase. As a consequence there is increased production and excretion of the precursors ALA and coproporphyrin (COPRO) with increased circulatory protoporphyrin (PROTO) usually bound to zinc. In the red cell, diminished synthesis of monooxygenases (cytochromes P450) compromises drug oxidation and lead is bound to haemoglobin.

8.1.1.1 Protoporphyrin levels

Lead interferes with the conversion of protoporphyrin to haem by ferrochelatase. The protoporphyrin exists under these circumstances primarily as zinc protoporphyrin, with a proportion remaining free (Chisolm & Brown, 1979).

The relationship between protoporphyrin, either free or as the zinc chelate, in blood and blood lead is one which could be interpreted as showing a "threshold of effect" or as a continuum of effect. The exact mathematical relationship is inevitably the choice of the investigator since the uncertainties in the measurement of blood lead and blood protoporphyrin would allow the fitting of the data to either of these relationships. The threshold concept is satisfactory to those that seek the "no-effect

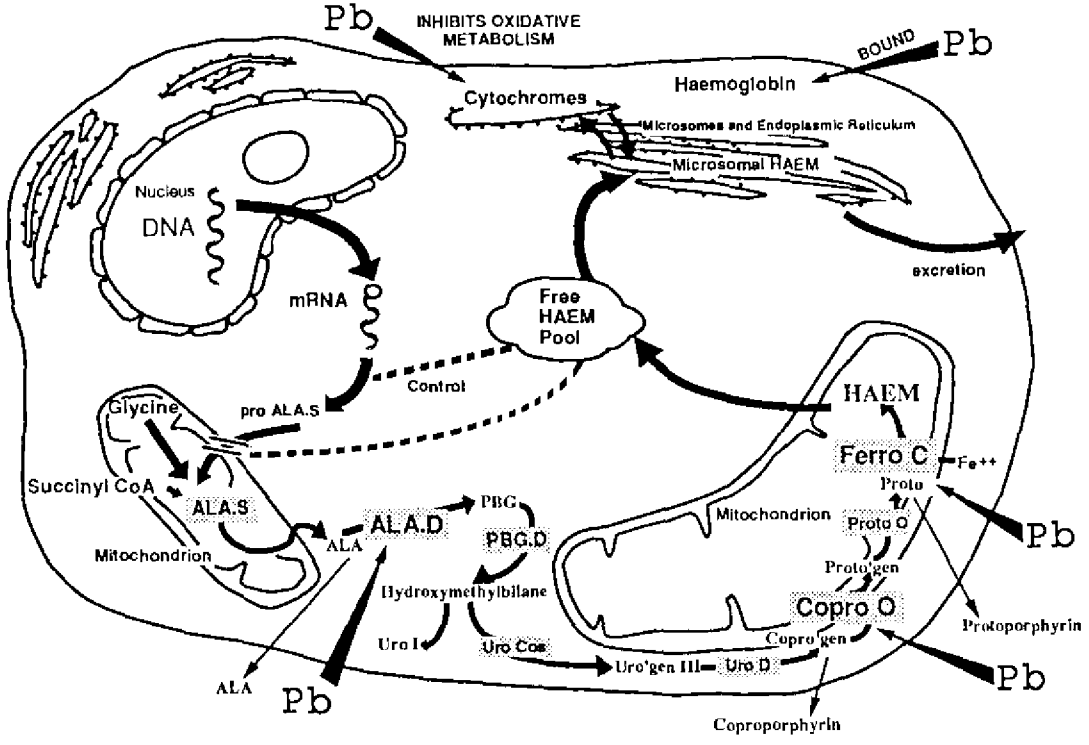

Fig. 13. The effects of lead on haem synthesis (personal communication by M. Moore to the IPCS, 1993)

level" (Succop et al., 1989), since it provides the start point of an analytical identification process. The continuum of effect is, however, much more plausible in a biological sense, since the idea of a level at which "no effect" will occur is unlikely in a biological system.

The figures for the relationship between PbB and zinc protoporphyrin are confused in any population by iron status (Marcus & Schwartz, 1987), and it is thus unlikely that measurement of zinc protoporphyrin, either alone or compared with haemoglobin status, will provide an accurate estimation of PbB levels less than 0.96 μmol/litre (20 μg/dl). In a study of the relationship between PbB levels and erythrocyte protoporphyrin concentration for 2004 urban children (Piomelli et al., 1982), it was concluded that a threshold is apparent and occurs at a PbB level of between 0.72 and 0.86 μmol/litre (15 and 18 μg/dl). This is consistent with the data of Roels et al. (1976), which show a clear discontinuity at around 1.2 μmol/litre (25 μg/dl). Marcus & Schwartz (1987) re-analysed data from the NHANES II survey of 264 children. No positive correlation between PbB and zinc protoporphyrin was noted below 0.96 μmol/litre (20 μg/dl).

Other reports which present relevant data are Roels et al. (1976); Piomelli et al. (1982); Hammond et al. (1985); Rabinowitz et al. (1986); Roels & Lauwerys (1987). In the presence of iron deficiency the observed threshold is likely to be lower (Mahaffey & Annest 1986; Marcus & Schwartz, 1987). At first sight it would seem inappropriate to consider thresholds that are determined in the presence of potential iron deficiency.

A study by Koren et al. (1990) of maternal and umbilical cord lead and free erythrocyte porphyrin (FEP) levels for 95 mother-infant pairs showed a correlation between maternal and cord PbB, with maternal levels exceeding neonatal levels. Most cord PbB levels were below 0.33 μmol/litre (7 μg/dl), and 11 were below the detection limit. The cord blood FEP (0.86 μmol/litre) level was consistently higher than maternal FEP (0.53 μmol/litre) but was not statistically correlated. The elevated cord blood FEP values were attributable to immature haem synthesis and high erythrocyte volume rather than the presence of lead.

8.1.1.2 *Coproporphyrin levels*

One of the earliest observed effects of lead poisoning was a rise in coproporphyrin excretion in the urine, due to inhibition of

coproporphyrinogen oxidase (Campbell et al., 1977). Although often cited as a good measure of lead exposure it is clear that the importance of the measure of current environmental levels of exposure is small. This is because the excretion levels do not rise significantly until the PbB excretion is greater than 1.92 μmol/litre (40 μg/dl) (Meredith et al., 1978).

8.1.1.3 δ-Aminolaevulinic acid levels in urine and blood

Like protoporphyrin, circulating and excreted levels of ALA are likely to be best described as a continuum of effect. Elevated levels of this compound are of importance since neurological features of lead exposure have been ascribed in part to increased circulating levels of ALA (Moore et al., 1987). The rise in concentration during lead exposure is a function first of decreased activity of ALA dehydratase (ALAD), which is uniquely sensitive to lead toxicity, and subsequently of increased activity of the initial and rate-limiting enzyme of haem biosynthesis, ALA synthase (Meredith et al., 1978). It is inappropriate to discuss haem biosynthesis control mechanisms here; suffice it to say that blocking this pathway by lead lowers free haem levels, which feedback to ALA synthase (Moore et al., 1987). The special relationship between ALAD activity and lead exposure has been best described as a negative exponential and has been used as a measure of lead exposure in population surveys (Berlin & Schaller, 1974).

The immediate effect of the inhibition of ALAD will be an increased level of ALA in the blood, which will then lead to increased urinary excretion. The plasma levels of ALA are elevated in the presence of higher lead levels. This has been seen in a number of studies (Haeger-Aronsen, 1960; Meredith et al., 1978; O'Flaherty et al., 1980).

Meredith et al. (1978) measured ALA metabolism in 48 male lead-exposed workers (aged 22-56 years, PbB 4.2 ± 1.4 μmol/litre, 87 ± 29 μg/dl), who were compared with control subjects (28 male, 9 female, 18-52 years of age, PbB 1.3 ± 0.4 μmol/litre, 27 ± 3.3 μg/dl). They found increasing levels of circulating ALA associated with PbB that reached a plateau when the PbB level was in excess of 3 μmol/litre (62 μg/dl) and ALA exceeded 4 μmol/litre. At higher blood ALA levels, urinary excretion of ALA increased exponentially, consistent with decreased tubular reabsorption. The authors suggested that there was a "critical" tissue lead concentration of around 2 μmol/litre (41 μg/dl). This

study showed some continuity of the correlation down to the lowest PbB value of the control group, namely 0.86 μmol/litre (18 μg/dl). However, these data were interpreted to show that effects are only demonstrable above a PbB level of 1.44 μmol/litre (30 μg/dl).

Other studies show direct correlations between PbB level and urinary ALA (Selander & Cramer, 1970; Lauwerys et al., 1974), although these correlations are not seen as low as those in the study of Meredith et al. (1978). The data of Selander & Cramer (1970) showed a clear threshold effect at about 1.02 μmol/litre (40 μg/dl) in occupational subjects.

Roels et al. (1976) reported data over a range of PbB levels from 0.24 to 1.92 μmol/litre (5 to 40 μg/dl) in children which showed essentially no correlation with urinary ALA.

Data obtained from 39 men and 36 women in the general population showed that increased urinary excretion of ALA occurred at PbB levels of more than 1.68 μmol/litre (35 μg/dl) in women and more than 2.16 μmol/litre (45 μg/dl) in men (Roels & Lauwerys, 1987). The sensitivity of the haem synthesis pathway to increased lead exposure was in the order: children ≥ women ≥ men.

On balance, it would appear that lead has discernible effects on the urine level of ALA at a PbB level of around 1.68 μmol/litre (35 μg/dl).

8.1.1.4 δ-Aminolaevulinic acid dehydratase levels

δ-Aminolaevulinic acid dehydratase (ALAD) is commonly measured for its activity in samples of haemolysed blood; the result may or may not be corrected for haematocrit value. The measure of enzyme activity will reflect the amount of enzyme present as well as the effect of inhibition of the enzyme.

Studies in the general population have confirmed the correlation and the apparent lack of a threshold for inhibition of ALAD in different age groups and exposure categories (Roels et al., 1976; Chisolm et al., 1985; Roels & Lauwerys, 1987). A negative linear relationship between PbB and ALAD activity was found between mothers and their newborn babies (cord blood); PbB levels ranged from 0.14 to 1.44 μmol/litre (3-30 μg/dl) (Roels et al., 1976). Roels & Lauwerys (1987) reported a similar

relationship in a population of 143 children aged 10-13 years having PbB levels of 0.19-1.97 μmol/litre (4.7-41 μg/dl).

In the study of Roels et al. (1976) a large number of children were studied. Although the authors drew a regression line which suggested that the effects continued to very low levels, the data between 0.24-0.72 μmol/litre (5-15 μg/dl) were very scattered, and the regression at low levels appeared to be rather speculative. It was considered that the lead level above which an effect level is demonstrable from these data was 0.48 μmol/litre (10 μg/dl).

8.1.1.5 δ-Aminolaevulinic acid synthase

Aminolaevulinic acid synthase (ALAS) levels are determined by a feedback mechanism which is dependent on haem levels. There appear to have been relatively few studies on serum ALAS, although some consideration is given in a report by Meredith et al. (1978). However, insufficient data were available to establish effect levels for lead exposure.

8.1.1.6 Other effects of decreased haem synthesis

The potential impact of a reduction in the body pool of haem and haem precursors is shown in Fig. 14. It is evident that the multiple effects on haem metabolism from lead exposure can lead to adverse effects in organs and systems other than the erythropoietic system.

8.1.2 Vitamin D

Formation of the most important vitamin D metabolite, 1,25-dihydroxyvitamin D, is by 1 α-hydroxylation of 25-hydroxyvitamin D in the kidney. This is mediated by 25-hydroxyvitamin D-1 α-hydroxylase, a cytochrome P450-dependent enzyme in the mitochondria of the renal tubules. Serum concentrations of 1,25-dihydroxyvitamin D are measured in children as an indicator of the effects of lead on the enzyme system mediating the initial hydroxylation. However, other factors such as dietary intake and the physiological needs for calcium and phosphorus, and levels of calciotropic hormones such as parathyroid hormone, can regulate the production and circulating concentrations of 1,25-dihydroxyvitamin D (Rosen & Chesney, 1983).

Several studies have provided information on the effect of lead on the circulating concentrations of 1,25-dihydroxyvitamin D.

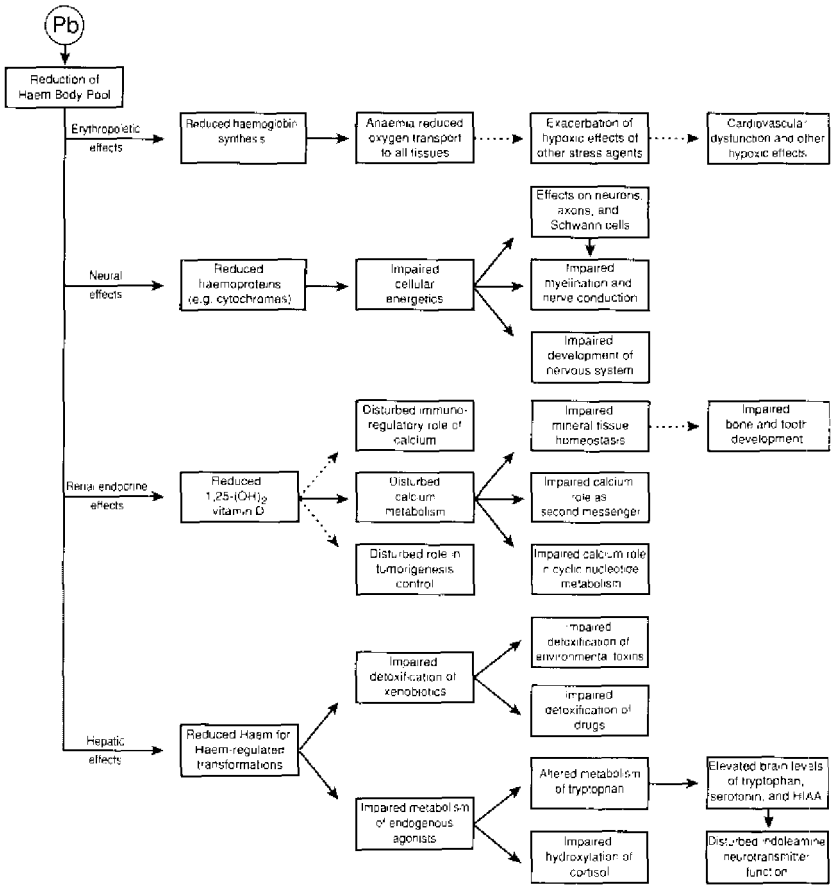

Fig. 14. Potential multi-organ impact of reduction of the haem body pool by lead (US EPA, 1986a)

Rosen et al. (1980) studied children with PbB levels in the range of 1.58-5.76 μmol/litre (33-120 μg/dl). While the most striking decreases in serum 1,25-dihydroxyvitamin D occurred in children whose PbB level was 2.97 μmol/litre (62 μg/dl), the effect was considered to be evident in the range of 1.58-2.64 μmol/litre (33-55 μg/dl) when compared to an age- and race-matched control group with PbB levels in the range of 0.48-1.248 μmol/litre (10-26 μg/dl).

Mahaffey et al. (1982) measured serum 1,25-dihydroxyvitamin D in 177 subjects aged 1-16 years. PbB lead measurements were performed in 105 of these children and ranged from 0.576 to 5.76 μmol/litre (12 to 120 μg/dl). A curvilinear relationship between serum 1,25-dihydroxyvitamin D concentration and PbB was noted in children aged 2 to 3 years. Details of the dietary intake of the subjects were not available.

Koo et al. (1991) studied 105 children, aged 1 to 3 years and with detailed lead exposure history from birth, to determine the effect of chronic low to moderate lead exposure. The average lifetime PbB concentration was 0.23-1.13 μmol/litre (4.8-23.6 μg/dl) and was greater than 0.96 μmol/litre (> 20 μg/dl) in only three children. With a range of concurrent PbB concentrations of 0.29-2.11 μmol/litre (6-44 μg/dl). The children generally had adequate dietary intakes of calcium, phosphorus and vitamin D. An effect of lead was found on serum concentrations of calcium, phosphorus, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and parathyroid hormone, and on bone mineral content. In the presence of adequate nutritional status, lead exposure at low levels (leading to a PbB level of less than 0.96 μmol/litre or 20 μg/dl) appears to have no demonstrable effect on circulating concentrations of total and ionized calcium, magnesium, phosphorus, calciotropic hormones including 1,25-dihydroxyvitamin D, parathyroid hormone and calcitonin, or bone mineralization as indicated by single photon absorptiometry. At higher levels there is a demonstrable effect on 1,25-dihydroxyvitamin D.

8.1.3 *Dihydrobiopterin reductase*

This enzyme (DHBR) is part of the synthesis/salvage cycle which controls the hydroxylation of tyrosine, tryptophan and phenylalanine. It is thus central to the synthesis of the catecholamines. Lead has been shown to inhibit the synthesis of tetrahydrobiopterin from dihydrobiopterin by dihydrobiopterin reductase (Leeming & Blair, 1980; McIntosh et al., 1985) in rat

brain. In humans the exact relationship between PbB and plasma biopterins has not been properly defined.

8.1.4 Nicotinamide adenine dinucleotide synthetase

A recent study of nicotinamide adenine dinucleotide (NAD) synthetase in erythrocytes indicates that this enzyme is sensitive to inhibition by lead (and zinc) and is a sensitive indicator of lead exposure. Zerez et al. (1990) found NAD synthetase activity reduced in three subjects with elevated PbB levels in the range 1.63-3.46 μmol/litre (34-72 μg/dl).

8.1.5 Nutritionally affected groups

A body of evidence, summarized and discussed by Mahaffey (1985), indicates that a high dietary calcium intake tends to decrease lead absorption and retention in infants, young children and adults. Other evidence suggests that in groups including children, with self-selected diets, low dietary calcium intakes are associated with a greater prevalence of elevated PbB levels (Mahaffey, 1985).

Some human data indicate that adults with low iron states have an increased absorption of both iron and lead (Watson et al., 1980, 1986). In children, particularly those from low-income families, there is often an association between iron deficiency and elevated PbB (Yip & Dallman, 1984; Mahaffey, 1985). While this by itself does not indicate a causal relationship, when considered in the context of data on adults and animals, it suggests that iron deficiency in children can result in increased lead absorption.

Alcoholics and people who consume excess alcohol may be at increased risk of adverse effects from lead. In animal studies, alcohol and lead synergistically inhibit ALAD, hepatic glutamic oxaloacetic transaminase and glutamic pyruvic transaminase activities (Flora & Tandon, 1987) supporting the hypothesis regarding risks to humans.

8.2 Haematopoietic system

Lead-induced anaemia can be a direct consequence of inhibition of haem biosynthesis; it is not necessarily associated with iron deficiency. It may be associated with alterations of globin syntheses (Albahary, 1972). More importantly, the synthesis of α- and β-globin chains may become asynchronous (White & Harvey, 1972).

8.2.1 Anaemia

Based on data published by Lilis et al. (1978), Baker et al. (1979), Grandjean (1979), and earlier data, the threshold PbB level for a decrease in haemoglobin has been estimated to be 2.40 μmol/litre (50 μg/dl) for occupationally exposed adults (US EPA, 1986a).

Grandjean et al. (1989a) demonstrated the reduced ability of the erythropoietic system to regenerate after blood withdrawal (0.45 litre) in 25 lead-exposed battery workers (average PbB level 2.14 μmol/litre, 44.5 μg/dl) compared with 25 age-matched controls (average PbB level 0.35 μmol/litre, 7 μg/dl). The haematological parameters, except for erythropoietin were otherwise comparable for the two groups. The effect was attributed to an effect on haem synthesis and possible decreased erythrocyte survival in lead-exposed workers. Lead has been found to depress serum levels of erythropoietin, a hormone which regulates erythrocyte formation (Graziano et al., 1991), which might also affect the reserve capacity for erythropoiesis.

The PbB threshold for decreased haemoglobin levels in children is estimated to be approximately 1.92 μmol/litre (40 μg/dl) (IPCS, 1977). However, a cross-sectional epidemiological study of 579 children, aged 1-5 years in 1974, living in close proximity to a primary lead smelter showed that adverse effects on haematocrit may occur at lower PbB levels (Schwartz et al., 1990). Anaemia, defined as a haematocrit below 35%, was not found at PbB levels of less than 0.92 μmol/litre (20 μg/dl). There was a strong non-linear dose-response relationship at higher PbB levels, which was influenced by age.

Kutbi et al. (1989) studied 200 boys aged 6-8 years. The mean PbB was 0.33 μmol/litre (6.9 μg/dl; range 0.07-1.14 μmol/litre or 1.4-23.8 μg/dl). Subdividing the group at 0.72 μmol/litre (15 μg/dl), they found a negative correlation between PbB level and all haematological values for the "upper normal" (N = 7) compared with the "normal" group (N = 193). The pattern of haematological parameters was described as predictive of microcytic anaemia.

Anaemia has been commonly associated with the adverse effects of occupational lead exposures. It is an effect that is easily diagnosed clinically and is recognized as a marker of lead toxicity. Anaemia may result from either a decrease in haemoglobin

production or an increase in the rate of destruction of erythrocytes. An analysis, made in 1974, of the association between PbB levels and haematocrit in 579 children (1-5 years of age) living near a primary lead smelter has recently been presented (Schwartz et al., 1990). A haematocrit value of less than 35% was used to indicate an adverse effect. It should be noted that the effect of iron deficiency was not taken into account in analysing the results. The study concluded that there was no adverse effect of lead at PbB levels below 0.96 μmol/litre (20 μg/dl). Furthermore, the risk of having a haematocrit value below 35% for 1-year-olds was 2% at PbB levels between 0.96 and 1.87 μmol/litre (20 and 39 μg/dl). The degree of iron deficiency may account for a substantial proportion of this 2%. In this study, the level at which an effect of lead on the induction of anaemia was demonstrable was about 1.92 μmol/litre (40 μg/dl).

8.2.2 *Pyrimidine-5'-nucleotidase activity*

Inhibition of erythrocyte pyrimidine-5'-nucleotidase leads to accumulation of pyrimidine nucleotides, which has been associated with induction of basophilic stippling.

Impaired function of erythrocyte pyrimidine-5'-nucleotidase occurs in lead-exposed workers and as a genetically induced enzyme deficiency. In *in vitro* systems the enzyme is inhibited by lead, cadmium, mercury and zinc ions (and perhaps other metal ions) (Paglia et al., 1975; Pagliuca et al., 1990; Ichiba & Tomokuni, 1990).

Graphs of PbB concentration against erythrocyte pyrimidine-5'-nucleotidase activity in children have been reported for 21 children aged 2-5 years (Angle & McIntire, 1978) and for 42 aged 1-5 years (Angle et al., 1982) who participated in a preventative programme because they had previously had PbB levels above 1.44 μmol/litre (30 μg/dl) or zinc protoporphyrin (ZPP) greater than 60 μg/dl. Both plots show considerable scatter although there was a significant inverse logarithmic correlation. However, data relating to the reproducibility, precision and accuracy of assessing inhibition of erythrocyte pyrimidine-5'-nucleotidase were not presented.

This test may be capable of analytical refinement when assessment of the sensitivity to lead (and other metals) exposure might more reasonably be made. It does not yet appear likely to provide a routine measure for low-lead exposure assessment.

8.2.3 Erythropoietin production

Graziano et al. (1991) found depressed serum erythropoeitin levels in females at mid-pregnancy and at delivery associated statistically with PbB level. Erythropoietin is a glycoprotein produced in the renal proximal tubules which regulates both steady-state and accelerated erythrocyte production. The study was not adequate to define a dose-response relationship.

8.3 Nervous system

8.3.1 Historical perspective

Gross toxic effects of lead on the nervous system were reported by ancient Greek physicians. A brief summary of such reports, and those of Roman physicians and 18-19th century toxicologists, was published by Kazantzis (1989). The syndrome was known as "painter's colic", which included abdominal pain, constipation and paralysis, symptoms now covered by the term "lead encephalopathy".

Lead colic was usually accompanied by effects on the nervous system (lead palsy) in cases of acute and chronic poisoning, which were often but not always fatal. Lead poisoning was well recognized as an occupational hazard. However, it was also associated with consumption of lead-contaminated water, wine, cider, rum from the West Indies, and food prepared or stored in lead or lead-glazed utensils. For example, Kazantzis (1989) described cases of lead poisoning in girls resulting from consumption of drinking-water kept in lead-lined cisterns, and also described the Devonshire colic attributed by Sir George Baker in 1767 to the consumption of cider prepared in presses made of lead or lead alloys.

The early toxicologists clearly recognized that the dose (exposure) and form of lead was important in relation to absorption and were able to demonstrate the presence of lead in tissues of fatal cases of poisoning. There are many individually described, detailed case studies in their writings.

8.3.2 Neurotoxic effects in adults

Despite the long recognition of lead poisoning, new clinical cases continue to be the subject of published reports (Cueto et al., 1989; Kocak et al., 1989; Zuckerman et al., 1989; Friedman &

Weinberger, 1990; Gupta et al., 1990; Mitchell-Heggs et al., 1990; Nosal & Wilhelm, 1990; Sharma et al., 1990; Schneitzer et al., 1990; Veerula & Noah, 1990). Although they are important, the numbers of these poisoning cases are comparatively small compared with the population at risk to the potential effects of exposure to lead from environmental and dietary sources. Of particular recent concern have been the possible neurotoxic effects on the developing child.

8.3.2.1 Central nervous system

In a study of 158 secondary lead smelter workers, Lilis et al. (1977) found that 64% reported CNS symptoms and that there was early occurrence of symptoms within 1 year of exposure. PbB concentrations were elevated (about 3.36 μmol/litre or 70 μg/dl) at the time of examination but many of the subjects had received chelation therapy.

Fischbein et al. (1979) noted CNS symptoms in 21 of 81 employees of law enforcement agencies working in firing ranges. Symptoms correlated with PbB levels and were present in three-quarters of subjects having a PbB level ≥ 2.4 μmol/litre (50 μg/dl).

Hanninen et al. (1979) reported that 49 lead-exposed workers (including 21 male and 8 female storage battery and 16 railroad engineering workshop employees) whose PbB level had never exceeded 3.36 μmol/litre (70 μg/dl) experienced more subjective symptoms than a control group; excess symptoms were proportional to lead uptake.

Fischbein et al. (1980) studied 90 telephone cable splicers having intermittent exposure to lead. They reported that 26 complained of CNS symptoms (mean PbB level of 1.36 μmol/litre, 28.4 μg/dl, and ZPP of 70.3 μg/dl) compared with controls (mean PbB level of 1.32 μmol/litre, 27.4 μg/dl, and ZPP of 49.3 μg/dl).

Awad El Karim et al. (1986) studied 92 lead acid battery workers and compared them with 40 oil mill worker controls. They found CNS symptoms in 50% of lead-exposed workers and measured PbB levels in 46 subjects working in different sections of the plant. More than 95% of exposed workers had PbB levels above 1.92 μmol/litre (40 μg/dl), whereas the mean PbB in the control group was 1.0 μmol/litre (21 μg/dl).

Impairment of psychological and neuropsychological test performance has been reported for lead-exposed workers (Hanninen et al., 1979; Hogstedt et al., 1983; Parkinson et al., 1986; Araki et al., 1986a,b; Huang et al., 1988a; Stollery et al., 1989, 1991).

The critical flicker fusion test has been reported to be a sensitive indicator of CNS changes associated with exposure to lead. Wooller & Melamed (1978) found significantly lower critical flicker fusion in subjects with PbB levels above 2.88 μmol/litre (60 μg/dl) than in those with levels below 0.96 μmol/litre (20 μg/dl). Williamson & Teo (1986) found a significant decrease in mean flicker fusion in 59 lead-exposed workers (mean PbB > 2.3 μmol/litre or 48 μg/dl) compared with matched controls. However, Gennart et al. (1992b) found no difference between lead-exposed workers (mean PbB level 2.45 μmol/litre or 51 μg/dl, N = 98) and controls (mean PbB level 1.00 μmol/litre or 20.9 μg/dl, N = 85).

Stollery et al. (1989) studied the performance of 91 men, occupationally exposed to inorganic lead, in a series of tests designed to assess cognitive function. Subjects were grouped in "low" (mean PbB 0.48 μmol/litre or 10 μg/dl, mean ZPP 8.7 μg/dl, N = 28), "medium" (mean PbB 1.44 μmol/litre or 30.1 μg/dl, mean ZPP 22.4 μg/dl, N = 27) and "high" (mean PbB 2.43 μmol/litre or 50.7 μg/dl, mean ZPP 58.8 μg/dl, N = 36) ranges of PbB concentrations. Results showed that occupational exposure to lead impaired performance in a range of tests (sensory motor reaction time, memory, attention, verbal reasoning, spatial processing). Workers having PbB levels in excess of 1.92 μmol/litre (40 μg/dl) showed clear evidence of impairment on tests of serial reaction time and category search. The authors concluded that sensory motor, rather than cognitive, requirements of many psychological tasks provide the most sensitive index of the early effects of chronic low level lead exposure.

In a follow-up study (Stollery et al., 1991), 70 workers were re-tested (three times within 8 months). Performance deficits in the "high" (mean PbB 2.49 μmol/litre or 51.8 μg/dl, mean ZPP 77.4 μg/dl, N = 22) group were not altered by practice or continued exposure. The main deficit was a slowing of sensory motor reaction time coupled with difficulties in remembering incidental information. There was little evidence of impairment in workers having PbB levels less than 1.92 μmol/litre (40 μg/dl).

Finally, it appears that neuroelectrophysiological testing is a sensitive and objective indicator of the CNS effects of lead. The results of Araki et al. (1986b, 1987, 1992) using short-latency somatosensory and visual evoked potentials and auditory event-related potential (P300) indicate that subclinical electrophysiological effects of lead occur not only in peripheral nerves but also in the CNS.

8.3.2.2 *Peripheral nervous system*

Peripheral neuropathy is a common sign of chronic, high level lead exposure, often manifesting as weakness in the upper or lower limbs. At lower levels of lead exposure, nerve conduction velocity (NCV) has provided a more sensitive indicator of peripheral nerve dysfunction. More than 30 published studies have measured the conduction velocity of electrically stimulated sensory and motor nerves in workers exposed to lead. However, these studies have yielded somewhat mixed results, with many showing a decrease in NCV in relation to lead exposure (generally indexed as PbB concentration) and a few showing no effect or occasionally even an increase in NCV associated with lead exposure (Seppäläinen & Hernberg, 1980; Davis & Svendsgaard, 1990).

Various reasons may underlie this lack of uniformity in NCV findings. For example, studies may differ in methodological features, in the characterization of lead exposure (e.g., single time-point versus time-weighted average PbB levels) or in the handling of confounding variables such as nerve temperature and age of subject (Ehle, 1986). Other important factors accounting for some of the apparent inconsistency in this area of research may be the possible antagonistic effect of zinc to lead and differences in nerves selected for measurement in different studies (e.g., slow versus fast fibres (Araki et al., 1986c; Murata & Araki, 1991). A statistical meta-analysis and critical review of 32 NCV studies by Davis & Svendsgaard (1990) indicated that the median motor nerve shows effects of lead more reliably than other nerves (e.g., median sensory or ulnar).

Despite these complications, certain key well-conducted studies provide compelling evidence of a causal relationship between lead exposure and reduction in NCV. Araki et al. (1980) measured median motor NCV before and after PbB levels of workers were lowered through chelation therapy. Depending on the amount of reduction in PbB level achieved by chelation and on a given worker's baseline NCV, significantly improved NCV was

measured in 7 out of 14 lead-exposed workers. For all 14 workers the improvement in NCV was significantly correlated with the decrease in PbB level ($r = -0.573$, $P < 0.001$).

In another key study, Seppäläinen et al. (1983) followed workers prospectively from the beginning of their employment in a battery plant, dividing them into two exposure categories (above and below the median PbB level of 1.44 μmol/litre (30 μg/dl). Median motor NCV was significantly reduced in the workers with blood lead levels above 1.44 μmol/litre (30 μg/dl) at 1-, 2-, and 4-year evaluation points, despite attrition (and reduced statistical power) that resulted in only five subjects per group after 4 years. Based on this well-conducted prospective study, 1.44 μmol/litre (30 μg/dl) would appear to be the lowest-observed-adverse-effect level for reduced NCV in adults. Although another well-conducted prospective study (Spivey et al., 1980) was unable to find an effect of lead on NCV at higher exposure levels, NCV in the median nerve was not measured in that study. Triebig et al. (1984) reported a dose-dependent decrease in NCV at PbB levels above 3.36 μmol/litre, no dose-effect relationship being detectable below this concentration.

8.3.2.3 Autonomic nervous system

There have been two reports of tests for autonomic nervous function following lead exposure. Teruya et al. (1991) conducted a cross-sectional survey of 172 male workers exposed to lead (mean PbB level, 1.73 μmol/litre or 36 μg/dl, range 0.24-3.648 μmol/litre or 5-76 μg/dl), by measuring electrocardiographic R-R interval variability (CV_{RR}). Age-adjusted CV_{RR} during deep breathing in workers with PbB levels above 1.44 μmol/litre (> 30 μg/dl) was significantly decreased as compared to those with PbB levels less than 0.96 μmol/litre (< 20 μg/dl). In addition, significant dose-response and dose-effect relationships were observed between the PbB levels and R-R interval variation during deep breathing among the workers with PbB levels above 0.96 μmol/litre (> 20 μg/dl).

In a study reported by Murata & Araki (1991), the R-R interval (CV_{RR}) and two component coefficients of variation in the R-R interval (C-CV_{RSA}) were measured in 16 gun metal foundry workers exposed to lead, zinc and copper (mean PbB level, 1.63 μmol/litre or 34 μg/dl, range 0.768-2.88 μmol/litre or 16-60 μg/dl). The CV_{RR} and component C-CV_{RSA} (respiratory sinus arrhythmia) were significantly lower in the workers than in age-

matched controls, whereas the C-CV_{MWSA} (Mayer wave-related sinus arrhythmia) was unaffected. The authors noted that zinc may have been antagonistic to the lead effects in this study. Since the CV_{RR} during deep breathing and the component C-CV_{RSA} of respiratory sinus arrhythmia reflect parasympathetic activity, these two reports indicate potential dysfunction of the autonomic nervous system (mainly, parasympathetic activity) at average PbB levels of approximately 1.68 μmol/litre (35 μg/dl).

8.3.3 Neurotoxic effects in children

The majority of the epidemiological research on the health effects of lead has been focused on children because, in comparison with adults, they are more vulnerable to lead in several respects (Davis & Grant, 1992). For example, children typically engage in hand-to-mouth activities (sucking fingers, putting food or other objects in the mouth) that result in greater ingestion of lead than adults normally experience. Also, because of their greater absorption and retention of lead, the body burdens in children resulting from a given external exposure level tend to be higher than adults. Furthermore, the relatively greater exposures and body burdens of children occur during sensitive periods of development. Finally, it appears that children are generally more sensitive to the toxicological effects of lead at a given internal exposure (PbB) level. The lowest-observed-effect levels for various end-points (e.g., encephalopathy, anaemia, reduced haemoglobin, elevated EP, slowed NCV, impaired neurobehavioural function) are lower in children than in adults (US EPA, 1986a, 1990).

Section 8.3.3.2 describes findings from the main epidemiological cross-sectional studies that have been published since 1979. This constitutes a very substantial collection of research findings but has certain interpretive limitations, particularly the lack of information on exposure history.

More recent research effort has concentrated on prospective epidemiological studies of birth cohorts repeatedly evaluated, mostly up to the school age years. These prospective studies are described in section 8.3.3.3.

Section 8.3.3.4 presents a quantitative overview of the collective evidence from the prospective studies and discusses their interpretation and the problems of inferring causality from such observation data.

8.3.3.1 Historical perspective

While there have undoubtedly been cases of lead poisoning in children as long as lead has been used by man, most of the attention was previously given to cases of poisoning as a result of occupational exposure in adults. In 1892 Gibson and colleagues in Australia reported a case series of ten young children with lead colic. It was not until twelve years later that peeling paint in the children's homes was identified as the lead source (Gibson, 1904).

In 1943, Byers & Lord (1953) reported the results of an important study, the first to suggest that there were neurological after-effects of lead poisoning, in the absence of cerebral oedema and high intracranial pressure, following acute lead encephalopathy. However, in other cases it was felt that neurological manifestations disappeared if the ingestion of lead was stopped (McKhann & Vogt, 1933). The case series of 20 school-age children had been hospitalized for lead poisoning but without signs of acute lead encephalopathy, and all were later discharged as cured. At follow-up, only one of the children was making satisfactory progress at school. The children were described as showing a variety of symptoms, including poor academic achievement, intellectual deficits, sensory-motor deficits and behaviour disturbance.

In the years following the findings of Byers & Lord (1953), a number of case control studies were carried out that examined mental retardation (Beattie et al., 1975) or hyperactivity (David et al., 1972).

In addition, as a result of the growing concern about the dangers of lead encephalopathy, studies were set up to investigate the possibility that subclinical levels of lead (i.e. levels producing no overt signs of lead encephalopathy) cause more subtle neurological damage to children. Many of these studies investigated children identified by screening clinics as having raised lead burdens, but others were sited around smelters or lead works where children were found to have elevated lead levels. The studies were important in determining the areas of functioning which might be affected, and in drawing attention to the methodological problems involved in carrying out such studies. The main difference between the smelter studies or studies around lead works, and clinical studies is that in the former the primary source of environmental lead is known. In the hospital or clinical studies it is likely that the ingestion of paint flakes, or less often leaded putty, was in most cases the primary cause of the excess

lead exposure, although the exact reason for the increased lead burden is rarely known.

Clinical and smelter studies were carried out in the United Kingdom and USA and in general investigated children with PbB levels above 1.92 μmol/litre (40 μg/dl), and compared their performance with that of children with levels below this value.

Although some of the clinical and smelter studies found a lead-associated deficit (Perino & Ernhart, 1974; Landrigan et al., 1975), others did not (Lansdown et al., 1974). In general the studies were methodologically flawed, with small samples lacking in statistical power, biased ascertainment of subjects or controls, and inadequate control for potentially confounding co-factors. The large majority did not control for parental intelligence, which is the variable most strongly associated with child IQ. These studies were, however, important in suggesting an association between body lead levels and performance, and also in demonstrating that there is an association between social disadvantage and higher body lead levels.

8.3.4 Population-based cross-sectional studies on children

Most of the general population-based epidemiological cross-sectional studies have, in addition to intelligence tests, included extensive batteries of tests covering several other areas of psychometric functioning, such as academic attainment, behaviour, gross motor abilities and fine motor co-ordination, reaction time, visuo-spatial skills and memory, and auditory memory. There are differences in the tests used, and in the areas of functioning investigated, and the results are less consistent and more difficult to interpret than those relating to IQ tests. For that reason this section will focus mainly on results relating to intelligence tests, and results from other functional domains will be mentioned briefly where appropriate.

There are many cross-sectional population studies using either blood or teeth as the primary measure of lead body burden, and only the more informative, in terms of providing information on risk assessment, will be included. The majority of the studies described used either a full or short form of the Wechsler Intelligence Scale for Children - Revised (WISC-R or its translations) as the measure of intelligence. Exceptions are the studies of Fulton et al. (1987), which used the British Ability Scales (BAS), Harvey et al. (1988), which used Wechsler Pre-school

and Primary Scale of Intelligence (WPPSI), and Schroeder et al. (1985) and Hawk et al. (1986), where the Stanford-Binet Intelligence Scale was used.

8.3.4.1 *Tooth lead studies*

a) Needleman et al. (1979)

A total population of 3329 children aged 6-7 years, attending schools in two working class towns near Boston, USA, were asked to donate their shed deciduous teeth. Of these 70% (2335) children did provide teeth. A 1-mm slice of tooth consisting primarily of dentine, was split in half, and one portion was analysed by ASV. Children whose initial tooth slice was in the highest 10th percentile (> 20 μg/g) or the lowest 10th percentile (< 10 μg/g) were provisionally classified into a high or low lead group. A total of 524 children were originally classified into these lead groups, but 254 of these children were not tested for a number of reasons, and the results for another 112 were excluded from data analysis for medical reasons, or because a second tooth analysis provided a discordant result. The results for 158 children (58 high lead children and 100 low lead children) were presented. Thirty-nine non-lead variables were scaled and coded, and those which were found to differ between the lead groups at the 10% level were controlled as covariates. The covariates controlled were father's socioeconomic status, mother's age at subject's birth, number of pregnancies, mother's education and Peabody Picture Vocabulary score. After this was done the children in the high lead group performed significantly less well on the IQ test with a 4½ point difference between the groups.

b) Winneke et al. (1983)

A total of 115 children aged 7-12 years living in the vicinity of a lead/zinc smelter in Stolberg, Germany, who had provided at least one incisor tooth, were investigated. Whole tooth lead measures ranged from 2 to 32 μg/g, with a geometric mean of 6 μg/g. There was a marginally significant negative association between lead level and (short-form) verbal IQ after taking age, gender, perinatal risk factors and social confounding factors into account. There was a difference of 4.6 IQ points when children with tooth lead levels above 10 μg/g were compared with those with levels below 4 μg/g. Significant negative associations were also observed between tooth lead and the error score of Bender

Gestalt shape copying test and performance on the Vienna reaction time device.

c) Smith et al. (1983); Pocock et al. (1987)

The target population for the study by Smith et al. (1983) (also known as the Institute of Child Health/University of Southampton study) was 6875 children aged 6-7 years attending schools in one of three areas in or near London. In all, 7407 teeth were donated by 4105 children. Whole tooth analysis of intact incisor teeth donated by eligible children was carried out and children whose tooth lead level (expressed on an ashed weight basis) was in the lowest percentile (< 2.5 μg/g), approximately at the 50th percentile (5-5.5 μg/g) or above the 90th percentile (> 8.0 μg/g) were invited to participate. The sample was stratified by social grouping. Of the 432 children selected, 403 participated in the study. Parental interviews were carried out in the home, and information on a wide range of social and familial variables was collected. There was a 5 point difference in IQ scores between the high and low lead groups before controlling for any covariates, but this was reduced to 2 points once covariates associated with IQ score were controlled. The authors concluded that social factors explain the differences in test performance to such a degree that the small differences that remain may be due to other social factors not measured. The study underlined the importance of the social environment for the child's performance and recognized the importance of the relationship between body lead burden and social disadvantage.

Blood samples were taken from 93 children 3-6 months after shedding a tooth and after psychometric testing was completed. The range of PbB levels in this group was 0.336-1.296 μmol/litre (7-27 μg/dl), except for one measurement of 2.064 μmol/litre (43 μg/dl), and the mean was 0.614 μmol/litre (12.8 μg/dl). The correlation of PbB and PbT was 0.5.

A reanalysis of this data by Pocock et al. (1989) employed multiple regression techniques, using an "optimal" regression strategy. The results were comparable to those previously reported. Interactional analyses showed no evidence of any differential association with lead in different social groups, but revealed a significant interaction between PbT and child gender. Significant negative association between PbT and IQ was found in boys but not in girls.

d) Fergusson et al. (1988a,b,c)

This study was carried out in Christchurch, New Zealand, on a sub-sample of a birth cohort of 1265 children born in 1977. Teeth were collected from 1035 children, and a dentine "chip" was analysed to provide a PbT estimate for 996 children. The mean dentine lead level was 6 μg/g. Children from disadvantaged backgrounds had higher mean lead levels than those from more advantaged backgrounds, and this difference persisted when other social environmental factors (such as the effects of housing, proximity to main roads, and childhood pica) were taken into account. A WISC-R and reading test were administered to children at ages 8 and 9 years, and results were given for 724 children at age 8 and 644 children at age 9. Small correlations between IQ scores and dentine lead were found, but control for confounding variables reduced these to statistical non-significance for both ages (a correlation of -0.03 to -0.05). Parental IQ was assessed. Control for pica as a test of reverse causality further reduced the associations between outcomes and PbT.

e) Hansen et al. (1989); Lyngbye et al. (1990a,b); Grandjean et al. (1991)

Children entering schools in the town of Aarhus, Denmark, were asked to donate shed teeth. Of a potential sample of 2414 children, 1291 (54%) provided usable teeth. A sample of circumpulpal dentine was obtained from each tooth and analysed by AAS. The mean lead level in dentine was 10.7 μg/g, with a log normal distribution and a range from 0.40 to 168 μg/g. The correlation of whole tooth lead and circumpulpal dentine measures were low. Average circumpulpal dentine levels were about five times higher than average whole tooth measures. Subsequent analysis of PbB from samples obtained two to three years later showed an overall mean PbB level of 0.25 μmol/litre (5 μg/dl), with a geometric mean of 0.28 μmol/litre (range 0.08-0.63 μmol per litre or 1.66-13.1 μg/dl) in children selected for the high lead group, and a mean of 0.18 μmol/litre (range 0.08-0.70 μmol/litre or mean 3.74 μg/dl, range 1.66-14.56 μg/dl) in children selected for the low lead group, which confirms this as a low exposure group. Children whose level of lead in circumpulpar dentine was above 18.7 μg/g (8%, N = 110) were selected for the high lead group, and they were matched on gender and socioeconomic status (SES) with children whose circumpulpar dentine levels were below 5 μg/g. A comprehensive list of exclusions, including neurological and medical conditions, atypical social situations, and those who

did not wish to take part, reduced the sample to 156 children for whom results were presented. Initial analysis (by matched pair t-test) showed a difference of 6 IQ points on full-scale WISC scores, with a difference of nearly 9 points in verbal IQ scores. The association of IQ measures with circumpulpar dentine lead levels was evident across different socioeconomic groups. Confounders associated with circumpulpar dentine lead levels (such as pregnancy variables, SES, mother's educational status and child's gender) were entered into a stepwise regression model, and explained only a small portion of the variance. Lead levels in the dentine accounted for a significant (2.8%) of the total variance in full scale IQ. Parental IQ was not controlled.

f) Rabinowitz et al. (1991)

From 764 eligible children (attending grades 1 to 3 in 7 selected schools in Taiwan), 940 deciduous teeth were collected, the majority being incisors. The average age of students was 6.7 years. Two of the schools were near lead smelters. Lead levels were determined in 862 teeth from 692 children using the Boston method which analysed a "dentine chip" (Rabinowitz et al., 1989). The mean value was 4.3 μg/g of dentine. In all, 493 children were tested using the Ravens Coloured Progressive Matrices Test (CPM) and the IQ equivalents were related to tooth lead levels. Confounders were selected from a set of 40, based on associations with lead and IQ. After correction for seven confounding variables (social and perinatal factors), the highly significant raw exposure-effect association ($r = -0.32$) was markedly reduced for the full sample to statistical insignificance, although a significant lead-CPM association remained for the subsample of girls ($b = -1.8$; $SE = 0.78$; $P < 0.02$).

8.3.4.2 Blood lead studies

a) Winneke et al. (1985)

In a further study by this group carried out in the lead/zinc smelter town of Nordenham, Germany, 114 out of 378 children (46%) for whom cord PbB levels were available were tested at 6-7 years of age. The range of cord PbB levels was 0.19-1.49 μmol/litre (4-31 μg/dl) and for current PbB levels was 0.19-1.10 μmol/litre (4-23 μg/dl); the means for both perinatal and current PbB levels were 0.39 μmol/litre (8.2 μg/dl, SD = 1.6). After correction for confounders by means of a stepwise multiple regression analysis, few significant associations between PbB levels and performance were observed. There was a marked influence

of social background factors, but little influence on short-form full IQ score (current PbB accounted for 0.3% additional variance), and a borderline decrease in performance IQ (PbB accounting for 2.4% of the variance). In general, the associations were rather stronger with current PbB levels than with cord PbB measures. The strongest associations were found with the error scores of the difficult version of the Vienna reaction time task.

b) Harvey et al. (1984)

From 483 eligible children from the city of Birmingham, United Kingdom, 187 out of 284 contacted were examined at 30 months of age. The average PbB level from venous samples was 0.75 μmol/litre (15.6 μg/dl, SD = 4). Cognitive ability was assessed by means of four tests from the British Ability Scales (BAS) and three tests from the Stanford-Binet Intelligence Scale. The raw correlation between PbB level and IQ was -0.17 ($P < 0.05$). Subsequent multiple regression analysis with a predetermined set of confounders and a sample size of 48 yielded an insignificant association between lead and IQ.

c) Harvey et al. (1988)

In a second study, 201 out of 337 eligible children, aged 5.5 years, from the inner city area of Birmingham, United Kingdom, were studied. The mean PbB level was 0.614 μmol/litre (12.8 μg/dl, SD = 4). No significant associations between PbB level and IQ (WPPSI) were observed after correction for confounding factors. Apart from some statistically significant associations between PbB level and reaction time, none of the remaining tests showed a significant correlation with PbB level after confounder-control.

d) Yule et al. (1981)

Children (N = 166), aged 6 to 12 years, living in the vicinity of a leadworks in outer London were examined. PbB levels from venous samples ranged from 0.336 to 1.58 μmol/litre (7 to 33 μg/dl, geometric mean = 0.648 μmol/litre or 13.5 μg/dl). After controlling for social class as the only confounder, significant negative associations were found for IQ (WISC-R; full-scale- and verbal-, but not performance-IQ). An average IQ difference of 7 points was found when comparing children with PbB levels of 0.62 μmol/litre (13 μg/dl) or more with those of 0.576 μmol/litre (12 μg/dl) or less. Significant inverse associations were also found

between PbB level and scores on tests of attainment, i.e. reading and spelling but not mathematics.

A group of 9-year-old children from a middle class area of London were studied. Subjects were divided into low PbB (N = 80 and PbB of 0.336-0.576 μmol/litre, 7-12 μg/dl) and high PbB (N = 82 and PbB of 0.624-1.15 μmol/litre, 13-24 μg/dl) groups for testing the association between PbB level and IQ. No significant association between PbB level and IQ was found before or after controlling for covariates (Lansdown et al., 1986).

e) Schroeder et al. (1985)

One hundred and four children from a high risk population, aged 10 months to 6.5 years and with PbB levels ranging from 0.288 to 2.83 μmol/litre (6-59 μg/dl) were tested for intellectual development using age-appropriate tests. After control for social confounding a significant negative association was found between PbB level and IQ. Fifty children of this cohort were reassessed 5 years later when all PbB levels were below 1.44 μmol/litre (30 μg/dl). Neither initial nor current PbB level was significantly related to later IQ.

f) Hawk et al. (1986)

In an effort to replicate the above-mentioned findings, 75 children from the same group, then aged 3 to 7 years, and having a mean PbB level of 0.998 μmol/litre (20.8 μg/dl), range 0.29-2.256 μmol/litre (6-47 μg/dl), were examined using the Stanford-Binet test. There were no significant interactions between PbB level and factors including age, sex, maternal IQ, quality of the care-giving environment (HOME), or socioeconomic status. There was a statistically significant negative association between PbB level and IQ, although the characteristics of the regression coefficient for lead depended on which covariates were included in the model. For the final regression model that best controlled for confounding with the greatest precision, i.e. the most accurate and precise model, containing lead, maternal IQ, HOME and gender, highly significant inverse associations were found between both mean and maximum PbB levels and IQ.

g) Fulton et al. (1987)

Five hundred and one children, aged 6-9 years, out of 1210 eligible children from 18 primary schools in central Edinburgh,

Scotland, were tested for an association between PbB level, IQ and attainment. The sample comprised all children in the top quartile of the PbB distribution, and a random subsample (approximately 1 in 3) of the remainder. The geometric mean PbB level was 0.55 μmol/litre, range 0.16-1.63 μmol/litre (11.5 μg/dl, range 3.3-34.0 μg/dl). After correction for 31 potential confounders a significant negative association between PbB level and IQ (BAS) was found. There was a dose-response relation with no evidence of a threshold. For purposes of statistical analyses, children were placed into 10 groups of about 50 each on the basis of PbB level. The mean PbB level was 0.27 μmol/litre (5.6 μg/dl) in the lowest and 1.06 μmol/litre (22.1 μg/dl) in the highest group; there was a difference of 5.8 IQ points between the two groups. The size of the effects of lead was small relative to that of the other factors (0.9% of a total of 45.5% explained by the full model).

h) Hatzakis et al. (1989)

Five hundred and thirty-three children out of 1038 eligible from four primary schools in the vicinity of the old lead-mining and lead-smelting industrial complex of Lavrion in Greece were examined neuropsychologically. The mean PbB level from venous samples was 1.14 μmol/litre, range 0.355-3.067 μmol/litre (23.7 μg/dl, range 7.4-63.9 μg/dl). In order to control for confounding factors, several regression models were evaluated. Starting with a set of 24 potential confounders, an optimal model containing 17 potentially confounding variables was finally developed for testing the PbB/IQ association. The continuous PbB variable was divided into five equally wide classes from equal/below 0.715 μmol/litre (14.9 μg/dl, low) to equal/above 2.16 μmol/litre (45.0 μg/dl). After correction for confounders, a highly significant negative association was found between PbB level and IQ (WISC-R). A persistent decrease in IQ was only observed at PbB concentrations above 1.2 μmol/litre (25 μg/dl). The adjusted full-scale IQ difference between "high" and "low" PbB children was 9.1 points. Highly significant negative associations with PbB were also found for the Bender Gestalt test and the Vienna Reaction Device, without any indication of a threshold.

i) Silva et al. (1988)

Five hundred and seventy-nine socioeconomically advantaged 11-year-old children with an average PbB level of 0.53 μmol/litre (11 μg/dl), range 0.19-2.4 μmol/litre (4-50 μg/dl) were tested in

Dunedin, New Zealand. Because the crude inverse association between blood lead and IQ was not statistically significant, subsequent multivariate analyses were not carried out.

j) European multicentre study

The results from a multicentre study in Europe were reported by Winneke et al. (1990). The study linked eight institutions from eight European countries; four of the individual study groups were from areas near smelters and the others were more general populations. A common study protocol with inherent quality assurance elements was developed to achieve comparability between the individual studies. In all, 1879 children, aged 6-11 years, were studied; however, for some of the tests the sample size was reduced to only 971 children. The PbB level ranged from 0.24 to 2.88 μmol/litre (5 to 60 μg/dl). Overall statistical evaluation was done using a uniform predetermined confounder model containing age, gender, occupational status of the father, and mother's education. The inverse association between PbB level and IQ (four subtests from the WISC-R) was of only borderline statistical significance. An IQ decrement of about 3 points was calculated for a PbB increase from 0.24 to 0.96 μmol/litre (5 to 20 μg/dl). The associations between the error scores on the Bender Gestalt Test and the Vienna Reaction Device were statistically significant and more consistent across study groups, although the outcome-variance explained that lead never exceeded 0.8%. The data did not allow for the identification of a threshold.

8.3.4.3 Follow-up studies

a) Bellinger et al. (1984)

A follow-up of some of the children investigated by Needleman et al. (1979) was conducted when the children were approximately eleven years old. Twenty-two of the original elevated lead group and 48 children from the low lead group were traced, as well as a group of 52 children who had not been tested previously, but whose lead levels in a "dentine chip" (from teeth analysed at the time of the previous study) fell into the mid-range between the high and low lead groups. Children in the elevated lead group were significantly younger than those in the other two groups. Information on IQ from group-administered Otis Lennon Mental Ability tests, conducted 1 to 2 years previously, was collected from school records for 15, 52 and 34 children from the elevated, mid-range and low groups, respectively. Scores were

inversely related to previously obtained lead measures, with a 7-point difference in mean scores between the high and low lead groups (t-ratio = 1.65, P = 0.1). No current measures of lead status were available.

b) Winneke et al. (1989)

Out of 114 children first tested at age 6 (Winneke et al., 1985) 76 were retested at age 9. The range of PbB levels had been 0.187-1.09 μmol/litre, geometric mean = 0.39 (3.9-22.8 μg/dl, geometric mean = 8.2) at age six and was 0.21-1.027 μmol/litre, geometric mean 0.37 (4.4-21.4 μg/dl, geometric mean 7.8) at age 9 (r = 0.82). After correction for the same set of confounders used at age 6 (age, gender, social background), most of the findings that had been found to be significant at age 6, i.e. those related to reaction performance (Vienna Reaction Device), remained virtually unchanged three years later. The authors concluded that this observation cannot necessarily be taken to indicate persistence, because internal exposure had essentially remained unchanged over three years.

c) Needleman et al. (1990)

A follow-up assessment was made of 132 young adults first investigated by Needleman et al. (1979) at the age of 6-7. Those retested were not representative of the group of 270 tested 11 years earlier, as they had slightly lower childhood dentine lead levels, came from higher SES families, and were more likely to be female. Current PbB level was assessed from 48 subjects and none was above 0.336 μmol/litre (7 μg/dl). A behavioural evaluation including a word reading test, and a neurobehavioural assessment was administered to each subject, and a self-report of delinquency was obtained. In addition school records were reviewed. Multiple regressions indicated that higher levels of dentine lead in childhood was associated with lower reading scores, lower class rank, increased absenteeism, and poorer performance on some of the neurological tests in young adulthood. Comparing subjects with dentine lead levels greater than 20 μg/g with the lowest lead group, children in the high lead group were much more likely to drop out of school (unadjusted odds ratio 4.6; adjusted odds ratio 7.4, CI 1.4-40.8) and to have a reading disability (unadjusted odds ratio 3.9; adjusted odds ratio 5.8, CI 1.7-19.7). Adjustment for covariates made little impact on most of the outcomes.

8.3.4.4 Conclusions and limitations of cross-sectional studies

A number of general issues are evident from looking at the cross-sectional studies as a group. In most studies a negative association between lead measures and IQ measures is found in uncontrolled data. This difference is usually in the range of 4 to 6 IQ points and most marked in verbal IQ. Most studies also confirmed the positive association between lead measures and indicators of social disadvantage, whether this was indicated by SES, maternal education, or other more detailed indicators of non-optimal child-rearing environments, such as marital quality or maternal depression. When these social and other confounding factors are controlled, the effect has, in most cases, been to reduce the strength of the association between lead measures and IQ, although it remains in the same direction. When maternal intelligence has not been controlled, the impact on the association between lead and IQ measures of correction for covariates tends to be smaller. Where more detailed social measures have been controlled, the impact on the magnitude of the lead-IQ association has been greater. Associations have, in general, been stronger with verbal IQ than with performance IQ.

The cross-sectional nature of these studies, and also the fact that many used a single measure of current exposure, limited their usefulness in answering questions relating to the natural history of the association between lead exposure and outcomes, including whether there were critical periods of exposure, and whether lead associated deficits were persistent or reversible.

Findings from follow-up studies are difficult to interpret. Needleman et al. (1990) interpreted their findings as indicating the persistence of the effects of lead. Identifying persistence or irreversibility in this context has many problems, due to the stability of a number of other (non-lead) factors. In addition, sampling biases, or failure to control for important covariates in the initial or follow-up stages may lead to apparent persistence of an effect. A further difficulty is that it is unusual to find a cohort where exposure profiles permit easy assessment of persistence.

Neurobehavioural effects detected at age seven or later usually persist in later follow-up studies conducted in other (non-lead) areas of research, and for this reason it is more likely than not that lead-associated deficits detected during childhood will be detectable later. However, there are not enough data to conclude that this is the case. Animal data, in which persistence of effects

has been shown after cessation of exposure, do provide support for the irreversibility of lead-induced behavioural toxicity.

8.3.5 *Prospective epidemiological studies on children*

8.3.5.1 *Common elements*

The international prospective cohort studies shared a common design of pre- or perinatal recruitment, with the principal measure of prenatal exposure being the lead concentration in whole blood taken antenatally or at birth. To facilitate later comparison of results, meetings have been held at which common protocols (within the constraints of local conditions) were agreed (Bornschein & Rabinowitz, 1985; Smith, 1989).

The protocols were similar in terms of the instruments of neurobehavioural assessments, which were well standardized and validated for the populations to which they were applied, and although the frequency of assessment varied between studies, it was agreed that all studies would make an assessment during infancy, in the later pre-school period and, if possible, in the school age years.

All studies conducted several assessments of PbB concentration but at varying frequency, and all studies participated in some form of quality assurance/quality control (QA/QC) programme for the assessment of lead exposure. QA/QC procedures were also used to establish inter-examiner reliability (where more than one examiner was used) for psychometric and covariate assessments. The importance of such procedures was recently discussed (SAHC, 1993).

In assessing dose-effect relationships between lead exposure and outcome variables, most studies used several indices of exposure, including both measures of PbB concentration at particular ages and average measures of exposure within the lifetimes of the study subjects.

All studies used data analysis procedures which took simultaneous account of covariates selected for statistical and substantive considerations.

8.3.5.2 Study descriptions

a) Boston study

The study population was recruited from 11 837 infants born at the Brigham and Women's Lying-In hospital in Boston between April 1979 and April 1981 (Bellinger et al., 1984). On the basis of cord PbB levels of approximately 2500 children, the 90th, 50th and 10th percentiles were identified and used as eligibility criteria for enroling 249 children in three exposure groups: low (< 0.14 μmol/litre or 3 μg/dl, N = 85), medium (0.288-0.336 μmol/litre or 6-7 μg/dl, N = 88) and high (> 0.48 μmol/litre or 10 μg/dl, N = 76). No child had a cord PbB level greater than 1.2 μmol/litre (25 μg/dl).

Exclusion criteria included birth complications or medical conditions associated with developmental difficulties (e.g., gestational age < 34 weeks, Down's syndrome), a non-English speaking family or residence in an area considered unsafe for home visitors. The cohort consisted largely of children from intact middle and upper-middle class families. Approximately 85% of the children were white.

Capillary blood collected at ages 6, 12, 18 and 24 months was analysed for lead by ASV. Venous blood collected at ages 57 months and at 10 years was analysed for lead by AAS. In contrast to other prospective cohorts, the mean PbB level did not rise postnatally and indeed never exceeded 0.384 μmol/litre (8 μg/dl).

The principal psychometric tests included the Bayley Scale of Infant Development at 6, 12, 18 and 24 months, the McCarthy Scales of Children's Abilities at 57 months and the Wechsler Intelligence Scale for Children - Revised and the Kaufman Test of Educational Achievement at age 10 years. After age 2 years, the mean level of performance was above the expected population mean (e.g., mean full scale IQ at age 10 years = 119) (Bellinger et al., 1992).

A variety of potential confounding factors was assessed including maternal IQ, the quality of rearing environment (HOME scores at 6, 24, 57 and 120 months) and prenatal, perinatal and postnatal medical and socio-demographic factors.

b) Cincinnati study

Women attending prenatal clinics in predesignated lead-hazardous residential areas of Cincinnati, Ohio, USA, were consecutively recruited from 1979 to 1984 (Dietrich et al., 1987) Prenatal exclusions were for maternal prenatal alcohol and drug abuse, psychosis, diabetes, mental retardation; neonatal exclusions included birth weight under 1.5 kg and gestational age (by physical examination) below 35 weeks. Furthermore, recruited infants had to have an Apgar score of 6 or more at 5 min postpartum and to have no serious medical conditions. Of the mothers, 87% were single and 86% were receiving public assistance. The final follow-up sample of 305 infants who attended their second clinic visit at 3 months of age was 85% African-American and 50% female.

Mean prenatal maternal PbB levels as assessed by ASV were 0.38 ± 0.177 μmol/litre (8.0 ± 3.7 μg/dl). Mean neonatal PbB levels were also low at 0.221 ± 0.134 μmol/litre (4.6 ± 2.8 μg/dl). Following the development of prewalking progression and normal hand-to-mouth behaviours, PbB levels began to rise, peaking at around 21 months with a mean of approximately 0.89 μmol/litre (18 ± 6 μg/dl). Approximately 35% of the sample had at least one PbB concentration equal to or greater than 1.2 μmol/litre (25 μg/dl) sometime during the first 5 years of life, while 79% exceeded 0.72 μmol/litre (15 μg/dl) during the same period (Dietrich et al., 1991, 1992). Virtually all children (95%) exceeded 0.48 μmol/litre (10 μg/dl) during the first 5 years of life. Postnatal PbB concentrations were assessed on a quarterly basis beginning at 10 days postpartum. The vast majority of blood samples were collected by venepuncture.

Major neurobehavioural assessments included the Bayley Scales of Infant Development administered at 3, 6, 12 and 24 months of age. The Kaufman Assessment Battery for Children was administered at 4 and 5 years. A comprehensive examination of gross and fine neuromotor functions (the Bruininks-Oseretsky Scales) was administered at 6 years. Finally, performance on the Wechsler Intelligence Scale for Children - Revised was assessed following school entry at 6.5 years.

Intellectually, this was a low functioning cohort with a mean full-scale IQ at 6.5 years of 86.9 ± 11.3 points (Dietrich et al., 1993a).

Covariates measured included assessments of obstetrical and perinatal complications, birth anthropometrics, tobacco and alcohol consumption, observational assessments of the quality of care-taking in the home at 6, 12, 24 and 36 months, social class, iron status and various aspects of child health likely to affect neurobehavioural performance (e.g., otitis media, sensory deficits, allergies, seizure disorders). Maternal IQ was assessed postnatally. All medical and psychometric testing was conducted at a single welfare clinic located in the heart of the recruitment area.

c) Cleveland

Five hundred and forty-three infants delivered to women at a large inner city general hospital between February 1981 and March 1982 were considered for inclusion in this study of the joint or independent effects of fetal alcohol exposure and lead on child development (Ernhart et al., 1985). Due to pre-term birth or illness, 16% were excluded from further study. Also excluded were mothers reporting the use of narcotics and those with identifiable psychological disorders. The sample was predominantly white (65%) and of lower SES. Approximately 50% of mothers were alcoholics.

PbB concentrations were assessed by AAS (208 mothers at delivery and in 178 cords resulting in 142 mother-infant pairs with complete prenatal lead exposure data). Postnatally, blood samples were analysed for approximately half the birth cohort at ages 6 months, two years and three years of age. At least one perinatal or postnatal PbB concentration was available for each of 285 children with developmental data past the neonatal period (Ernhart et al., 1987, 1989a,b).

Mean maternal PbB concentrations (N = 185) were low (0.31 ± 0.086 μmol/litre or 6.5 ± 1.8 μg/dl) and mean cord PbB concentrations (N = 162) were also low (0.29 ± 0.10 μmol/litre or 6.0 ± 2.1 μg/dl). Postnatally, mean PbB concentrations (N = 151) were 0.48 ± 0.16 μmol/litre (10.0 ± 3.3 μg/dl) at 6 months, 0.80 ± 0.28 μmol/litre (16.7 ± 5.9 μg/dl) at 2 years (N = 165) and 0.80 ± 5.9 μmol/litre (16.7 ± 5.9 μg/dl) at 3 years. The lowest and highest PbB levels recorded postnatally were 0.24 and 2.016 μmol/litre (5 and 42 μg/dl), respectively.

Neurobehavioural assessment included selected sub-scales of the Brazelton Neonatal Behavioural Assessment Scales and Graham Rosenblith Behavioural Examination of the Neonate at > 24 h

postpartum, the Kent Infant Development scale at 6 months, the Bayley Scales of Infant Development at 6, 12 and 24 months, the Stanford-Binet Intelligence Scale at 3 years, and finally the Wechsler Preschool and Primary Scale of Intelligence at approximately 5 years of age. All assessments beyond the neonatal period were conducted in subjects' homes.

Intellectual attainment in this high risk, socioeconomically disadvantaged cohort was typically low as shown by a mean full-scale IQ at approximately 5 years of 87.5 ± 16.6 points (Ernhart et al., 1989a).

In addition to the usual assessments of obstetrical/perinatal complications and neonatal status, other covariates measured included the Michigan Alcoholism Screening Test, the Peabody Picture Vocabulary Test as an assessment of maternal intelligence, and the Authoritarian Family Ideology Scale. Women were also questioned as to their consumption of alcohol and tobacco during pregnancy. Observational assessments of care-taking quality in the home were conducted at 1, 2, 3 and 4 years.

d) Glasgow study

The study group for CNS outcomes consisted of 151 subjects drawn from an initial sample of 885 families exposed to various levels of dietary lead, principally due to a plumbosolvent water supply (Moore et al., 1989). All subjects were born in the United Kingdom and spoke English as a first language. The sample was divided into three groups of approximately equal numbers (matched for social class) based on maternal prenatal PbB levels: high (> 1.44 μmol/litre or 30 μg/dl), medium (0.72-1.2 μmol/litre or 15-25 μg/dl) and low (< 0.48 μmol/litre or 10 μg/dl). The SES of the sample ranged from the chronically unemployed to the professional classes.

PbB levels were assessed postnatally at 1 and 2 years of age and found to be 0.734 and 0.777 μmol/litre (15.3 and 16.2 μg/dl), respectively.

Measurements of neurobehavioural outcome where the Bayley Scales of Infant Development were used were administered at 1 and 2 years of age.

Covariates considered in the data analysis included a measure of obstetrical complications, birth weight, birth order, SES of the

father in postnatal follow-up years 1 and 2, and observational assessments of care-taking quality in the first and second years of follow-up.

e) Kosovo Study

Five groups of infants from two communities in Kosovo, Yugoslavia, were studied (Graziano et al., 1990; Wasserman et al., 1992). Mitrovica was the site of a lead smelter, refinery and battery plant, and Pristina an area of minimal lead exposure. Three groups were recruited from Mitrovica on the basis of cord PbB concentration: (1) < 0.72 μmol/litre (< 15 μg/dl, N = 78); (2) 0.72-0.96 μmol/litre (15-20 μg/dl, N = 99); (3) > 0.96 μmol per litre (> 20 μg/dl, N = 217). Two groups were recruited from Pristina: (4) a group with cord PbB levels < 0.72 μmol/litre (< 15 μg/dl) and (5) a group matched to children in group (3) in terms of the distribution of maternal and paternal education. Grouping was not considered in the statistical analysis. The total cohort (N = 541) was largely Albanian and Serbian. Infants with CNS defects, chromosomal anomalies, distant residence and twin pairs were excluded.

PbB level and various indices of iron status (EP, Hb, serum ferritin) were measured in venous blood collected in mid-pregnancy, delivery and at postnatal ages 6, 12, 18 and 24 months. Mean PbB level amongst children in Mitrovica exceeded 0.96 μmol/litre (20 μg/dl) at all ages, reaching 1.68 μmol/litre (35 μg/dl) at 24 months. Amongst children in Pristina, the mean PbB level was below 0.48 μmol/litre (10 μg/dl) at all ages.

The Mental Scale of the Bayley Scales of Infant Development was administered at ages 6, 12, 18 and 24 months, and the Motor Scale at 6 and 12 months. At 24 months, the mean Mental Development Index in the cohort (n = 392) was 105.2 (SD = 18.1).

Anthropometric measurements and assessments of child and family health, diet, and demographic status were carried out at each age. An adaptation of the HOME Scale was administered at ages 3 and 4 years and maternal IQ was assessed using the Raven's Standard Progressive Matrices.

f) Port Pirie study

Port Pirie (population 16 000 in 1979) is an industrial town 200 km north-west of Adelaide, South Australia, with a large and

long-standing smelting facility (Wigg et al., 1988). Over the period 1979-1982, a cohort of 723 children from Port Pirie and surrounding rural areas was recruited into the study. The cohort represented a 90% sample of all children born in the area during this period.

Lifetime lead exposures were estimated from venous PbB concentrations obtained antenatally (at 14-20 weeks of gestation, and 32 weeks), at delivery (maternal and cord blood), and from capillary samples taken postnatally at ages 6, 15, and 24 months, and annually thereafter. Lead concentrations in all samples were determined by AAS.

At the time that each blood sample was collected, the nurse interviewer also conducted structured interviews to obtain information on a range of demographic, familial, behavioural, medical and social environmental factors. HOME scores were assessed when the child was 3 and 5 years of age. Maternal IQ was also assessed. The Bayley Scales of Infant Development was administered at 2 years, the McCarthy Scales of Children's Abilities at 4 years and the Wechsler Intelligence Scale for Children - Revised version (WISC-R) at 7 years.

g) Sydney study

A total of 318 children was recruited from among infants born at three maternal hospitals between April 1982 and March 1983 (Cooney et al., 1989a). Exclusion criteria included prematurity, low birth weight, severe medical problem, single or non-English speaking mother or maternal drug or alcohol problems. All children were white and generally represent a middle-class population.

PbB concentration was measured in maternal venous blood during hospitalisation (geometric mean = 0.388 μmol/litre or 8.1 μg/dl, geometric SD = 0.067 μmol/litre or 1.4 μg/dl). Additional blood samples were collected at 6-month intervals to age 4 years and at ages 5 and 7 years. Up to 24 months of age, approximately 50% of the blood samples were capillary, while almost all samples collected subsequently were venous. Geometric mean PbB levels between 6 months and 4 years were in the range of 0.48-0.72 μmol/litre (10-15 μg/dl), falling to 0.39 and 0.37 μmol/litre (8.3 and 7.7 μg/dl) at ages 5 and 7, respectively.

The Bayley Scales of Infant Development were administered at ages 6, 12 and 24 months, the McCarthy Scales of Children's Abilities at ages 3 (n = 215) and 5 (n = 200), and the Wechsler Intelligence Scale for Children - Revised at 7 years (n = 175). All assessments, at least until age 5, were conducted in the child's home. The mean Mental Development Index and General Cognitive Index (GCI) scores were in the intellectual normal range of 107 to 117 with a mean general cognitive index at 4 years of 107.3 ± 14.2.

Covariates measured included maternal IQ, quality of care-taking environment, obstetrical and postnatal factors.

8.3.5.3 Summary of differences between studies

The prospective studies differed to such an extent that it would be surprising if they yielded identical findings. This does not mean that the studies cannot be compared, merely that these differences and their potential impact on study findings must be acknowledged in any assessment of the studies as a group (Bellinger & Stiles, 1993). There are substantial differences in the degree of confounding between lead exposure and the other correlates of poor developmental outcomes. For example, mean maternal IQ ranges from 121 (Boston) to 74-75 (Cleveland, Cincinnati), reflecting vast cohort differences in socioeconomic standing and child-rearing context.

The studies also varied substantively in terms of the lead exposure profiles observed. Site differences resulted in considerable variability in postnatal lead exposures depending on exposure patterns (residence near primary lead smelters, residence in deteriorated housing, proximity to traffic, and quality of domestic drinking-water).

Despite broad similarities in the approaches to data analysis, there were substantial differences in the form in which the findings were reported, impeding direct comparison of study results. Results were diversely reported in terms of partial correlation coefficients and standardized and unstandardized regression coefficients, and there was variable use of raw (untransformed) and log exposure measures. Most, but not all studies presented their results in a manner conducive to some kind of quantification of dose-effects relationships.

Clearly the variation in numbers of participants available to individual studies (both initially, and as a consequence of attrition) has a direct effect on the statistical power of each study - which is also affected by the degree of confounding.

8.3.5.4 Results of studies

a) Infancy and early preschool assessments

The pattern of findings in infant and early preschool assessments for which the principal instrument of assessment was the Bayley Scales of Infant Development is inconsistent. Using different indices of *in utero* exposure (e.g., prenatal, at delivery, cord or neonatal PbB levels), three of the prospective studies found associations with slower sensorimotor development up to 6 months or 1 year of age (Ernhart et al., 1987; Dietrich et al., 1987, 1989) or up to 2 years of age (Bellinger et al., 1987), but these tended to attenuate over time (Dietrich et al., 1990; Bellinger et al., 1991a). Other studies did not observe statistically significant adjusted relationships of prenatal exposure with slower sensorimotor development (Moore et al., 1989; Wigg et al., 1988; Cooney et al., 1989a,b; Wasserman et al., 1992).

Two studies observed an inverse association between postnatal lead exposure on mental development in later infancy (Wigg et al., 1988; Wasserman et al., 1992), although in one study it was PbB level at 6 months of age (Wigg et al., 1988) and in the other study it was the level at 24 months (Wasserman et al., 1992) that was most predictive.

b) Later preschool and school age assessment

Despite some inconsistency in the pattern of findings in infants, there has been a convergence of positive findings on later neurobehavioural outcomes in the prospective studies. This may reflect:

1) the greater reliability and precision of measurement attained with assessments of the older child; or

2) an effect of lead on abilities that cannot easily be tested during infancy (e.g., executive, regulative and organizational skills, higher order reasoning).

c) Boston study

Among 169 children assessed at age 57 months, the major finding was an association between PbB level at 2 years of age and the GCI of the McCarthy Scales. There was a decrease of 2.95 ± 1.42 GCI units for an increase in PbB of 0.48 μmol/litre (10 μg/dl). Since the group had an average PbB level of 0.336 μmol/litre (7.0 μg/dl) over 2 years, this decrement was relevant to a range of approximately 0.19–0.67 μmol/litre (4–14 μg/dl) Bellinger et al., 1991a).

At 10 years of age, 148 children were reassessed. PbB concentration at 2 years of age was inversely associated with the WISC-R Full Scale IQ. Each 0.48 μmol/litre (10 μg/dl) increase was associated with a 5.8 point decline in IQ (95% CI 1.7 to 9.9) (Bellinger et al., 1992).

PbB concentration at 24 months was also inversely related to the Battery composite score in the Kaufman Test of Educational Achievement (Brief form) (-0.89 ± 0.24). The skills assessed were mathematics, reading and spelling.

The point estimates associated with other postnatal ages were generally in the same direction but only PbB level at 2 years revealed conventional statistical significance. Other specific neuropsychological tests did not reveal a clear pattern of neuropsychological deficit (Stiles & Bellinger, 1993).

d) Cincinnati study

The Kaufman Assessment Battery for Children was administered to approximately 260 children at 4 and 5 years of age (Dietrich et al., 1991, 1992). The principal findings at 4 years were that higher neonatal PbB levels were associated with poorer performance on all Kaufman subscales. However, this inverse association was limited to children from the poorer families. Following full covariate adjustment, few statistically significant associations between postnatal PbB levels and Kaufman scales could be found. However, the results did suggest a weak relationship between postnatal PbB levels and performance on a Kaufman subscale which assesses visual spatial and visual-motor integration (adjusted regression coefficient -0.12 SE not published).

At 5 years of age, postnatal PbB levels were associated with poorer performance an all subscales of the Kaufman Battery. However, after adjustment for covariates, few statistically significant relations remained. Nevertheless, as at 4 years of age, the subscale assessing visual-spatial and visual-motor skills was most sensitive, with average lead exposure during the 4th year of life being significantly associated with performance (-0.12 units per 0.048 μmol/litre or per μg/dl, SE not published).

At the age of 6.5 years, 253 children in the Cincinnati cohort were administered the WISC-R (Dietrich et al., 1993a). The major findings were that postnatal PbB concentrations were inversely associated with full-scale IQ and performance IQ. Following statistical adjustment for covariates, including maternal IQ and quality of home care, a statistically significant relationship was retained between postnatal PbB concentrations at nearly all ages (and including lifetime averages) and Performance IQ. Further analysis revealed that average lifetime PbB concentrations in excess of 0.96 μmol/litre (20 μg/dl) were associated with deficits in IQ of the order of 7 points, when compared with children with mean concentrations of less than 0.48 mol/litre (10 μg/dl). The regression coefficient for Performance IQ on mean lifetime PbB level was -0.26 (± 0.12) IQ units per 0.048 μmol/litre or per μg/dl. This corresponded to a 2.6 unit decrement associated with a 0.48 μmol/litre (10 μg/dl) movement in lifetime average PbB level, for which the average (interpolated graphically) is close to 0.67 μmol/litre (14 μg/dl).

At 6 years of age, the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP) was administered to 245 children in the Cincinnati Cohort (Dietrich et al., 1993a). Following statistical adjustment for covariates, neonatal PbB levels were associated with poorer performance on a measure of upper-limb speed and dexterity and the fine-motor composite. Postnatal PbB levels also remained significantly associated with poorer scores on measures of bilateral coordination, visual-motor control, upper-limb speed and dexterity, and the fine motor composite.

Children having an average mean lifetime PbB level of approximately equal to or exceeding 0.43 μmol/litre (9 μg/dl) appeared to experience a deficit in both fine and gross motor skills relative to children in the lowest PbB quartile. Children in the highest average lifetime PbB quartile had scores on the gross-motor subtest assessing bilateral coordination of approximately 0.5 standard deviations (2.5 points) lower than their counterparts

in the lowest quartile. Children in the highest average lifetime quartile also scored more poorly in the fine-motor functioning, having scores of approximately 0.6 standard deviations lower (6.3 points) than those in the lowest quartile.

e) Cleveland study

The WPPSI was administered to 242 children at the age of 4 years and 10 months (Ernhart et al., 1989a). Statistically significant correlations between IQ (full scale and subscales) and PbB level measured pre- and perinatally and at ages 2 and 3 years (and a lifetime postnatal average) became non-significant after adjustment for covariates. No estimates for effect size were presented in the original report (Ernhart et al., 1989a).

f) Glasgow study

No neurobehavioural assessments were carried out beyond 2 years of age (Moore et al., 1989).

g) Kosovo study

No results beyond 2 years of age were reported (Graziano et al., 1990; Wasserman et al., 1992).

h) Port Pirie cohort study

The principal finding at 4 years was an inverse association of McCarthy Scales of Children Abilities (MSCA) scores (General Cognitive Index (GCI), Perceptual Performance and Memory) with most indices of lead exposure (McMichael et al., 1988). After adjustment for covariates, the association of GCI was not significant at certain specific ages. However, it remained significant for the integrated postnatal average for which an effect size of 7.2 GCI points lost in association with an increase of lifetime average PbB level from 0.5 to 1.5 μmol/litre (10.4-31.2 μg/dl) was estimated.

Between 7 and 8 years of age the IQ of 494 children was assessed with the WISC-R (Baghurst et al., 1992). After adjustment for covariates there was little association with pre- and perinatal lead exposure assessments but significant decrements in full-scale IQ of between 3.7 and 4.8 points (depending on age) for each (natural) log unit increase in lifetime average PbB concentration were observed. The estimated effect size for the

lifetime average exposure up to 3 years of age was a loss of 5.3 IQ points in association with an increase in PbB level from 0.48 to 1.44 μmol/litre (10 to 30 μg/dl).

The Block Design subscale of the WISC-R, which tests spatial abilities, exhibited the strongest association with lead exposure and estimated effect sizes were stronger in girls than boys for both the MSCA and WISC-R.

i) Sydney study

At the age of 4 years, 207 children were assessed with the McCarthy Scales of Children Abilities (MSCA) and virtually no significant associations with any measures of PbB were observed (Cooney et al., 1989b).

Follow-up assessments in 175 children using WISC-R at age 7 also yielded no associations (crude or adjusted) with blood lead history (Cooney et al., 1991).

8.3.5.5 Questions prospective studies have not answered

A disappointment of the prospective studies was their inability to reach any obvious consensus on the behavioural phenotype associated with low-level lead exposure, or on age(s) of critical sensitivity. This latter fact may reflect the phenomenon of intra-individual "tracking", whereby an individual maintained approximately consistent ranking with respect to his or her PbB concentration at any age, or it may reflect the need for chronic exposure over extended periods in order for causal effects to become apparent.

8.3.5.6 Attempting a consensus

As discussed previously, no clear delineation of an age (or age range) of maximal sensitivity to lead exposure has emerged from the prospective studies, and there is a diversity of reporting styles which makes attempts to compare studies and establish a consensus of opinion very difficult.

Nevertheless, it would appear essential to attempt some sort of synthesis of studies performed so far, given that the social and economic consequences of preventing an adverse health effect are potentially enormous.

A meta-analysis by Needleman & Gatsonis (1990) concluded that the overall pattern of results was most unlikely to have occurred by chance. As an approach to the problem of obtaining the "best" estimate of the effect of lead exposure on neurobehavioural development, a common estimate of the partial correlation between lead burden and IQ was determined. However, in order to derive such an estimate with some degree of certainty, it is essential to find a common outcome, and to identify studies for which at least broadly comparable exposure measures are available.

Schwartz (1993) has identified three prospective studies and five cross-sectional studies that examined the association of lead exposure as determined by PbB concentrations with full scale IQ. For the prospective studies, the exposure measures used were 24-months PbB level (Boston) and lifetime average up to 3 years of age (Cincinnati and Port Pirie).

There was only one measure for each of the cross-sectional studies. Despite the compromises necessary for such a comparison, the estimated effect sizes for an increase in PbB level from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl) for all seven studies lay between 1 and 6 IQ points lost (with five of the studies lying between 1 and 4), and the associated 95% confidence limits only just embraced the value zero for 3 of the 7 studies.

Thus, a broad consensus does emerge from a rough comparison. From the estimates summarized by Schwartz (1993), a weighted mean for the six coefficients accompanied by a standard error of 0.4 was estimated to be 2.6 IQ units lost for an increase in PbB from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl).

8.3.6 *Task group overview and interpretation of prospective studies on children*

8.3.6.1 *Rationale*

As a complement to the narrative review, prepared by the Task Group, a quantitative overview of the findings of the prospective studies was considered to be a valuable means of assessing the overall strength of evidence for an association between blood lead summary measures and school age IQ.

While individual studies vary somewhat in their design and their analysis strategies, their underlying objectives are closely related. For any generally applicable conclusions on general

population lead exposure and its effect on intellectual attainment to be reached, some consistency of evidence across studies is highly desirable.

Since any single study has considerable random error in estimating a relationship, a quantitative overview (or meta-analysis) can be a valuable means of defining what is the plausible magnitude of statistical association between PbB measures and child IQ.

It seems appropriate, given the quite different types of study design, to present two separate meta-analyses dealing with prospective studies and cross-sectional studies, respectively.

Any such meta-analysis needs cautious interpretation. The caveats in drawing causal inferences from statistical associations apply to any meta-analysis just as they do to individual studies. Any increase in statistical precision regarding the magnitude of association does not eliminate the potential for bias in any observational study on human populations.

8.3.6.2 The prospective studies

There are four prospective studies: Boston (Bellinger et al., 1992); Sydney (Cooney et al., 1989a,b); Cincinnati (Dietrich et al., 1993a); and Port Pirie (Baghurst et al., 1992) which presented quantitative results in a form suitable for an overview (i.e. with regression coefficients and standard errors). The Task Group concentrated on school age assessment because:

a) the studies used the same outcome measure (WISC-R), which is widely accepted and has been previously evaluated in cross-sectional studies; and

b) intellectual assessment at primary school age (6-10 years) is, perhaps, of greatest overall relevance in reaching a consensus on the public health importance of childhood lead exposure.

Unfortunately, the Cleveland study did not publish findings in the same quantifiable manner. The potential impact of this apparently "negative" study on the overall evidence will be discussed in section 8.3.6.2(c).

a) Measures of exposure, outcome and association

All four studies have used blood lead as the measure of body lead burden, but the timing and frequency of examinations has varied as has the choice of summary measures (averages over time).

In a meta-analysis it seems appropriate to concentrate on measures of association after adjustment for confounders. While there is some variation in choice of confounders, the two key covariates (mother's IQ and HOME scores) appear in all four studies.

The Port Pirie study used the logarithm of the PbB concentration in the multiple regression analysis while the other three studies used untransformed PbB concentration. This difference in statistical style can be reconciled by converting the lead regression coefficients to estimated changes in IQ for a specific increase in PbB concentration, i.e. from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl). This equals 10 times the regression coefficient (as published) for the Boston and Cincinnati studies and log 2 times the regression coefficient for the Port Pirie study.

It is recognized that the specific subscales of performance and verbal IQ are of separate interest (e.g., the performance IQ has been rather consistently shown to be more reliably associated with postnatal lead exposure amongst the prospective studies (McMichael et al., 1988; Bellinger et al., 1991a; Dietrich et al., 1991, 1992, 1993b). However, it appears more important to focus on full-scale IQ as the primary outcome measure, otherwise concerns about post-hoc selection may be raised. Such full-scale IQ was measured at age 6.5, 7 and 10 years in the Cincinnati, Port Pirie, Sydney and Boston studies, respectively.

b) Display of individual study findings

Since most studies have not shown perinatal PbB level to be predictive of intellectual performance, attention will be focused on the various measures of postnatal PbB level. In fact, there are seven such measures in each study that have been related to full-scale IQ in the reports. Tables 21 and 22 summarize the magnitude of association together with the standard error for all reported analyses, each after adjustment for confounders.

Table 21. Magnitude of association between blood lead and full-scale IQ from four prospective studies

	No. of children	Age at which blood lead was measured	Estimated change in full-scale IQ[a]
Boston	148	year 1	0.0 (1.6)
		year 1½	-1.2 (1.8)
		year 2	-5.8 (2.1)
		year 5	-2.6 (2.9)
		year 10	-4.6 (5.2)
		mean of years 2-5	-8.2 (2.8)
		mean of years 2-10	-8.6 (3.4)
		mean of 6 months to 10 years (unpublished)	-5.7 (3.2)
Cincinnati	251	mean of year 1	0.1 (1.4)
		mean of year 2	-0.2 (0.8)
		mean of year 3	-1.3 (0.9)
		mean of year 4	-1.5 (1.0)
		mean of year 5	-2.3 (1.1)
		mean of year 6	-3.3 (1.4)
		mean of years 1-6	-1.3 (1.1)
Port Pirie	490	mean of first 15 months	-2.8 (1.4)
		mean of years 1-2	-3.2 (1.5)
		mean of years 1-3	-3.3 (1.6)
		mean of years 1-4	-3.2 (1.7)
		mean of years 1-5	-3.0 (1.7)
		mean of years 1-6	-2.8 (1.7)
		mean of years 1-7	-2.6 (1.7)
Sydney	175	mean of years 1 and 2	-2.7 (2.8)
		mean of years 3, 4 and 5	-1.9 (1.9)
		year 7	-1.4 (1.7)
		mean of years 1-7	-1.6 (2.2)

[a] From 0.48 to 0.96 μmol/litre (10 to 20 μg/dl) blood lead (and its standard error) after adjustment for confounders

Except for the earliest postnatal PbB values in the Boston and Cincinnati studies, the adjusted associations between PbB level and IQ are consistently negative (i.e. inverted). However, the "random noise" in each study's analysis means that there is considerable variation in levels of statistical significance. Hence, there is a need for a more systematic overview combining the evidence from all studies.

Table 22. Association between blood lead levels and full-scale IQ from ten cross-sectional studies

	No. of subjects	Estimated change in full-scale IQ[a]
Lavrion, Greece	509	-2.7 (0.7)
Edinburgh, Scotland	501	-2.6 (0.9)
Greenwich, England	129	-5.6 (3.2)
European, multi-centre		
Bucharest, Romania	301	-0.4 (2.6)
Budapest, Hungary	254	+0.8 (1.8)
Modena, Italy	216	+0.9 (4.2)
Sofia, Bulgaria	142	+2.2 (2.3)
Dusseldorf 1, Germany	109	-4.6 (4.5)
Dusseldorf 2, Germany	109	-3.9 (5.1)
Zagreb, Croatia	48	-1.5 (4.5)

[a] From 0.48 to 0.96 µmol/litre (10 to 20 µg/dl) blood lead (and its standard error) after adjustment for confounders

c) A quantitative overview

The prime difficulty here is the different choices of PbB summaries in the four studies. In undertaking a meta-analysis it would have been better if all studies had essentially the same PbB measures in their multiple regressions. Possible choices might have been (i) a specific time point, e.g., 2 years or (ii) the means over a specific interval, e.g., 0 to 5 years.

However, from the available analyses, some broadly similar summaries can be chosen, as follows:

i) There is some advantage in considering the mean PbB level over a number of years, since it summarizes cumulative exposure

and also achieves a more reliable ranking of individuals than a single value. The available long-term means are:

Boston:	mean of 6 months to 10 years (D. Bellinger, personal communication to the IPCS, 1993)
Cincinnati:	mean of years 1 to 6
Port Pirie:	mean of years 1 to 7
Sydney:	mean of years 1 to 7

Although they differ in frequency and age range, these three summaries should be very highly correlated with one another. The resultant meta-analysis is displayed in Fig. 15. Each of the individual study confidence intervals includes zero, indicating that significance at $P < 0.05$ was not reached. However, the combined evidence, weighting studies according to the inverse of their variance, produces a weighted mean decrease in full-scale IQ of 2 points for a 0.48-μmol/litre (10-μg/dl) increase in PbB level, with 95% confidence interval from -0.3 points to -3.6 points ($P = 0.01$).

ii) An alternative approach is to consider PbB level at a specific time or average over shorter intervals of time. For this approach, the analyses of these studies are most comparable during the first three years, as follows:

Boston:	2 year measure
Cincinnati:	mean of year 3
Port Pirie:	mean of years 1 to 3
Sydney:	mean of years 1 and 2

This second meta-analysis is displayed in Fig. 16. The data here support an inverse association more strongly than in Fig. 15, and the combined evidence estimates a mean decrease of 2.6 IQ points for a 0.48-μmol/litre (10-μg/dl) increase in PbB level, with 95% confidence interval from -1.2 points to -4.0 points ($P < 0.001$).

However, it should be noted that the estimates here are heavily dependent on the choice of time points for PbB level. For instance, if one instead chose:

Boston:	1.5 year measure
Cincinnati:	mean of year 2
Port Pirie:	mean of years 1 and 2
Sydney:	mean of years 1 and 2

then the combined estimate is roughly halved in magnitude and is of borderline significance.

One needs to recall that the other prospective study, carried out in Cleveland (Ernhart et al., 1989a), has no equivalent data, but reported no significant association. This study comprised about 150 evaluated children, and would influence the overall evidence in a less significant direction if the data were able to be included.

8.3.6.3 *A quantitative assessment of the cross-sectional studies*

There have been more cross-sectional studies that have related body burden to full-scale IQ in school-age children, but they cannot all be included in a single meta-analysis. Here attention is focused on the PbB studies, and it would be appropriate subsequently to undertake an equivalent meta-analysis of the tooth lead studies. The studies included have differed in the number and nature of covariates. In particular, in most of the groups within the London and European multi-centre study (MCS), maternal IQ has not been controlled. Studies in which regression coefficients could not be obtained were excluded. Since the studies not included in the analysis account for only a small fraction of the total children investigated, their exclusion has a negligible effect on the meta-analysis estimates of effect size.

The following studies are included in the meta-analysis:

Lavrion, Greece	(Hatzakis et al., 1989)
Edinburgh	(Fulton et al., 1987)
London (Greenwich)	(Yule et al., 1981)
European multi centre study	(Winneke et al., 1990)

The European multi-centre study comprises seven separate analyses for children in Bucharest, Budapest, Modena, Sofia, Dusseldorf (two studies) and Zagreb. The Lavrion centre in this study was separately reported by Hatzakis et al. (1987).

As in the meta-analysis for the prospective studies, individual cross-sectional studies varied as to whether the logarithm of the PbB level or untransformed PbB level was used in the multiple regression analysis. Hence, as before, all associations are expressed in terms of the estimated changes in full-scale IQ for a change in PbB level from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl), after adjustment for confounders, as shown in Table 13.

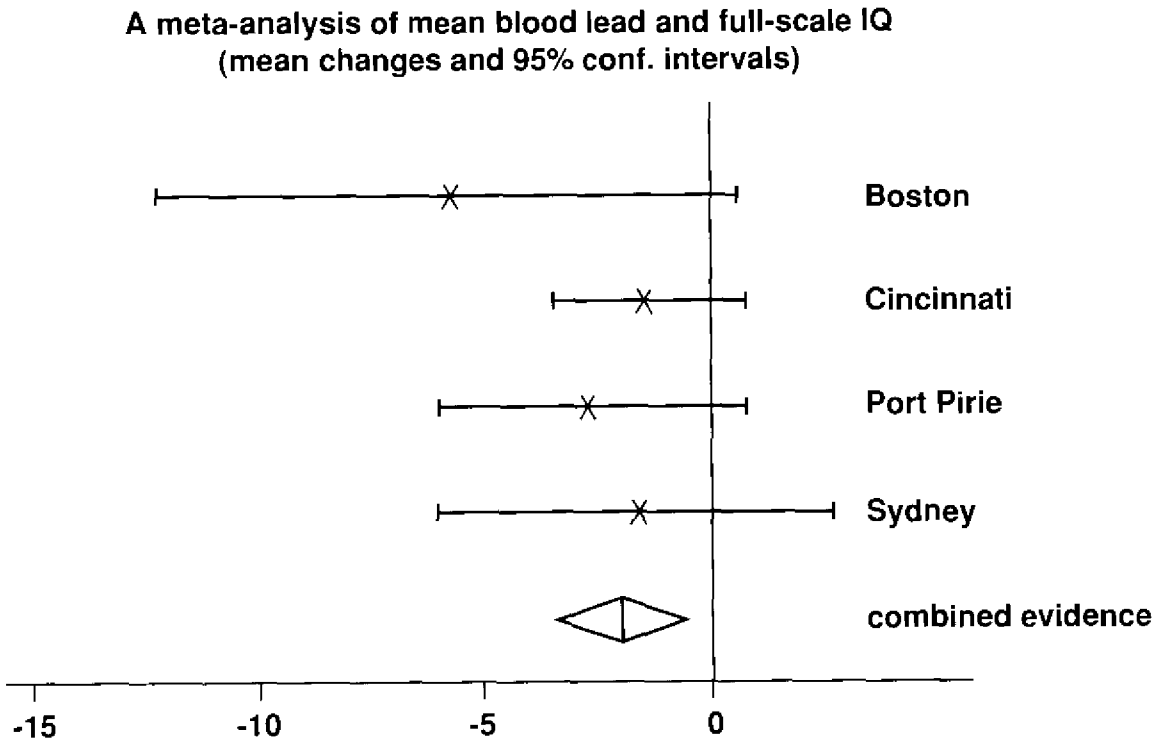

Fig. 15. Estimated mean change in IQ for an increase in blood lead level from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl) in prospective studies

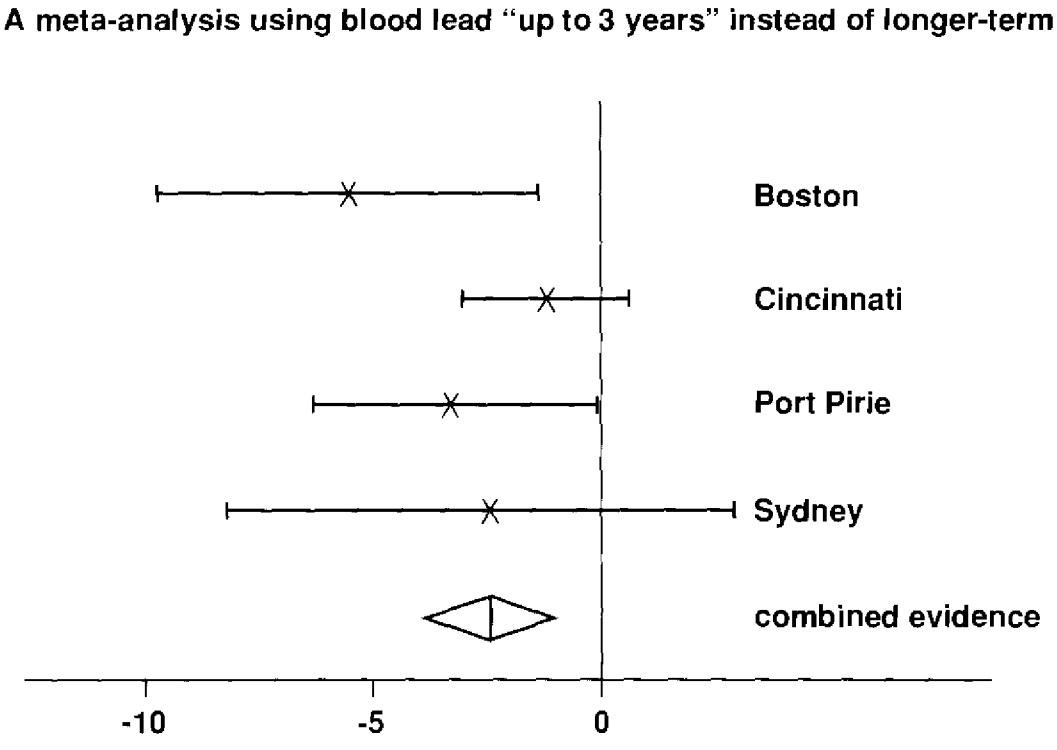

Fig. 16. Estimated mean change in IQ for an increase in blood lead level from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl)

Fig. 17 shows these estimates and their 95% confidence limits for the 10 study samples. Only the two largest studies (Lavrion and Edinburgh) show statistically significant inverse associations, as indicated by confidence intervals entirely to the left of zero. The limited statistical power of the other studies is reflected in their wide confidence intervals. Despite the considerable variation in the study designs (e.g., sample selection, choice of confounders), there is no evidence of statistical heterogeneity. In other words, all the confidence intervals overlap and the heterogeneity test is not statistically significant.

A combination of the evidence from all of these cross-sectional studies produces a more precise overall estimate of association, as shown in Fig. 17. This meta-analysis of the cross-sectional studies estimates that full-scale IQ is reduced by 2.15 points for an increase in PbB level from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl), with a 95% confidence interval from -1.2 points to -3.1 points ($P < 0.001$).

8.3.6.4 Task group overview of cross-sectional studies

a) Methods of controlling for confounders

A particular methodological concern in the cross-sectional studies is the manner in which they have taken account of confounding factors in deriving adjusted estimates of associations between body lead burden and neuropsychological performance, in particular IQ.

The three aspects of the problem are:

i) Which potential confounders are measured? There is considerable variation between studies here, suggesting that no individual study can have fully corrected for the full range of parental and social influences on IQ.

ii) How were confounders selected for inclusion in the analysis? Some studies include confounders solely on the basis of their strength of association with outcome (IQ), while others have given attention to their association with body lead burden. It is difficult to assess the extent to which these differences would affect the results, but the former is more generally accepted statistical practice.

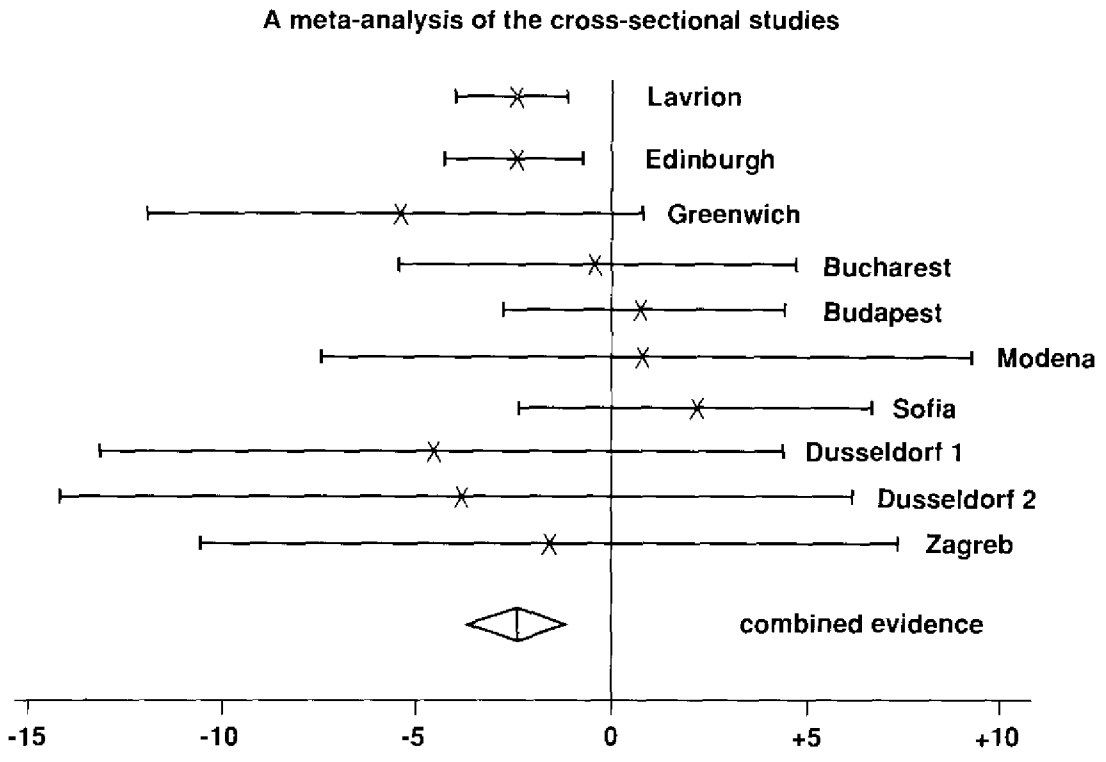

Fig. 17. Estimated mean change in IQ for an increase in blood lead level from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl) in cross-sectional studies

iii) Which statistical analysis strategy was employed in reaching a final model? Most studies have adopted some form of multiple regression technique, but have varied as to whether forward selection (i.e. model building), backwards selection (i.e. model collapsing) or more arbitrary choices of final model were employed. In the larger studies, the choice between such strategies is unlikely to matter, but in smaller studies the greater play of random variation could make the results dependent on the statistical technique.

b) What they told us

In most studies a negative association between lead measures and IQ measures is found in uncontrolled data. This difference is usually in the range of 4 to 6 IQ points. Most studies also confirmed the positive association between lead measures and indicators of social disadvantage, whether this is indicated by SES, maternal education or other more detailed indicators of non-optimal child-rearing environments, such as marital quality or maternal depression. When these social and other confounding factors are controlled, the effect has been, in most cases, to reduce the strength of the association between lead measures and IQ, although it remains in the same direction. Where maternal intelligence has not been controlled, the impact of correction for covariates tends to be smaller, and where more detailed social measures have been controlled, the impact has been greater.

c) What they did not tell us

The cross-sectional nature of these studies, and the fact that many used a single measure of current exposure, limited their usefulness in answering questions relating to the natural history of the association between lead exposure and outcomes, including whether there were critical periods of exposure, and whether lead-associated deficits were persistent or reversible. Equally they were limited in the information that could be obtained relating to the natural history of confounders. They were also unable to answer questions of reverse causality.

8.3.6.5 *An interpretation of the overview of prospective and cross-sectional studies*

The above meta-analyses of the prospective studies and cross-sectional studies reveal a consistency between studies which points towards a "collectively significant" inverse association between

PbB level and full-scale IQ. Taking the results in Fig. 15 as a guideline, there appears to be a mean decrease in full-scale IQ of the order of 2 IQ points for a change in mean PbB level from 0.48 to 0.96 μmol/litre (10 to 20 μg/dl).

Below this range, uncertainties are increased, concerning firstly the existence of an association and secondly estimates of the magnitude of any putative association. The relatively limited numbers of children in most studies with PbB levels below this range, the strong contributions of confounding variables, and limitations in the precision in analytical and psychometric measurements combine to lower statistical power to detect associations and to estimate their magnitude.

The key question is whether this statistical association is directly attributable to the causal influence of lead on child IQ. It is important to consider alternative explanations as follows:

a) *Chance* The consistency of alternative analyses and the level of significance achieved suggest that chance cannot be a complete explanation. However, the confidence intervals are relatively wide, so that the magnitude of true association could be as low as a < 1-point (rather than a 2-point) deficit, or as high as > 3 points.

b) *Confounding factors* The adjusted lead/IQ associations tend to be substantially weaker than the unadjusted associations, which indicates that confounding factors are important. Since none of the studies can claim to have taken complete account of confounders, (e.g., father's IQ is not included), it seems likely that some of the remaining lead/IQ relationship, after adjustment, may still be attributable to a degree of unexplained confounding.

c) *Reverse causality* One initial justification for the prospective studies was that they could measure early exposure to lead and relate it to later child development, thus removing the problem of reverse causality potentially present in the cross-sectional studies. However, it has turned out that very early lead exposure, e.g., in the perinatal period, is not related to school-age IQ. The question arises as to whether children of lower IQ could exhibit behaviour patterns at earlier ages, e.g., around age 2 and older, which could enhance their uptake of lead. Perhaps, such reverse causality remains a possibility even in the prospective studies.

d) *Selection biases* The positive studies may perhaps be more likely to report in more quantitative details, as indicated by the

absence of relevant data from Cleveland in the prospective studies. Post-hoc selection based on the more significant PbB concentrations may lead to exaggerated estimates.

It is a matter of debate and conjecture as to the extent to which these four issues should inhibit claims of a causal relationship in the prospective studies. The essential problem is that observational epidemiology cannot provide definitive evidence of causality when the key statistical association is weak, the temporal relationship is unclear and major confounders are present.

8.3.7 Hearing impairment in children

Schwartz & Otto (1987) reported that the probability of elevated pure-tone hearing thresholds at 500, 2000 and 4000 Hz increased significantly with increasing PbB level in 4519 subjects (4-19 years of age) who participated in the NHANES II study. Variables included in the backwards stepwise regression models included information derived from medical history, clinical examinations, and assessment of developmental milestones.

Schwartz & Otto (1991) examined data for subjects (6-19 years of age) from the Hispanic Health and Nutrition Examination Survey (HHANES) study which included three distinct ethnic groups. After excluding 283 subjects with previous ear problems (discharges, ruptured ear drums or tinnitus), data for 3262 were analysed. The authors concluded that increasing PbB level in the range 0.36-0.86 μmol/litre (7-18 μg/dl) was associated with approximately 2 dB loss of pure-tone hearing at frequencies of 500, 1000, 2000 and 4000 Hz.

Dietrich et al. (1992) assessed the relationship between scores on a test of sensory auditory processing (SCAN) and prenatal/postnatal PbB concentrations in 215 subjects drawn from the Cincinnati prospective cohort study. Higher prenatal, neonatal and postnatal PbB concentrations were associated with more incorrect identification of common monosyllabic words presented under conditions of muffling. Other variables associated with impaired central auditory processing were pure-tone audiometry results, social class, quality of caretaking in the home, birth weight, gestational age, a measure of obstetrical complications, and consumption of alcohol during pregnancy. Following adjustment for these co-factors, lifetime average PbB concentration remained significantly and inversely associated with SCAN performance.

8.4 Renal system

Acute exposure to lead is known to cause proximal renal tubular damage, characterized by generalized aminoaciduria, hypophosphataemia with relative hyperphosphaturia, and glycosuria (Chisolm, 1962). Cellular structural changes include nuclear inclusion bodies, mitochondrial changes and cytomegaly of the proximal tubular epithelial cells (Cramer et al., 1974). Diagnosis of lead-induced altered renal function or disease is difficult since there are no specific indicators; blood urea nitrogen (BUN) and creatinine levels become elevated only when two-thirds of renal function has been lost (Bernard & Becker, 1988).

8.4.1 *Clinical studies*

From a study of seven men occupationally exposed to lead in a shipyard during oxy-acetylene flame cutting of lead-painted steel hulls, Cramer et al. (1974) concluded that there is a continuum of morphological and functional change in the pathogenesis of chronic lead nephrotoxicity. Each subject was treated in hospital 3 or more days after recent exposure and PbB levels exceeded 3.36 μmol/litre (70 μg/dl) in all cases. On the basis of microscopic examination of biopsy tissue, nuclear inclusion bodies were reported in proximal tubular cells during the early phase but there was no impairment of renal function. In a second phase, there was fibrosis associated with asymptomatic azotaemia and reduced glomerular filtration rate but without demonstrable proximal tubular dysfunction; renal failure was not seen in the study.

Weeden et al. (1979) diagnosed lead nephropathy in 15 lead workers, all having reduced glomerular filtration rates. Renal biopsies of six of the subjects showed focal interstitial nephritis in addition to non-specific changes in the proximal tubules. At the time of examination, PbB levels for 11 of the 15 workers were within the range 1.92-3.84 μmol/litre (40-80 μg/dl).

Baker et al. (1979) reported increased BUN and decreased creatinine clearance in 28 workers, all of whom had relatively prolonged, high-dose lead exposure in lead smelting or chemical manufacturing.

A study by Maranelli & Apostoli (1987) of 60 workers, described as "lead poisoned" and having PbB levels of 3.45 ± 0.80 μmol/litre (71.9 ± 16.6 μg/dl), found no definitive correlation

between PbB, lead in urine after chelation, and BUN, serum creatinine and serum uric acid.

8.4.2 Epidemiological studies

8.4.2.1 Occupational cohorts

Several recent studies of lead-exposed workers provide further information relating to dose-effect relationships. The emphasis in these studies was on lead and its possible association with adverse effects on health. However, exposure to other potentially toxic substances in the working and living environment should not be overlooked/ignored.

For example, Buchet et al. (1980) examined 25 male lead smelter workers and 88 male control workers. The PbB levels of the lead workers were in the range 1.62-2.94 μmol/litre (33.8-61.3 μg/dl) for a mean of 13.2 years (range 3.1-29.8 years) of lead exposure. The PbB levels for the controls were in the range 0.26-1.64 μmol/litre (5.5-34.2 μg/dl). There were no differences for parameters of renal function between the groups and no signs of clinical renal impairment. It was concluded that a PbB level of less than 2.98 μmol/litre (62 μg/dl) is not associated with renal toxicity.

N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal enzyme present in renal tubular cells. This enzyme is a sensitive but non-specific indicator for early sub-clinical nephrotoxicity. In a study on 29 lead-exposed workers, Meyer et al. (1984) found increased NAG in urine, but there was no correlation with PbB level. However, NAG level was found to be normal in the 5 subjects with PbB levels exceeded 3.36 μmol/litre. These authors speculated that long-term high exposure to lead may deplete the kidneys of NAG or render it insensitive to the effects of lead exposure.

Verschoor et al. (1987) studied 155 male lead workers and 126 control workers who were matched for age, smoking habits, socioeconomic status and duration of employment. The PbB levels of the lead workers were in the range of 0.43-4.71 μmol/litre (8.3-97.6 μg/dl) compared with the controls 0.15-0.96 μmol/litre (3.1-18.8 μg/dl). The lead workers had elevated ZPP levels (34-292 μmol/mol haemoglobin) compared with controls (10-35 μmol/mol haemoglobin). No significant differences were found for various indicators of renal function; all urinary and serum parameters were within normal ranges. There were no differences

in protein excretion patterns and no signs of renal impairment. However, the authors found that NAG levels in the lead-exposed workers were higher than control values and increased with increasing PbB levels. They concluded that lead exposure resulting in PbB levels of under 3.0 μmol/litre (62 μg/dl) can affect renal tubular functions as measured by NAG excretion; lead appeared to affect the tubular parameters more than the glomerular parameters in moderately exposed workers.

Ong et al. (1987) examined 158 male and 51 female lead battery or smelter workers and 30 control workers. The lead workers had 1-36 years exposure with an average of 10.8 ± 8.0 years and PbB levels in the range of 0.14-3.84 μmol/litre (3-80 μg/dl); only five workers exceed 2.88 μmol/litre (60 μg/dl). The authors found a weak but statistically significant positive association between PbB and blood urea nitrogen, and between PbB and serum creatinine, and that creatinine clearance was reduced with increasing PbB level. NAG levels in the lead-exposed workers were significantly higher than control values and increased with increasing urine lead level when the data were adjusted for age. These authors concluded that a relatively low PbB level can affect renal function.

Not all investigators have found parallel association between PbB and NAG levels. Gennart et al. (1992b) compared 98 lead-exposed lead acid battery workers (mean PbB level 2.45 μmol/litre, 51 μg/dl, geometric mean ZPP 10.2 μg/g Hb) with 85 controls (mean PbB level 1.00 μmol/litre, 20.9 μg/dl, geometric mean ZPP 2.84 μg/g Hb) recruited from other departments in the same factory. None of the indicators of renal function (retinol-binding protein, β_2-microglobulin, albumin or NAG in urine, or creatinine or β_2-microglobulin in serum) were correlated with PbB level, duration of exposure or ZPP, or showed significantly different mean values between the lead-exposed and control groups of workers.

Cardenas et al. (1993) recently evaluated 27 different indications of renal dysfunction in 50 workers exposed to lead and 50 controls. There were significant increases in urinary NAG and sialic acid in the lead exposed group. These changes may represent minor cellular modifications rather than significant functional or irreversible renal damage. There was a significant decrease in urinary 6-keto $PGF^{1\alpha}$ and a significant increase in TXB^2. These eicosanoid changes may reflect systemic functional vascular changes rather than an effect of lead on the kidney.

8.4.2.2 General population

An epidemiological survey on 283 persons in Scotland, from households with water lead concentrations in excess of 100 μg/litre, revealed a close correlation between water lead content and PbB and serum urea concentrations (Campbell et al., 1977). The frequency of renal dysfunction in individuals with elevated PbB concentrations (> 2 μmol/litre or > 41 μg/dl) was significantly greater than that of age- and sex-matched controls.

Pocock et al. (1984) measured serum creatinine, urate and urea concentrations in 7364 British men, and 74 subjects had PbB levels equal to or greater than 1.8 μmol/litre (37.3 μg/dl). The authors concluded that there was no indication that exposure to lead at concentrations commonly encountered in Britain was responsible for impaired renal function.

Staessen et al. (1992) investigated the relationship between lead exposure and renal function as part of a cross-sectional population study of the health effects of environmental exposure to cadmium. Creatinine clearance, PbB and ZPP were measured in a random population sample of 965 men (geometric mean PbB level was 0.55 μmol/litre or 11.4 μg/dl) and 1016 women (geometric mean PbB level was 0.36 μmol/litre or 7.5 μg/dl). Creatinine clearance rate (mean was 99 ml/min in men, 80 ml/min in women) was inversely correlated with PbB and ZPP levels before and after adjustment for age, body mass index and diuretic treatment. Also positively correlated were serum β_2-microglobulin and PbB level in men, serum β_2-microglobulin and ZPP in men and women, and serum creatinine and ZPP in men. Impaired renal function could not be explained by exposure to cadmium or by elevated blood pressure. The authors concluded that exposure to lead may impair renal function in the general population. However, the study could not exclude the possibility that renal impairment may lead to an increase in PbB level.

8.4.2.3 Cohort mortality studies

"Lead poisoning" was a diagnosis given to 241 workers employed for 1-30 years at the Port Pirie lead smelter between 1928-1959 by a State medical board. Death registration records for the period 1930-1977 identified 140 deaths among the group. The cause of death profile was compared with that of 695 other male decedents, predominantly production workers and a smaller number of office workers. Age-standardized mortality analysis

revealed a substantial excess of deaths attributed to chronic nephritis and to cerebral haemorrhage. The rates for lead-poisoned workers exceeded those for the other workers, and both exceeded the rates for the Australian general male population. The rates decreased over successive calendar periods but excess rates persisted for chronic nephritis up until 1977 (McMichael & Johnson, 1982).

8.5 Cardiovascular system

Two persistent issues have been under intense study since publication of Environmental Health Criteria 3: Lead (IPCS, 1977):

a) whether lead is a factor in hypertension and, if so, whether there is a causal relationship;

b) whether lead is contributory to cardiovascular effects influencing morbidity or mortality.

8.5.1 Blood pressure

8.5.1.1 Studies on occupationally exposed cohorts

From a study of 431 white male police officers 24-55 years of age (Moreau et al., 1982; Orssaud et al., 1985), it was concluded that systolic and diastolic blood pressure was related to PbB level, the correlation being greatest for the younger subjects and decreasing with age. Statistical adjustment was made for alcohol consumption and body mass index, but not for smoking. The magnitude of observed association between systolic pressure and PbB level in this small study was somewhat greater than in the larger general population studies cited below.

Parkinson et al. (1987) studied 270 lead battery workers and 158 non-exposed workers and compared lead exposure with systolic and diastolic blood pressures. After controlling for age, education, income, cigarette smoking, alcohol consumption and exercise, there was a small and non-significant association. The average PbB level of lead-exposed workers was 1.92 ± 0.62 μmol/litre (40 ± 13 μg/dl), whereas in non-exposed workers it was 0.34 ± 0.24 μmol/litre (7 ± 5 μg/dl).

8.5.1.2 Studies in the general population

The possible relationship between PbB concentration and blood pressure has been examined in several large-scale population

studies. These include the British Regional Heart Study (BRHS), the US NHANES II (National Health and Nutrition Examination Survey) and studies in Wales, Denmark, Canada and Belgium.

The BRHS is a prospective study of 7735 men, initially aged 40-59 years, from 24 British towns, who were first examined in 1978-1980 (Shaper et al., 1981). The median PbB level was 0.7 μmol/litre (14.5 μg/dl). The initial findings (Pocock et al., 1984), which indicated a lack of association between PbB level and blood pressure, were later re-examined to take account of potential confounding factors such as alcohol, smoking and town of residence. Pocock et al. (1988) noted that 95% confidence intervals for systolic and diastolic blood pressure plotted against PbB concentrations overlapped and showed no elevation even at the highest observed PbB concentration. Applying statistical techniques to adjust mean systolic and diastolic blood pressure measurements for body mass index, age, alcohol consumption, cigarette smoking and town of residence showed signs of a weak association, particularly for diastolic pressure and PbB level. Multiple regression analysis showed that adjustment for personal characteristics but not for town of residence rendered both systolic and diastolic regressions on log PbB insignificant, chiefly because alcohol consumption is an important confounder, being positively related to both blood pressure and PbB level. Introducing an extra adjustment for town of residence made the systolic and diastolic regressions highly statistically significant, even though the associations were weak. These cross-sectional data indicated that for every doubling in PbB level (e.g., from 0.8 to 1.6 μmol/litre) there are estimated mean increases of 1.45 mmHg (95% confidence interval 0.47-2.43 mmHg) in systolic blood pressure and 1.25 mmHg (95% confidence interval 0.65-1.85 mmHg) in diastolic blood pressure.

The NHANES II study, a USA national cross-sectional survey carried out in 1976-1980, included PbB and blood pressure measurements in a general population sample of 5803 men and women aged 12-74. Geometric mean PbB levels were around 0.72 μmol/litre (about 15 μg/dl) for men and approximately 0.53 μmol/litre (11 μg/dl) for women. Several authors have examined these data for possible PbB and blood pressure associations.

In an analysis controlling for the confounding factors of age, race and body mass index, Harlan et al. (1985) and Harlan (1988) found a significant association between PbB level and blood

pressure for men but not for women. White males aged 40-59 years from the same data set were analysed by Pirkle et al. (1985), and the correlation between PbB level and blood pressure was confirmed. In further analysis of the whole age range, adjustments for possible time trend and geographical site effects did not affect the significance of the association in males (Landis & Flegal, 1988; Schwartz, 1988), although its magnitude did become somewhat less pronounced.

Gartside (1988) applied a method of forward stepwise regression to PbB and blood pressure data from NHANES II and reported that the results for white men, white women and black men were contradictory and lacked consistency and reliability. He noted that the overall average was too small to conclude association between PbB level and blood pressure in this study.

Two surveys were carried out in Wales by Elwood et al. (1988a,b). The Welsh Heart Programme carried out in 1985 provided complete PbB, blood pressure and other data for 865 men and 856 women aged 18-64. The geometric mean PbB level for men was 0.56 μmol/litre (11.6 μg/dl) and for women was 0.43 μmol/litre (9.0 μg/dl). In neither sex was there a significant correlation between PbB level and systolic or diastolic blood pressure. The second study was in a cohort of men aged 49-65 years living in Caerphilly, Wales. The geometric mean PbB level (N = 1137) was 0.61 μmol/litre (12.7 μg/dl). Complete data from 1137 subjects, ranking blood pressure readings according to PbB level, did not reveal any trend in the percentage of subjects with systolic pressure above 160 mmHg. The authors corrected only for age as a confounding factor.

Data from a Canadian study (Neri et al., 1988) collected during 10 months in 1978-1979 for 2193 subjects aged 25-64 showed a weak but statistically significant association between PbB level and diastolic blood pressure.

Grandjean et al. (1989b) studied 504 men and 548 women residing in Glostrup (Denmark) at age 40; 451 men and 410 of the women were followed-up five years later. Average PbB levels for the men at 40 and 45 years of age were 0.62 μmol/litre (13 μg/dl) and 0.43 μmol/litre (9 μg/dl), and for the women 0.43 μmol/litre (9 μg/dl) and 0.29 μmol/litre (6 μg/dl), respectively. All correlations found between PbB and blood pressure became insignificant when blood haemoglobin and alcohol intake were entered into multiple regression analyses; an independent effect of

low-level lead exposure on blood pressure could not be distinguished.

Möller & Kristensen (1992) examined 1052 men and women in Copenhagen, Denmark, in 1976, and re-examined them in 1981 and 1987 (men only). Initial mean PbB levels were 0.65 μmol/litre (13.6 μg/dl) in men and 0.46 μmol/litre (9.6 μg/dl) in women, and had fallen by around 30% 5 years later. For men, there was no significant association between PbB level and blood pressure (or between changes in PbB level and blood pressure) after adjustment for confounders (tobacco, alcohol, body mass and physical activity). For women, the association between PbB level and diastolic (but not systolic) blood pressure remained significant on both occasions, even after controlling for confounders.

A Belgium study (Dolenc et al., 1993) included 827 men and 821 women (mean age 25) whose mean PbB levels were 0.56 and 0.34 μmol/litre (11.6 and 7.07 μg/dl), respectively. After adjustment for covariates (body mass index), pulse rate and serum creatinine and serum calcium levels), systolic blood pressure was inversely associated with PbB level in men ($P < 0.05$). There were no significant PbB associations for diastolic blood pressure in men or for either pressure in women.

A study of 398 male and 133 female civil servants (Staessen et al., 1990) showed geometric mean PbB levels of 0.58 μmol/litre (12.06 μg/dl) and 0.46 μmol/litre (9.56 μg/dl) in men and women, respectively. Taking the data for both sexes together, there were statistically significant positive associations between PbB level and systolic and diastolic blood pressures ($r = +0.11$ in each case) but these became non-significant after adjustment for confounders (sex, age, BMI, pulse, δ-glutamyltranspeptidase (δ-GTP) and serum calcium level).

Another cross-sectional study involving only women was performed in Boston (Rabinowitz et al., 1987). Cord PbB levels (mean 0.33 μmol/litre, 6.9 μg/dl) among 3851 women correlated with both the systolic ($r = 0.08$) and diastolic ($r = 0.05$) blood pressures measured during and before delivery. Multivariate models of pregnancy hypertension as a function of age, parity, haematocrit, diabetes, ponderal index, and race were improved when lead was included as a predictor. Lead appeared to have a small but demonstrable association with pregnancy hypertension and blood pressure at delivery, but not with eclampsia.

In an overview of the BRHS, NHANES II and Welsh studies, Pocock et al. (1988) concluded that with overlapping confidence limits the data provided weak but reasonably consistent evidence of lead and blood pressure associations. They noted that the NHANES II data on 2254 men in the USA indicate a slightly stronger association between PbB level and systolic blood pressure, whereas data from over 2000 men in Wales did not show a statistically significant association. They inferred that a causal relationship could not be concluded from any of the epidemiological studies.

Staessen et al. (1994) have undertaken a more extensive meta-analysis of nearly all of the above studies and some other smaller ones as well. This amounted to a total of 19 studies with 28 210 subjects. They found that the association between PbB level and blood pressure was similar in both sexes. In all studies combined, a two-fold increase in PbB concentration was associated with a 1.0 mmHg increase in systolic pressure (95% confidence interval (CI); 0.3 to 1.7 mmHg; $P = 0.008$) and a 0.7 mmHg increase in diastolic pressure (95% CI: 0.2 to 1.3 mmHg; $P = 0.02$). These authors conclude that the published evidence suggests a weak positive association between blood pressure and lead exposure, but any such relationship may not be causal and is unlikely to entail any public health implications regarding hypertension.

8.5.2 Other cardiovascular effects

As recorded previously (IPCS, 1977), there is good evidence that signs of clinical lead poisoning sometimes include evidence of toxic action on the heart. Kopp et al. (1988) reviewed the cardiovascular actions of lead and concluded that the degree of cardiovascular involvement during episodes of acute lead intoxication depends on the duration of exposure and dose. It is not known whether environmental exposure to lead affects the electrical or mechanical activity of the heart.

8.5.2.1 Occupational studies

There have been several studies relating to cardiovascular effects in lead-exposed occupational groups. However, as with any study of an occupational cohort, it is important to evaluate the strength of the cause-effect relationship, the nature or substance of other contributory factors and how well the workplace

"exposure" has been evaluated for other potential toxicants. Thus, the occupational hazards associated with work in lead smelting or lead battery operations include, but are not limited to, lead.

8.5.2.2 Studies in the general population

Pocock et al. (1988) found that after 6 years of follow-up of the BRHS cohort of 7735 middle-aged men, 316 of the men had major ischaemic heart disease and 66 had had a stroke. After allowance for confounding effects of cigarette smoking and town of residence, there was no evidence that PbB was a risk factor for these cardiovascular events.

Möller & Kristensen (1992) studied 1052 men and women in Copenhagen, Denmark, and related blood pressure to subsequent cardiovascular morbidity and mortality over a 14-year period. There were significant positive associations between PbB level and both coronary and cardiovascular disease in univariate analysis, but these became non-significant after controlling for confounders.

a) Clinical studies

Boscolo & Carmignani (1988) measured plasma renin activity in hospitalized lead-exposed workers and concluded that synthesis or release of renin is increased by short or moderate exposure to lead and decreased with prolonged exposure.

b) Epidemiological studies

Kirkby & Gyntelberg (1985) found a significantly higher incidence of ischaemic ECG changes in a study of lead smelter workers (20%, mean PbB level 2.45 μmol/litre, 51 μg/dl), compared with matched non-exposed controls (6%, mean PbB level 0.53 μmol/litre, 11 μg/dl). There was also a slight (4-5 mmHg) increase in diastolic blood pressure in the lead workers compared with the controls.

c) Cohort mortality studies

Two studies (Cooper, 1988 and Fanning, 1988) reported an increased mortality rate of lead workers due to circulatory disease, but no such relationship was found in reports of studies by Gerhardsson et al. (1986) or Selevan et al. (1988). Gerhardsson et al. (1986) examined a lead-exposed sub-cohort of 437 from a

study cohort of 3832 male workers first employed at a copper smelter before 1967 and followed up from 1950 to 1981. There was no excess mortality due to ischaemic heart disease or cerebrovascular disease in the lead-exposed worker sub-cohort. Selevan et al. (1988) found no association between lead exposure and deaths due to hypertensive diseases in a review of mortality in a cohort of male hourly workers at a lead smelter. There were many confounding factors in each of these studies.

8.5.3 Summary

Despite intensive efforts to define the relationship between body burden of lead and blood pressure or other effects on the cardiovascular system, no causal relationship has been demonstrated in humans and the mechanisms remain obscure.

There is experimental evidence from animal studies indicative of an effect of lead on blood pressure, and several mechanisms have been proposed to explain these observations (see section 7.4).

8.6 Gastrointestinal effects

8.6.1 Occupational exposure

Colic is a well-recognized symptom of acute lead poisoning and is still reported in groups of lead-exposed industrial workers. Of particular concern are the reports of intoxication caused by acute exposure (inadequate protective measures) to lead associated with removal of lead-based paint by burning or sand-blasting and the demolition of lead-containing industrial plants. Symptoms of colic include abdominal pain, constipation, cramps, nausea, vomiting, anorexia, weight loss and decreased appetite.

Symptoms in adults typically occur at PbB levels of 4.8-9.6 μmol/litre (100-200 μg/dl) but have been noted at levels as low as 1.92 μmol/litre (40 μg/dl) (Baker et al., 1979; Haenninen et al., 1979; Awad El Karim et al., 1986; Pollock & Ibels, 1986; Muijser et al., 1987; Holness & Nethercott, 1988; Marino et al., 1989; Pagliuca et al., 1990; Schneitzer et al., 1990).

Positive histories of lead colic were given by 40 workers in a cohort of 158 secondary lead smelter workers who participated in a clinical field survey (Lilis et al., 1977). It was reported most frequently by those having PbB levels above 3.84 μmol/litre (80 μg/dl) at the time of examination and was not found where

ZPP was within the normal range. Thirty percent of workers having ZPP > 200 μg/g Hb had experienced symptoms.

In a study of a population of 585 black South African factory workers, Irwig et al. (1978) reported that the incidence of abdominal pain increased with increasing PbB level: it was 12% for the first quartile (PbB ≤ 3.28 μmol/litre or ≤ 68 μg/dl), 23% for the second (3.28-4.14 μmol/litre or 68-86 μg/dl), 24% for the third (4.15-5.14 μmol/litre or 86-107 μg/dl) and 37% for the fourth (≥ 5.15 μmol/litre or ≥ 107 μg/dl).

In a cross-sectional clinical study of 90 telephone cable-splicers by Fischbein et al. (1980), 19 (21%) workers reported gastrointestinal symptoms (mean PbB level of 1.44 μmol/litre, or 30 μg/dl and mean ZPP of 66.6 μg/g Hb) whereas 71 (79%) reported no such symptoms (mean PbB level of 1.3 μmol/litre or 27 μg/dl and mean ZPP of 52.3 μg/g Hb).

8.6.2 *Exposure of children*

Colic is seen in children and US EPA (1986a) concluded that the lowest-observed-adverse-effect level was in the range of 2.88-4.80 μmol/litre (60-100 μg/dl).

8.7 Liver

There appears to be no new evidence relating human body lead burden to effects on the liver, but it has been suggested that the effects of lead on haem synthesis may alter the functional capacity of the hepatic cytochrome P-450 system to metabolize drugs.

8.7.1 *Occupational exposure*

Fischbein et al. (1977) tested five demolition workers acutely exposed to lead for a period of 3 months prior to the study. They found that the plasma half-life of an oral dose of antipyrine was within the range for normal healthy volunteers; it was shorter in each subject after chelation therapy but still within the normal range. The plasma half-lives of phenylbutazone were also within the normal range but were unaffected by chelation therapy.

8.7.2 *Exposure of children*

Saenger et al. (1984) found decreased urinary excretion of 6-β-hydroxycortisol in 26 children with a mean PbB level of

2.11 μmol/litre (44 μg/dl); the decreased formation of the metabolite was attributed to lead inhibition of the cytochrome P-450-dependent mixed-function oxidases.

8.8 Reproduction

While it is generally accepted from early literature that lead adversely affects the reproductive process in both men and women, the evidence is mostly qualitative and dose-effect relationships have not been established.

Most new information relates to reports of occupational cohorts and of populations living in polluted areas near industrial plants. There is qualitative evidence that lead is toxic to the reproduction system in both men and women. However, there are insufficient data to provide the basis for estimation of dose-effect relationships in women.

8.8.1 Female populations

Nordstrom et al. (1978b) reported an increased frequency of spontaneous abortion in women living close to a smelter in northern Sweden. In a later report, Nordstrom et al. (1979) described the responses to a questionnaire completed by 511 of 662 women who had worked at the smelter and were born between 1930 and 1959. Spontaneous abortion rates were highest in those pregnancies in which the mother was employed during the pregnancy (13.9%) or had been employed before the pregnancy and was living close to the smelter (17%); the frequency rate was higher (19.4%) when the father worked at the smelter. However, it should be noted that the smelter produced copper and lead in addition to a number of other metallurgical and chemical products (Nordstrom et al., 1978a) and that the effects reported may not necessarily be attributable exclusively to lead.

A study of pregnancies in the centre and surrounding areas of the lead smelter town of Port Pirie showed that the incidence of miscarriages (22 or 23) and stillbirths (10 or 11) was higher in women living close to the smelter (McMichael et al., 1986). However, in a study of 639 Yugoslav women, the risk of spontaneous abortion was not increased (OR = 1.1, 95% CI: 0.9-1.4) among women with mean PbB levels of 0.77 μmol/litre (16.0 μg/dl) as compared with women with mean PbB levels of 0.25 μmol/litre (5.2 μg/dl) (Murphy et al., 1990). Risk did not vary with distance of residence from the smelter.

Some studies have found decreased length of gestation in women whose PbB levels were greater than 1.09 μmol/litre (23 μg/dl) (Moore et al., 1982), 0.58 μmol/litre (12 μg/dl) (Dietrich et al., 1986) or 0.72 μmol/litre (15 μg/dl) (McMichael et al., 1986). However, neither Bellinger et al. (1991b) nor Graziano et al. (1990) found decreases in gestational length or other parameters of pregnancy in women with elevated PbB levels.

In the Cincinnati prospective study, a significant reduction in birth weight associated with prenatal (maternal) PbB levels, after adjustment for covariates, was reported by Bornschein et al. (1989). In the Port Pirie prospective study of 749 pregnancies (McMichael et al., 1986), the proportion of pregnancies resulting in low birth weight singleton infants was more than twice as high in Port Pirie women (whose PbB levels averaged 0.50 μmol/litre, 10.4 μg/dl) than in women outside Port Pirie (average PbB level of 0.264 μmol/litre, 5.5 μg/dl). On the other hand, multiple regression analyses showed no significant association between low birth weight and maternal PbB level. In a cross-sectional study, Ward et al. (1987) reported a significant simple relationship between placental lead concentrations and reduced birth weight and head circumference.

Other studies have not shown a significant association between birth weight and lead exposure. The Kosovo prospective study failed to detect any evidence of lead-related birth weight reduction in more than 900 births (Murphy et al., 1990), and Ernhart et al. (1986) found no significant effect of lead on birth weight, birth length or head circumference.

8.8.2 *Male populations*

Reproductive effects from occupational exposure to lead include asthenospermia, hypospermia, teratospermia and hypogonadism (US EPA, 1986a; Braunstein et al., 1987).

In men, effects on sperm or the testes may result from chronic exposure to lead at blood levels of the order of 1.92-2.4 μmol/litre (40-50 μg/dl) (ATSDR, 1991).

Wildt et al. (1983) compared two groups of lead-exposed storage battery workers and concluded that the highly exposed group (PbB of more than 2.16 μmol/litre, 45 μg/dl) had decreased prostate/seminal vesicle function, low semen volume and poorer functional maturity of sperm.

Chowdhury et al. (1986) reported a significant decrease in sperm count and motility and an increased count of abnormal spermatozoa in lead-exposed men (average PbB level of 2.04 μmol per litre or 42.5 μg/dl) compared with controls (0.71 μmol/litre or 14.8 μg/dl). Assenato et al. (1987) also reported decreased sperm production in 18 battery factory workers having PbB levels of 2.4-2.93 μmol/litre (50-61 μg/dl).

In five out of six symptomatic lead intoxicated workers having PbB levels in the range of 1.87-4.7 μmol/litre (39-98 μg/dl) at the time of examination, Cullen et al. (1984) found defects of spermatogenesis, including oligospermia and azoospermia.

The results of Lerda (1992) also showed significant increases in asthenospermia and teratospermia among 38 battery workers with PbB levels of 1.95-4.7 μmol/litre (40.5-98.0 μg/dl) compared to a control group with PbB levels of 0.86-1.25 μmol/litre (17.6-26.0 μg/dl).

An epidemiological study by Lindholm et al. (1991) of 213 wives of lead workers and 300 matched controls suggested an association between paternal lead exposure and the risk of spontaneous abortion among the wives of lead workers when the PbB level exceeded 1.5 μmol/litre (31 μg/dl) close to the time of spermatogenesis. However, the authors acknowledged that exposure of the study subjects to other metals and organic solvents may have influenced the results of the study.

A weak association between paternal exposure, estimated from occupational history, and risk of esotropia (inward deviation strabismas) was noted in a case control study of 377 children aged 7 years (OR - 2.4, 95%, CI: 1.0-5.6) (Hakim et al., 1991). However, the increased risk was not dose-related, and the risk of exotropia (outward deviation) was not associated with higher paternal lead exposure.

8.8.3 Hormonal responses

Assenato et al. (1987) found no significant differences in FSH, testosterone, prolactin, LH and total neutral 17-ketosteroids levels between 18 lead battery workers (PbB level, 2.4-3 μmol/litre or 50-61 μg/dl) and 18 cement workers (PbB level, 0.9-1.1 μmol/litre or 18-22 μg/dl), despite the finding of oligospermia in the lead-exposed group.

Rodamilans et al. (1988) studied the endocrine status of 23 lead smelters in relation to the duration of lead exposure. Five workers exposed for less than 1 year (mean PbB level, 0.29 μmol/litre or 66 μg/dl) showed an increase in serum LH level, while that of testosterone remained normal. Eight workers exposed for 1-5 years (mean PbB level, 3.50 μmol/litre or 73 μg/dl) and 10 employed for more than 5 years (mean PbB level, 3.65 μmol/litre or 76 μg/dl) showed an increase in LH comparable with the group exposed for less than 1 year but there was a clear reduction in serum testosterone levels.

Gustafson et al. (1989) found a lower plasma FSH level in 25 moderately exposed workers (mean PbB level, 1.82 μmol/litre or 38 μg/dl) than in 25 matched controls. A lower mean serum LH level was reported by McGregor & Mason (1990) in 90 lead workers (mean PbB level, 2.20 μmol/litre or 46 μg/dl) than in controls; there was also a correlation between serum FSH and PbB levels. In an epidemiological study involving 122 current lead workers (PbB mean level, 1.69 μmol/litre or 35.1 μg/dl) and 49 non-exposed workers (PbB mean level, 0.4 μmol/litre or 8.3 μg/dl), Ng et al. (1991) found slightly higher plasma LH and FSH levels among the exposed workers. The testosterone level, however, was not significantly different between the two groups. In contrast, Gennart et al. (1992) did not find an effect of lead on various endocrine parameters (including FSH and LH levels) in a study population of 221 workers having a geometric mean PbB level of 2.45 μmol/litre (51.0 μg/dl). They suggested that the hypothalamic-pituitary system may not be influenced by moderate exposure to lead.

8.8.4 *Postnatal growth and stature*

Several reports have suggested that the physical growth and stature of children may be reduced by exposure to lead (e.g., Mooty et al., 1975; Johnson & Tenuta, 1979; Routh et al., 1979), but the influence of other factors (e.g., race and diet) has often made it difficult to isolate lead as a causal agent for such effects in human populations. Multivariate regression analyses of NHANES data for approximately 2700 children in the USA (Schwartz et al., 1986) provided more convincing evidence of a significant association between increasing PbB levels and reduced height, weight, and chest circumference after adjusting for age, race, sex and nutritional covariates.

8.9 Effects on chromosomes

As noted in Environmental Health Criteria 3: Lead (IPCS, 1977), the literature remains controversial concerning induction of chromosomal changes in human lymphocytes by *in vivo* exposure to lead. Most of the studies are of small numbers of subjects in occupational groups where lead was one of many potentially toxic agents. However, some of the difficulties arise because of the lack of standard procedures used for the assessment of chromosomal effects in cultured lymphocytes and from a lack of understanding of the health significance of chromosomal abnormalities.

Induced mitotic activity in peripheral lymphocytes and increases in the rates of abnormal mitosis were reported by Sarto et al. (1978). PbB levels in the range of 1.05-4.27 μmol/litre (22-89 μg/dl) were reported to be associated with increased incidence of chromosomal aberrations by Schmid et al. (1972) in 32 lead manufacturing workers, by Nordenson et al. (1978) in 18 smelter workers and by Al-Hakkak et al. (1986) in 19 lead manufacturing workers. It should be noted that exposure of worker to potentially hazardous agents other than lead was not documented in these studies.

Maki-Paakkanen et al. (1981) reported no change in chromosomal aberration frequency among workers with PbB levels in the range of 1.82-5.76 μmol/litre (38-120 μg/dl); weak effects were found by Huang et al. (1988b) when the PbB level exceeded 2.5 μmol/litre (52 μg/dl).

Qazi et al. (1980) reported increased numbers of cells with chromosome breaks in a baby having a cord PbB level of 2.88 μmol/litre (60 μg/dl) and a PbB level of 3.45 μmol/litre (72 μg/dl) at 2 weeks. The effect was seen at 6 weeks and at 3 months but not later (chelation therapy was given at 17 days and repeated at 5 months).

Bauchinger et al. (1977) tested blood taken from 38 children selected from a school situated close to a lead plant and in whom the PbB level was at least 1.44 μmol/litre (30 μg/dl). There was no increase in the frequency of aberrations.

Grandjean et al. (1983) examined 10 long-term workers at a lead storage battery plant. They found normal or slightly increased SCE rates in workers with a PbB level of 1.4-3.6 μmol/litre (29-75 μg/dl) and a ZPP level of 50-750 μmol/mol haemoglobin. The SCE increase was correlated significantly with ZPP level.

Huang et al. (1988b) studied 21 lead-exposed workers from a battery factory. They concluded that the SCE rate in workers with long-term exposure to lead increased significantly when the mean PbB level was 3.84 μmol/litre (80 μg/dl) or more. There were no significant differences in SCE rates among the low- and medium-exposed groups or the controls. These authors concluded that the effect of chromosome damage caused by lead is not very strong.

Dalpra et al. (1983) examined blood samples taken from 19 children living in a contaminated area near a smelter and having PbB levels in the range of 1.39-3.02 μmol/litre (29-63 μg/dl). They found no effect on SCE frequency.

8.10 Carcinogenicity

Much has been written regarding the evidence that lead is carcinogenic in humans (Moore & Meredith, 1979; Kazantzis, 1989; Goyer, 1992). In several large epidemiological studies no association was found which would associate lead with induction of cancer (Cooper & Gaffey, 1975; Kang et al., 1980; Cooper, 1981; McMichael & Johnson, 1982). One major difficulty in many of the studies was the concurrent exposure to potential carcinogens such as chromium (Davies, 1984), and there has seldom been any attempt to deal with the primary etiological agent (smoking) in the development of lung cancers associated with lead exposure.

8.10.1 Occupational exposure and renal cancer

There are two case reports and very limited other epidemiological evidence of an association between occupational exposure to lead and renal cancer. Confounding variables, including use of tobacco and exposure to other carcinogens, were not addressed (Baker et al., 1980; Lilis, 1981; Selevan et al., 1985; Cantor et al., 1986).

The age-standardized mortality ratio for cancer was low in the "lead poisoned" and other groups of workers from the Port Pirie study by McMichael & Johnson (1982). The authors concluded that lead poisoning did not increase the risk of cancer in humans.

8.10.2 Conclusion

Although some cohort mortality studies have indicated an association between lead exposure and renal disease, there is no association between renal cancer and lead in humans.

A Working Group convened by the International Agency for Research on Cancer (IARC) in 1987 concluded that the evidence for the carcinogenicity of lead and inorganic lead compounds in humans was inadequate.

8.11 Effects on thyroid function

8.11.1 Occupational groups

Robins et al. (1983) found low values for serum thyroxine and estimated free thyroxine in 7 of 12 workers having PbB levels above 2.11 μmol/litre (44 μg/dl). Both measures were correlated with PbB level in a cross-sectional study of 47 foundry workers. Serum thyrotropin and triiodothyronine levels were within the normal range for both study groups.

No such relationship was found in a study by Refowitz (1984) of a one-in-three random sample (N = 58) of male employees at a secondary copper smelter. No thyroid abnormalities were observed and there was no statistically significant relationship between PbB and serum thyroxine or an estimate of free thyroxine in serum.

Tuppurainen et al. (1988) studied 176 African male workers in Kenya and found that the duration of lead exposure correlated negatively with serum free thyroxine and serum total thyroxine. The correlation was strongest for the workers with the highest exposure intensity over time. PbB data were available from periodic medical examinations and average values (usually five determinations) were used. The mean PbB was 2.73 μmol/litre (56.8 μg/dl), range 1.01-6.47 μmol/litre (21-135 μg/dl), and there was a mean exposure duration of 7.6 years (range 1-20). The authors noted that current PbB level, as a point determination, was not associated with total or free thyroxine, triiodothyronine or thyrotropin in serum. They proposed that long-term, high-intensity exposure might be associated with depressed thyroid function.

Gennart et al. (1992b) included assessment of thyroid function as part of a study of lead-exposed workers. Data for serum levels of triiodothyronine, thyroxine, free thyroxine index and thyroid-stimulating hormone were within normal ranges for a group of 98 workers (mean PbB level, 2.45 μmol/litre or 51 μg/dl) and 85 controls (1.00 μmol/litre or 20.9 μg/dl). The lead exposure of this study group was considerably lower than in the workers in Kenya,

and it was suggested that thyroid function changes might not be indicators of moderate exposure to lead.

8.11.2 Effects in children

Siegel et al. (1989) tested 68 children for thyroid function and for PbB and found no statistically significant relationship between lead and total or free thyroxine.

8.12 Immune system

In a review of the effects of lead on the immune responses of experimental animals, Koller (1985) noted that there were few human studies.

8.12.1 Occupational exposure

There is some evidence that lead workers with PbB levels in the range of 1.0-4.10 μmol/litre (21-85 μg/dl) have increased susceptibility to infections (colds and influenza) and have a significant suppression of secretory IgA levels, a major factor in defence against respiratory and gastrointestinal infections (Ewers et al., 1982). There are also reports of impaired mitogen responses (reflecting T-lymphocyte function) to phytohaemagglutinin (Jaremin, 1983) and of increased numbers of suppressor T-cells (Cohen et al., 1989). However, on the basis of a study of 39 workers exposed to lead oxide (mean PbB level of 1.84 μmol/litre or 38.5 μg/dl) and 21 control subjects (mean PbB level of 0.57 μmol/litre or 11.8 μg/dl), Kimber et al. (1986) concluded that chronic lead exposure in man is not associated with the immunological changes that have been observed in rodent studies.

Coscia et al. (1987) found increased B-lymphocyte percentage and absolute count in workers currently exposed to lead with PbB levels exceeding 2.4 μmol/litre (> 50 μg/dl).

8.12.2 Children

A study of 12 pre-school children (Reigart & Graber, 1976) with PbB levels ≥ 1.92 μmol/litre (40 μg/dl) did not reveal altered immunity in comparison with a control group.

8.13 Effects on bone

The pharmacokinetics of the transfer of bone lead to other target organs and blood has been discussed by Smith & Hursh (1977), Marcus (1985a,b), Silbergeld et al. (1988) and Rabinowitz (1991) (see section 6.2.2).

Bone homoeostasis depends upon a complex interaction of its various components, i.e. minerals, cells and the extracellular matrix composed of collagenous and non-collagenous proteins (Marks & Popoff, 1988; Sauk & Somerman, 1991). Early work on the effects of lead on calcium homoeostasis and calcium-mediated function was reviewed by Pounds (1984). More recent work has been summarized by Pounds et al. (1991), particularly the effects of lead on hormone action, competition with calcium binding on calcium messenger systems, and the impaired synthesis of collagen or sialoproteins. Additional evidence for adverse effects of lead on the proteins in the mineral compartment, thus affecting bone homoeostasis, has been reported by Sauk & Somerman (1991).

8.14 Biomarkers for lead effects

The understanding and application of biomarkers for the assessment of effect is becoming more widespread (IPCS, 1994).

It is desirable to identify biomarkers of lead exposure and effect to provide easily measurable parameters that will facilitate the risk assessment process. At present PbB levels are frequently measured to assess both exposure and effect. Alternative biomarkers for lead which may be easily measured are of biochemical effects, particularly in the haem biosynthetic pathway.

However, the relationship between these effects and neurological impairment caused by lead has not been established. Measurement of these effects has also been used to provide biomarkers for exposure.

Anaemia has been associated with high levels of lead exposures in the occupational setting. However, clinical tests for haemoglobin are rather non-specific indicators of lead toxicity (Bernard & Becker, 1988). The steps within the haem biosynthetic pathway which have been used to measure effect are: 1) inhibition of δ-aminolaevulinic acid dehydratase (ALAD); 2) urinary excretion of δ-aminolaevulinic acid (ALAU); (3) the accumulation

of zinc protoporphyrin (ZPP) in erythrocytes arising from the inhibition of the enzyme ferrochelatase or the iron transport system.

There are several methodological problems related to the measurement of ALAD, and the benefit of measuring enzyme activity in blood in lieu of PbB determinations is not apparent (Mushak, 1989). Early work (Roels et al., 1976) indicated enzyme inhibition at PbB levels of 0.24 μmol/litre (> 5 μg/dl). However, the data at levels of 0.72 μmol/litre (< 15 μg/dl) appear scattered (Hernberg & Nikkanen, 1970; Granick et al., 1973).

Levels of ALA in urine have been used as an effect indicator of lead exposure (Meredith et al., 1978). ALAU levels were found to correlate with PbB levels as low as 0.864 μmol/litre (18 μg/dl), the correlation becoming much stronger at PbB levels above 1.92 μmol/litre (40 μg/dl) (Selander & Cramer, 1970). Given the present concern over effects in children at PbB levels well below 1.92 μmol/litre (40 μg/dl), the assay of ALAU concentrations may not be sensitive enough to be of any value.

The effects of lead on porphyrin levels, both coproporphyrin in urine and zinc protoporphyrin (ZPP) in blood, have been investigated as possible biomarkers for lead. Measurement of urinary coproporphyrin levels does not appear to be sensitive enough to be useful in assessing exposure to lead at present environmental levels. Excretion levels do not rise significantly until PbB levels exceed 1.92 μmol/litre (40 μg/dl) (Meredith et al., 1978). Other studies indicate that this assay may not be sensitive enough for biological monitoring at PbB levels between 0.96 and 1.20 μmol/litre (20 and 25 μg/dl). At present it would appear that ZPP has limited usefulness as a biological indicator of exposure at exposures leading to PbB levels lower than 1.20 μmol/litre (25 μg/dl) (Roels et al., 1976; Piomelli et al., 1982; Hammond et al., 1985; Marcus & Schwartz, 1987). The results may also be confounded by concurrent iron deficiency which will alter the levels of ZPP.

Vitamin D metabolism involves cytochrome P-450-dependent enzymes and thus may be affected by lead exposure. Measurement of serum levels of 1,25-dihydroxy-vitamin-D has been proposed as a sensitive biological monitor of lead exposure in children (Rosen et al., 1980; Mahaffey et al., 1982; Koo et al., 1991). However, it should be noted that dietary intakes of calcium and phosphorus, as well as circulating levels of parathyroid hormone

will regulate the production and circulating concentrations of this vitamin D metabolite, thus making correlations with PbB levels difficult without adequate information on the nutritional status of the population under study (Rosen & Chisney, 1983). In populations showing adequate nutritional status, lead at exposures leading to PbBs levels lower than 0.96 μmol/litre (20 μg/dl) does not appear to have a demonstrable effect on circulating levels of 1,25-dihydroxy-vitamin-D.

9. EVALUATION OF HUMAN HEALTH RISKS

9.1 Exposure assessment

Lead is a ubiquitous element detected in all environmental media. However, natural sources contribute only a small fraction of the amounts of lead found in air, food, water and dust. The majority of lead in these media arises from automobile and industrial emissions and from the use of lead-containing solder and paints. Adults and older children receive the largest proportion of lead intake from foods, whereas dust, soil and food all make significant contributions to the total lead intake of young children. The major contributions to lead in soil and outdoor dust are from the combustion of fossil fuels (principally leaded petrol), stationary sources such as smelters, and peeling and flaking of lead-based paint.

9.1.1 General population exposure

In the absence of specific stationary sources of lead, concentrations in ambient air are directly related to density of traffic and whether lead is still utilized as an additive in petrol. Reduction or elimination of lead in petrol in those countries which have instituted regulations has resulted in a decline by as much as eight-fold in ambient air concentrations of lead.

Levels of lead in indoor air are affected by the presence of cigarette smoke and dust from lead-painted surfaces. Without such sources, air lead levels indoors are about 60% of those in outdoor air.

For most adults, the total daily exposure to lead is via food, water and air. For infants aged up to 5 months, formula or breast milk and water are the main sources of lead. In children, an additional source of exposure is dust and soils. Absorption is dependent on the chemical form of lead, type of soil and particle size (bioavailability). Lead intake may be augmented from unusual sources such as folk remedies, cosmetics and hobby activity. Community contamination and workplace practices may contribute to lead exposure.

Food (including drinking-water and beverages) is the major source of lead exposure for the general population. Infants and children may receive an added lead burden from soil and dust.

The most significant foodstuffs will vary from country to country. In areas still utilizing lead-soldered cans, levels of lead are substantially higher. Depending upon lifestyles, there may be significant oral intake of lead from some alcoholic beverages and due to the leaching of lead from low temperature-fired ceramic containers.

Most drinking-water supplies contain lead levels lower than 5 μg/litre when they leave the treatment plant. However, where the water is known to be plumbo-solvent, up to 40% of the samples may exceed 100 μg/litre in homes where lead solder, lead pipes or brass fixtures have been used.

Absorption of lead from the lung is a function of particle size and pulmonary deposition pattern. Small particles (< 0.5 μm in diameter) characteristic of ambient air will be deposited deeply in the lungs with absorption rates of 90%. Larger particles, such as those that may be encountered in occupational settings, exhibit high deposition rates in the upper airway. Absorption of such particles will be a function of both dissolution in the lung and particle clearance to the gastrointestinal tract.

Human dermal absorption of inorganic lead through unabraded skin is of limited significance.

9.1.2 *Occupational exposures*

In addition to exposure to lead in ambient air, water and food, some workers may be exposed to airborne lead and dust within the workplace. Actual levels will vary according to the engineering design of the process equipment and the industrial hygiene practices utilized.

9.2 Critical issues related to exposure evaluation

In view of the heterogeneity of responses to lead within human populations, the complex interrelationships between exposure to lead and a biological indicator for internal dose require consideration of several key issues in order to assess human exposures.

9.2.1 *Sampling and analytical concerns*

Reliable comparisons of reported levels of exposure and/or dose can only be made where authors have described the analytical

and sampling procedures in sufficient detail to allow the reader to assess, for example, the integrity of the sampling procedures as well as the specificity, precision and accuracy of all analytical methods. Problems related to sampling cord blood also need to be considered.

Most studies have utilized analytical procedures of high quality. However, consideration must be given to blood collection procedures (finger stick versus venepuncture) when comparing results.

9.2.2 Data presentation

Inter-study comparisons of lead exposures are complicated by the variety of methods used to present results, including median values as well as geometric and arithmetic means. Some authors have used log-transformed data.

In assessing exposure from data on teeth, one must know which tooth and which compartment(s) within the tooth were sampled. In addition, if data are to be compared between studies, authors must state explicitly that all teeth analysed were without caries and were shed spontaneously.

The exposure index lifetime average blood lead (PbB) level has assisted in the assessment of cumulative exposures from serial PbB data. It should not be interpreted as being equivalent to a single PbB determination at a single point in life.

For some data/analytical purposes, age-specific PbB levels may be more appropriate than a lifetime average.

9.3 Relationship between exposure and dose

The most widely used surrogate for the absorbed dose is whole PbB concentration.

The relationship between PbB level and lead intake is curvilinear over a wide range of PbB values. On the basis of a single study of 17 infants, the relationship between PbB level and lead intake from food has been determined to be 0.0077 μmol lead/litre (0.16 μg/dl) per μg lead intake per day for a median PbB level of approximately 0.48 μmol/litre (10 μg/dl).

Most studies of the relationship between PbB level and lead exposure apply to a single environmental source, i.e. air, food, water or soil/dust. A summary of the relationship between PbB level and lead intake from individual media is given in Table 23.

Table 23. Representative relationships of blood lead median level to intake of lead for the general population[a]

	Population	
Median	Children	Adults
Air[b]	0.09 μmol Pb/litre per μg Pb/m^3 (1.92 μg Pb/dl)	0.079 μmol Pb/litre per μg Pb/m^3[c] (1.64 μg Pb/dl)
Water		0.003 μmol Pb/litre per μg Pb/litre (0.06 μg Pb/dl)
Food	0.01 μmol Pb/litre per μg Pb/day (0.16 μg Pb/dl)	0.002-0.003 μmol Pb/litre per μg Pb/day (0.04-0.06 μg Pb/dl)
Dust[b]	0.09 μmol Pb/litre per 1000 μg Pb/g (1.8 μg Pb/dl)	
Soil[b]	0.11 μmol Pb/litre per 1000 μg Pb/g (2.2 μg Pb/dl)	

[a] These data are provided for illustrative purposes only recognizing that the relationships are curvilinear in nature and are broad guidelines which will not apply at lower or higher levels of exposure.

[b] A value between 0.144 to 0.24 μmol Pb/litre or 3-5 μg Pb/dl per μg/m^3 is obtained when one considers indirect contribution through deposition on soil/dust.

[c] The air to blood lead relationship in occupational settings is best described by a curvilinear relationship having slopes between 0.02 and 0.08 μg/m^3 air. The slope is variable but lower than that found for humans in the general environment, which is between 1.6 and 1.9 μg/m^3.

9.4 Surrogate measures of dose

9.4.1 Blood

Whole PbB values are widely used as a measure of absorbed dose. However, it is believed that plasma lead concentrations may better reflect the "active" fraction of lead in blood and define the

relationship between PbB and tissue or organ accumulation (and effect), although there is little experimental data (because of analytical limitations). PbB is distributed between plasma and erythrocytes, with less than 5% being in the plasma. Most of the lead is bound to haemoglobin.

Venous and capillary blood levels are generally equivalent, provided that the sampling technique is adequate.

9.4.2 *Urine*

Urinary measurements of lead concentration are of limited value, although they are used occasionally as a screening test for occupational population groups.

9.4.3 *Bone*

Bone lead may be measured by non-invasive X-ray fluorescence, but this technique is limited in sensitivity at present.

9.4.4 *Tooth*

Shed deciduous teeth have been used to provide an index of exposure in early childhood. Interpretation of the analytical data is dependent on the type of tooth and the part of the tooth (whole tooth, dentine or circumpulpar dentine) analysed.

9.4.5 *Hair*

Hair is not useful for measurement of lead exposure.

9.5 Biochemical effects of lead

9.5.1 *Haem synthesis*

Evaluation of the quality of analytical data is an important aspect in considering reports describing effects attributed to lead. It should be noted that much of the data presented in this area has not been as vigorously scrutinized as, for example, psychometric study data.

An increase in erythrocyte protoporphyrin (EP) in children occurs between PbB levels of 0.72 and 1.2 μmol/litre (15-25 μg/dl). Increases in EP can be detected in men when the PbB level is above 1.20-1.44 μmol/litre (25-30 μg/dl), and in women

when it is above 0.96-1.44 μmol/litre (20-30 μg/dl). It should be noted that the effect of lead on haem is confounded by low iron status.

9.5.1.1 Urinary coproporphyrin

The coproporphyrin concentration in urine increases significantly with PbB levels in excess of 1.92 μmol/litre (40 μg/dl).

9.5.1.2 Urinary aminolaevulinic acid in children

In children 1-5 years old, there is a linear relationship with PbB in the range 1.2-3.6 μmol/litre (25-75 μg/dl). Data for children with PbB levels of 0.24-1.92 μmol/litre (5-40 μg/dl) show essentially no correlation with urinary aminolaevulinic acid (ALA) excretion. Elevation of urinary ALA level is evident at a PbB level of about 1.68 μmol/litre (35 μg/dl).

9.5.1.3 Urinary aminolaevulinic acid in adults

Urinary excretion of ALA increases in men at PbB levels above 2.16 μmol/litre (45 μg/dl) and in women above 1.68 μmol/litre (35 μg/dl).

9.5.1.4 δ-Aminolaevulinic acid dehydratase

There was a negative exponential relationship between PbB level and δ-aminolaevulinic acid dehydratase (ALAD) activity in a population of 10- to 13-year-old children with PbB levels in the range of 0.19-1.97 μmol/litre (4.7-41 μg/dl). An effect was seen at a PbB level of approximately 0.48 μmol/litre (10 μg/dl). There is an apparent lack of a clearly defined threshold for lead inhibition of ALAD in different age groups.

9.5.2 Vitamin D metabolism

In the presence of adequate nutritional status, PbB levels below 0.96 μmol/litre (20 μg/dl) appear to have no demonstrable effect on circulating concentrations of 1,25-dihydroxy-vitamin-D. A PbB level above 0.96 μmol/litre (20 μg/dl) is associated with a decrease in the serum level of 1,25-dihydroxy-vitamin-D.

9.5.3 Dihydrobiopterin reductase

Inhibition of dihydrobiopterin reductase has been shown in humans where the mean PbB level is as low as 0.48 μmol/litre (10 μg/dl).

A summary of some biochemical effects of lead is presented in Table 24.

Table 24. Biochemical effects of lead

Parameter	Blood lead level above which the biochemical effect is demonstrable with current techniques	
	μmol/litre	μg/dl
Protoporphyrin levels	0.96-1.44	20-30
Coproporphyrin levels	1.92	40
ALA urine levels	1.68	35
ALAD activity	0.48	10
1,25-dihydroxy-vitamin-D	0.96	20
Dihydrobiopterin reductase	0.48	10

9.5.4 Haemopoietic system

9.5.4.1 Anaemia in adults

The estimated PbB associated with a decrease in haemoglobin concentration is 2.40 μmol/litre (50 μg/dl).

9.5.4.2 Anaemia in children

Decreased haemoglobin levels in children occur at a PbB level of approximately 1.92 μmol/litre (40 μg/dl). Anaemia, defined as a haematocrit below 35%, is not found at a PbB level of less than 0.92 μmol/litre (20 μg/dl). The risk of having a haematocrit value below 35% for a 1-year-old child is 2% at a PbB level of 0.96-1.87 μmol/litre (20-39 μg/dl); the contribution of iron deficiency may account for a substantial proportion of this 2%. Induction of anaemia is demonstrable at 1.92 μmol/litre (40 μg/dl).

9.5.4.3 Erythrocyte pyrimidine-5'-nucleotidase

A reduction of 20% or more in erythrocyte pyrimidine-5'-nucleotidase activity is associated with PbB concentrations above 0.48 μmol/litre (10 μg/dl).

Effects of lead are demonstrable on a number of enzyme systems and biochemical parameters. The PbB levels, above which effects are demonstrable with current techniques for the parameters which may have clinical significance, are all greater than 0.96 μmol/litre (20 μg/dl). Some clinically insignificant effects on enzymes are demonstrable at lower levels of PbB.

9.6 Nervous system

9.6.1 Adults

9.6.1.1 Central nervous system

With acute lead exposure resulting in a PbB level in excess of 3.84 μmol/litre (80 μg/dl), severe encephalopathy and/or coma may occur. Central nervous system (CNS) symptoms are found in lead-exposed adults when there is a history of several years of exposure to lead at PbB levels that may not have exceeded 3.36 μmol/litre (70 μg/dl) and a PbB level at the time of clinical assessment of at least 1.92 μmol/litre (40 μg/dl).

Impaired neurobehavioural test performance has been found in lead-exposed workers. Changes in critical flicker fusion test have been detected at a PbB level of about 2.4 μmol/litre (50 μg/dl). Sensory motor function is generally more sensitive than cognitive end-points in many neurobehavioural evaluations, the lowest-observed-effect level being at about 1.92 μmol/litre (40 μg/dl).

It appears also that neuroelectrophysiological tests are sensitive indicators of the CNS effects of lead. Reductions in latencies of sensory evoked potentials and auditory event-related potentials have been found in workers with average PbB levels of approximately 1.92 μmol/litre (40 μg/dl).

9.6.1.2 Peripheral nervous system

Numerous studies have measured the conduction velocity of electrically stimulated sensory and motor nerves in workers exposed to lead. These nerve conduction velocity (NCV) studies

have yielded somewhat mixed results, with many showing a decrease in NCV in relation to lead exposure (indexed as PbB level) and a few showing no effect or occasionally even an increase in NCV associated with lead exposure. Differences in the nerves evaluated, methodologies, characterization of lead exposure, and control of confounding variables underlie some of the variability in results across studies. A statistical meta-analysis of 32 NCV studies has indicated that NCV is significantly reduced in lead-exposed workers compared to reference subjects, but that the median motor nerve shows more reliable effects of lead than other nerves. This collective view of the evidence is supported by key studies that provide compelling evidence of a causal relationship between lead exposure and reductions in NCV, extending to PbB levels as low as 1.44 μmol/litre (30 μg/dl). These effects may be reversible depending on the duration and level of exposure.

9.6.1.3 *Autonomic nervous system*

Two reports examining the electrocardiographic RR interval variability during deep breathing and the component CV of respiratory sinus arrythmia demonstrated dysfunctions at an average PbB level of 1.68 μmol/litre (35 μg/dl). These results suggest autonomic nervous system dysfunction, particularly the parasympathetic nervous system.

9.6.2 *Children*

Prospective and cross-sectional studies of children have demonstrated associations of lead exposure, measured by various indices, and intellectual performance. The association has been noted across a wide range of exposure levels and in a variety of populations before factors other than lead have been accounted for.

A key question is whether this statistical association is directly attributable to the causal influence of lead on child IQ. It is important to consider alternative contributory explanations, i.e. random chance, unexplained confounding factors, reverse causality and selection bias.

It is a matter of debate and conjecture as to the extent to which these four issues should inhibit claims of a causal relationship in the epidemiological studies. The essential problem is that observational epidemiology cannot provide definitive evidence of causality when the key statistical association is small, the temporal

relationship is unclear and major confounders are present. Animal studies provide qualitative support for the claim of a causal role for lead in affecting neuropsychoiogical performance, but provide limited assistance in establishing quantitative dose-effect relationships.

9.6.2.1 Type of effect

The clearest and most consistent associations have been found with global measures, such as IQ, where the largest body of evidence is available. Efforts to delineate the neuropsychological foundations of this association with a wide variety of tests of specific neuropsychological domains have not so far been successful.

9.6.2.2 Magnitude

Based on the evidence from cross-sectional and prospective studies of populations with PbB levels generally below 1.2 μmol/litre (25 μg/dl), the size of the apparent IQ effect (at ages 4 and above) is a deficit of between 0 and 5 points (on a scale of 100 with a standard deviation of 15) for each 0.48 μmol/litre (10 μg/dl) increment in PbB level, with a likely apparent effect size of between 1 and 3 points. At PbB levels above 1.2 μmol/litre (25 μg/dl), the relationship between PbB level and IQ may differ. Estimates of effect size are group averages and only apply to the individual child in a probabilistic manner.

Existing epidemiological studies do not provide definitive evidence of a threshold. Below the PbB range of 0.48-0.72 μmol/litre (10-15 μg/dl), the effect of confounding variables and limits in the precision of analytical and psychometric measurements increases the uncertainty attached to any estimate of effect. However, there is some evidence of an association below this range.

9.6.2.3 Reversibility/persistence

Whilst the IPCS Task Group could not unequivocally state that effects of early childhood exposure are persistent beyond childhood, because the current data are too meagre, it was held that neurobehavioural effects detected at age seven or later usually persist. Measures in later childhood tend to be more predictive of subsequent performance than those made earlier. It is more likely than not that effects seen during school years are to some degree

irreversible. This has also been observed in later follow-up studies conducted in other non-lead topics of child development research. One of the difficulties is that there are too few studies concerning long-term outcome in children with high early exposures and where the sources of exposure are subsequently removed.

Virtually no useful data are available on the effects on IQ of removing children from a "high" exposure environment to one of "low" exposure or on reduction of body lead burden in children. This is not to say that exposure should not be reduced when possible.

9.6.2.4 *Age-specific sensitivity*

From prospective studies it is not possible to determine an age of critical sensitivity. This reflects the findings that serial PbB measures taken at the age of 2 years and later are positively correlated with, the individual rankings remaining approximately constant, and this limits the ability to identify sensitive periods of exposure.

9.6.2.5 *Interactions/subgroups*

The evidence is inconclusive on whether apparent effects are more or less marked in different gender or socioeconomic status (SES) subgroups. However, where there are suggestions of SES-related differences, the apparent effects tend to be more marked in the lower SES subgroups.

9.6.3 *Animal studies*

Experimental animal studies of CNS effects provide support for the associations between PbB levels and neurobehavioural deficits described in human epidemiological studies of lead. There is supportive evidence both in terms of demonstrating causal relationships and in the levels of PbB at which such effects are observed, namely 0.528-0.72 μmol/litre (11-15 μg/dl). Moreover, they provide qualitative parallels in the nature of the effects described, as these effects include changes in learning and memory functions. Experimental animal studies indicate that these CNS effects may depend upon task complexity and can persist long beyond the termination of lead exposure. These studies also provide information possibly relevant to understanding mechanisms of effect. In addition, the experimental animal studies provide such evidence in the absence of the confounding

factors and co-variates, such as parental IQ, socioeconomic status, and quality of the home environment, that are problematic to human epidemiological endeavours, and in the absence of nutritional deficiencies that may arise in human populations.

9.7 Renal system

Renal function impairment was not associated with a PbB level below 3.0 μmol/litre (62 μg/dl) when measured by blood urea nitrogen and serum creatinine levels in lead workers. However, renal tubular effects were detected in workers with a PbB level below 3.0 μmol/litre when measured by more sensitive indicators such as NAG.

Most studies of the general population attempting to relate renal function impairment to PbB concentration have not demonstrated an effect with PbB levels below 1.8 μmol/litre (37.3 μg/dl). More sensitive indicators of renal function may indicate a renal effect of lead below this level.

9.8 Liver

Over-exposure to lead may inhibit drug metabolism in the liver.

9.9 Reproduction

9.9.1 Female

Studies on the risk of spontaneous abortion and reduced birth weight associated with maternal PbB levels below 1.44 μmol/litre (30 μg/dl) have yielded mixed results. Recent epidemiological studies have shown exposure-related perturbations in the length of gestation, significantly greater risks being associated with PbB levels of 0.72 μmol/litre (15 μg/dl) or more.

9.9.2 Male

PbB concentrations above 1.92 μmol/litre (40 μg/dl) have been shown to affect sperm morphology and function. At present, the reproductive consequences of these changes are unknown.

9.10 Blood pressure

A quantitative assessment of the collective evidence from all the observational studies in adults is made difficult by the fact that studies have adopted different policies regarding adjustment for potential confounding factors (e.g., alcohol consumption). In addition, quantitative findings from the two largest studies (BRHS and NHANES II) have depended on whether adjustment was made for geographical variations in blood pressure and blood lead.

The limited size of most observational studies has inevitably meant that they could not consistently demonstrate a statistically significant relationship. However, an overview of all the studies shows that evidence is consistent with the centre-adjusted analysis of the two main studies, i.e. there are very weak but statistically significant associations between PbB level and both systolic and diastolic blood pressures. The likely order of magnitude is that for any two-fold increase in PbB level (e.g., from 0.8 to 1.6 μmol per litre) there is a mean 1 mmHg increase in systolic blood pressure. The association with diastolic blood pressure is of a similar magnitude.

Animal studies have provided plausible mechanisms for an effect of lead on blood pressure. However, from such a small magnitude of statistical associations in the presence of important confounders, one cannot infer that low-level lead exposure is causally related to an increase in blood pressure.

The two population studies relating PbB to cardiovascular disease events show no statistically significant associations. Hence, there is no clear evidence to suggest that lead has an impact of public health importance as regards hypertension or risk of cardiovascular disease.

9.11 Carcinogenicity

Renal tumours occur in rats and mice administered high doses of lead. However, the evidence for the carcinogenicity of lead and inorganic lead compounds in humans is inadequate.

9.12 Immune system

There is no strong evidence in humans of an effect of lead on the immune system.

10. RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH

10.1 Public health measures

Public health measures should be directed towards reduction and prevention of exposure to lead by reducing the use of lead and lead compounds and by minimizing lead-containing emissions that result in human exposures. This can be achieved by:

a) phasing-out any remaining uses of lead additives in motor fuels;

b) further reducing the use of lead-based paints, with the objective of eliminating such paints;

c) development and application of methods for the safe and economical remediation of lead-painted homes and lead-contaminated soil;

d) elimination of the use of lead in food containers (e.g., in the seams of cans);

e) dissemination of information to assist with identification of glazed food containers which may leach lead into food placed, cooked or stored in the container;

f) eliminating any remaining agricultural uses of lead or lead compounds (e.g., lead arsenate as an insecticide);

g) identifying and reducing, or preferably, eliminating lead found as a contaminant or ingredient of folk remedies and cosmetics;

h) the use of materials and engineering practices to minimize plumbosolvency in water treatment and water distribution systems;

i) systematic examination of processes in which lead is used or recycled in order to identify and reduce lead exposure by means of improved engineering design, of operators, by-standers and the environment. Opportunities for technology transfer should be used whenever possible.

10.2 Public health programmes

Programmes should be developed:

a) to enhance data collection and to make available to the public information on the lead content of foodstuffs;

b) to facilitate identification of populations at high risk of exposure to lead on the basis of monitoring data for lead in food, air, water and soil;

c) that incorporate improved procedures for health risk assessment of population groups at risk of exposure to lead;

d) that promote understanding and awareness concerning the effects on human health associated with exposure to lead, while recognizing cultural sensitivities;

e) that place emphasis on adequate nutrition, health care and attention to socioeconomic conditions which may exacerbate the effects of lead present in the environment.

10.3 Screening, monitoring and assessment procedures

Methods for evaluating the effects and associated risks of exposure to lead require both improvement and further development or research. In the short term the following measures are needed.

a) Screening

i) Blood lead measurements should be recognized as the biomarker of choice for screening for previous exposure of children to lead.

ii) The sensitivity of the developing nervous system to the potentially harmful effects of lead is such that other biochemical measurements (e.g., erythrocyte protoporphyrin) are not sufficiently sensitive for assessment of infants and children.

b) Monitoring

i) More sensitive analytical methods should be developed for the reliable measurement of blood lead levels below 0.72 μmol/litre (15 μg/dl) to acceptable standards of precision and accuracy.

ii) There is a need for international analytical quality assurance programmes utilizing reference lead-containing materials.

iii) All publications containing blood lead measurement data should provide adequate data on current quality assurance and quality control.

iv) Data comparisons are made more difficult by differences in units and statistical techniques for data handling. Investigators should be encouraged to adopt internationally agreed practices (e.g., IUPAC units).

c) Assessment

i) Validated biomarkers are needed to define the relationship between measures of environmental (external) exposure and specific effects (biochemical or functional).

ii) Biomarkers indicative of deficits in cognitive performance are needed to facilitate assessment of risk.

iii) Improved methods are needed for the definition of outcome effects (especially IQ and neurobehavioural deficits) attributable to lead at blood lead concentrations of about 0.48 μmol/litre (10 μg/dl) or less.

iv) Further data are required to determine whether outcome effects on the nervous system attributed to lead are reversible or permanent.

v) Biomarkers for the renal effects of lead are needed to link renal damage with lead exposure and thereby improve assessment of risk of renal damage.

11. FURTHER RESEARCH

a) Research is required to improve the process for the assessment of risk associated with exposure to lead. Specifically this should cover:

   i) definition of the health significance of biochemical changes associated with exposure to lead, with particular attention to alterations associated with blood lead concentrations of about 0.72 μmol/litre (15 μg/dl) or less;

   ii) work to define the bioavailability of lead from different sources and to establish the relationship between exposure (sources and speciation) and body burden;

   iii) definition of the influence of host-related factors (particularly nutrition) affecting absorption and distribution of lead;

   iv) intensification of kinetic studies of lead to provide an improved data base for extrapolation between species;

   v) elucidation of mechanisms of accumulation and mobilization of lead from bone with particular attention to the influence of pregnancy and ageing on kinetics;

   vi) investigation of the pharmacokinetics of lead in the pregnant female in relation to transfer of lead to the developing embryo and fetus and factors that mitigate such transfer;

   vii) determination of the effects of pre- and post-natal exposure to lead;

   viii) improved definition of paternally mediated effects of lead exposure on the reproductive process and outcomes.

b) More general research needs include the following:

   i) rationalization of neurobehavioural tests used to assess performance in children and animals in order to permit comparisons of measurements and test data that use similar biological mechanisms;

ii) follow-up research (where possible) of historical cohorts of lead-poisoned adults to examine the sequelae;

iii) evaluation of intervention measures, such as lead abatement from home and soil, and chelation on reduction of blood lead levels and outcome effects on the central nervous system.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The carcinogenic potential of lead and lead compounds was last evaluated by the International Agency for Research on Cancer in 1987 (IARC, 1987b). There was inadequate evidence for the carcinogenicity of lead and inorganic lead compounds in humans, but sufficient evidence was available to show that specified inorganic lead compounds were carcinogenic in experimental animals. The overall evaluation placed lead and inorganic lead compounds in Group 2B, i.e. possibly carcinogenic to humans.

To protect workers from the adverse effects of lead on haem synthesis and on the peripheral and central nervous system, a health-based biological exposure limit of 1.92 μmol/litre (40 μg/dl) was recommended by a WHO Study Group (WHO, 1980). It was further recommended that blood lead (PbB) levels in women within the reproductive age range should not exceed 1.44 μmol/litre (30 μg/dl). Depending upon the background levels of PbB in the worker population, air lead levels should not exceed 30-60 $\mu g/m^3$ (WHO, 1980).

A drinking-water guideline value of 0.050 mg/litre was developed in 1984 (WHO, 1984). This guideline value has been revised recently to 0.01 mg/litre (WHO, 1993).

Lead was evaluated by a WHO Working Group developing air quality guidelines for Europe (WHO, 1987). Based on the assumption that PbB levels in 98% of the population would be maintained at levels below 0.96 μmol/litre (20 μg/dl), a guideline value in the range of 0.5-1.0 $\mu g/m^3$ (long-term average, such as annual mean) was recommended.

At the 41st meeting of the Joint FAO/WHO Expert Committee on Food Additives and Food Contaminants, a Provisional Tolerable Weekly Intake (PTWI) of 25 μg/kg body weight was recommended (FAO/WHO, 1993). This level refers to lead from all sources and was set to protect all humans, including infants and children. It was based on a model indicating daily intakes of lead between 3-4 μg/kg body weight by infants and children and is not associated with an increase in PbB concentrations.

Regulatory standards established by national bodies in several countries and the European Economic Community are summarized

in the legal file of the International Register of Potentially Toxic Chemicals (IRPTC, 1987).

REFERENCES

Aguilera de Benzo Z, Fraile R, & Carrion N (1989) Determination of lead in whole blood by electrothermal atomization atomic absorption spectrometry using tube and platform atomizers and dilution with Trito X-100. J Anal At Spectrom, **4**: 397-400.

Albahary C (1972) Lead and hemopoiesis: The mechanism and consequences of the erythropathy of occupational lead poisoning. Am J Med, **52**: 367-378.

Albert LA & Badillo F (1991) Environmental lead in Mexico. Rev Environ Contamin Toxicol, **117**: 1-49.

Alexander FW, Delves HT, & Clayton BE (1973) The uptake and excretion by children of lead and other contaminants. In: Barth D, Berlin A, Engel R, Recht P, & Smeets J ed. Environmental health aspects of lead: Proceedings, International Symposium, Amsterdam, The Netherlands, October 1972. Luxembourg, Commission of the European Communities, pp 319-331.

Al-Hakkak ZS, Hamamy HA, Murad AMB, & Hussain AF (1986) Chromosome aberrations in workers at a storage battery plant in Iraq. Mutat Res, **171**: 53-60.

Altmann L, Weinsberg F, Sveinsson K, Lilienthal H, Wiegand H, & Winneke G (1993) Impairment of long-term potentiation and learning following chronic lead exposure. Toxicol Lett, **66**(1): 105-112.

Alvares AP, Kapelner S, Sassa S, & Kappas A (1975) Drug metabolism in normal children, lead-poisoned children, and normal adults. Clin Pharmacol Ther, **17**: 179-183.

Anderson C & Danylchuk KD (1977) The effects of chronic low level lead intoxication on the Haversian remodeling system in dogs. Lab Invest, **37**: 466-469.

Angle CR & McIntire MS (1978) Low level lead inhibition of erythrocyte pyrimidine nucleotidase. Environ Res, **17**: 296-302.

Angle CR & McIntire MS (1979) Environmental lead and children: the Omaha study. J Toxicol Environ Health, **5**: 855-870.

Angle CR, McIntire MS, & Swanson MS (1982) Erythrocyte nucleotides in children - increased blood lead and cytidine triphosphate. Pediatr Res, **16**: 331-334.

Annest JL & Mahaffey KR (1984) Blood lead levels for persons aged 6 months-74 years: United States, 1976-1980. Hyattsville, Maryland, US Public Health Service (Report No. 223, Series 11) (DHHS Publication No. (PHS) 84-1683).

Annest JL, Pirkle JL, Makuc D, Neese JW, Bayse DD, & Kovar MG (1983) Chronological trend in blood lead levels between 1976 and 1980. N Engl J Med, **308**: 1373-1377.

Araki S & Ushio K (1982) Assessment of the body burden of chelatable lead: a model and its application to lead workers. Br J Ind Med, **39**: 157-160.

Araki S, Honma T, Yanagihara S, & Ushio K (1980) Recovery of slowed nerve conduction velocity in lead-exposed workers. Int Arch Occup Environ Health, **46**: 151-157.

Araki S, Aono H, Fukahori M, & Tabuki K (1984) Behaviour of lead and zinc in plasma, erythrocytes, and urine and ALAD in erythrocytes following intravenous infusion of CaEDTA in lead workers. Arch Environ Health, **39**: 363-367.

Araki S, Murata K & Aono H (1986a) Subclinical cervico-spino-bulbar effects of lead: A study of short-latency somatosensory evoked potentials in workers exposed to lead, zinc and copper. Am J Ind Med, **10**: 163-175.

Araki S, Yokoyama K, Murata K, & Aono H (1986b) Determination of the distribution of conduction velocities in workers exposed to lead, zinc and copper. Br J Ind Med, **43**: 321-326.

Araki S, Aono H, Murata K (1986c) Mobilisation of heavy metals into the urine by CaEDTA: Relation to erythrocyte and plasma concentrations and exposure indicators. Br J Ind Med, **43**: 636-641.

Araki S, Murata K, & Aono H (1987) Central and peripheral nervous system dysfunction in workers exposed to lead, zinc and copper: A follow-up study of visual and somatosensory evoked potentials. Int Arch Occup Environ Health, **59**: 177-187.

Araki S, Murata K, Yokoyama K, & Uchida E (1992) Auditory event-related potential (P300) in relation to peripheral nerve conduction in workers exposed to lead, zinc, and copper: Effects of lead on cognitive function and central nervous system. Am J Ind Med, **21**: 539-547.

Arnetz BB & Nicolich MJ (1990) Modelling of environmental lead contributors to blood lead in humans. Int Arch Occup Environ Health, **62**: 397-402.

Aslam M, David SS, & Healy MA (1979) Heavy metals in some Asian medicines and cosmetics. Publ Health (Lond), **93**: 274-284.

Assenato G, Paci C, Baser M, Molinini R, Candela RG, Altamura BM, & Giorgino R (1987) Sperm count suppression without endocrine dysfunction in lead-exposed men. Arch Environ Health, **42**: 124-127.

ATSDR (1993) Toxicological profile for lead. Atlanta, Georgia, US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (TP-92/12).

Aungst BJ, Docle JA, & Fung H (1981) The effect of dose on the disposition of lead in rats after intravenous and oral administration. Toxicol Appl Pharmacol, **61**: 48-57.

Awad el Karim MA, Hamed AS, Elhaimi YAA, & Osman Y (1986) Effects of exposure to lead among lead acid battery factory workers in Sudan. Arch Environ Health, **41**: 261-265.

Azar A, Trochimowicz HJ, & Maxfield ME (1973) Review of lead studies carried out at Haskell Laboratory: two year feeding study and response to hemorrhage study. In: Environmental health aspects of lead. Proceedings of an international symposium, Amsterdam. Luxembourg, Commission of the European Communities, pp 199-210.

Baghurst PA, McMichael AJ, Wigg N, Vimpani G, Robertson EF, Roberts RJ, & Tong S-L (1992) Life-long exposure to environmental lead and children's intelligence at age seven: the Port Pirie cohort study. N Engl J Med, **327**: 1269-1284.

Baker EL, Landrigan PJ, Barbour AG, Cox DH, Folland DS, Ligo RN, & Throckmorton J (1979) Occupational lead poisoning in the United States: clinical and biochemical findings related to blood lead levels. Br J Ind Med, **36**: 314-322.

Baker EL, Goyer RA, Fowler BA, Khettry U, Bernard DB, Adler S, White R, Babayan R, & Feldman RG (1980) Occupational lead exposure, nephropathy and renal cancer. Am J Ind Med, **1**: 139-148.

Barrio A & Badia J (1985) [Lead encephalopathy in adults.] Rev Med Chil, **113**(6): 564-567 (in Spanish).

Barltrop D (1969) Mineral metabolism in pediatrics. Oxford, London, Edinburgh, Melbourne, Blackwell Scientific Publishers.

Barltrop D (1972) Children and environmental lead. In: Hepple P ed. Lead in the environment: Proceedings of a conference. London, Institute of Petroleum, pp 52-60.

Barry PSI (1975) A comparison of concentrations of lead in human tissues. Br J Ind Med, **32**: 119-139.

Barry PSI (1981) Concentrations of lead in the tissues of children. Br J Ind Med, **38**: 61-71.

Barton JC, Conrad ME, Nuby S, & Harrison L (1978) Effects of iron on the absorption and retention of lead. J Lab Clin Med, **92**: 536-547.

Bauchinger M, Dresp J, Schmid E, Englert N, & Krause C (1977) Chromosome analyses of children after ecological lead exposure. Mutat Res, **56**: 75-79.

Beattie AD, Moore MR, Goldberg A, Finlayson MJ, Graham JR, Mackie TM, Main J, McLaren PA, Murdock KM, & Stewart FT (1975) Role of chronic lead exposure in the aetiology of mental retardation. Lancet, **1**: 589-592.

Beckett PH, Davis RD, & Brindley P (1979) The disposal of sewage sludge onto farmland: the scope of the problem of toxic elements. Water Pollut Control, **78**: 419-436.

Behari LR, Singh S, Tandon SK, & Wahal AK (1982) Lead poisoning among Indian silver jewellery makers. Ann Occup Hyg, **27**: 107-109.

Behne D (1980) Problems of sampling and sample preparation for trace element analysis in the health sciences. In: Bratter P & Schramel P ed. Trace element analytical chemistry in medicine and biology. Proceedings of the First International Workshop, Neuherberg, Federal Republic of Germany. Berlin, New York, Walter de Gruyter & Co., pp 769-782.

Beijer K & Jernelöv A (1984) Microbial methylation of lead. In: Grandjean P ed. Biological effects of organolead compounds. Boca Raton, Florida, CRC Press, pp 13-19.

Bellinger DC & Stiles KM (1993) Epidemiologic approaches to assessing the developmental toxicity of lead. Neurotoxicology, **14**: 151-160.

Bellinger DC, Needleman HL, Leviton A, Waternaux C, Rabinowitz MR, & Nichols ML (1984) Early sensory-motor development and prenatal exposure to lead. Neurobehav Toxicol Teratol, **6**: 387-402.

Bellinger DC, Leviton A, Waternaux C, Needleman H, & Rabinowitz M (1987) Longitudinal analyses or prenatal and post-natal lead exposure and early cognitive development. N Engl J Med, **316**: 1037-1043.

Bellinger D, Sloman A, Leviton A, Rabinowitz M, Needleman H, & Waternaux C (1991a) Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics, **87**: 219-227.

Bellinger D, Leviton A, Rabinowitz M, Allred E, Needleman H, Schoenbaum S (1991b) Weight gain and maturity in fetuses exposed to low levels of lead. Environ Res, **54**: 151-158.

Bellinger DC, Stiles KM, & Needleman HL (1992) Low-level lead exposure, intelligence and academic achievement: A long-term follow-up study. Pediatrics, **90**: 855-861.

Berlin A & Schaller KH (1974) European standardized method for the determination of δ-aminolevulinic acid dehydratase activity in blood. Z Klin Chem Klin Biochem, **12**: 389-390.

Bernard SR (1977) Dosimetric data and metabolic model for lead. Health Phys, **32**: 44-46.

Bernard BP & Becker CE (1988) Environmental lead exposure and the kidney. Clin Toxicol, **26**: 1-34.

Bernstein J, Evan AP, & Gardner KD (1987) Epithelial hyperplasia in human polycystic kidney disease. Its role in pathogenesis and risk of neoplasia. Am J Pathol, **129**: 92-101.

Bert JL, van Dusen LJ, & Grace JR (1989) A generalized model for the prediction of body lead burdens. Environ Med, **48**: 117-127.

Beyer WN & Cromartie EJ (1987) A survey of Pb, Cu, Zn, Cd, Cr, As, and Se in earthworms and soil from diverse sites. Environ Monit Assess, **8**: 27-36.

Biggins PDE & Harrison RM (1979) Atmospheric chemistry of automotive lead. Environ Sci Technol, **13**: 558-565.

Billick IJ & Gray VE (1978) Lead based paint poisoning research: review and evaluation 1971-1977. Washington, DC, US Department of Housing and Urban Development.

Bishop L & Hill WJ (1983) A study of the relationship between blood lead levels and occupational air lead levels. Am Stat, 37(4): 471-475.

Blair JA, Hilburn ME, Leeming RJ, McIntosh MJ, & Moore MR (1982) Lead and tetrahydrobiopterin metabolism: possible effects on IQ. Lancet, **April 24**, 964.

Body PE, Inglis GR, & Mulcahy DE (1988) Lead contamination in Port Pirie South Australia. Adelaide, Australia, South Australia Department of Environment and Planning (SADEP Report No. 101).

Bolger PM, Carrington CD, Capar SG, & Adams MA (1991) Reductions in dietary lead exposure in the United States. Chem. Speciation Bioavailab, 3(3/4): 31.

Bolter E, Butz T, & Arseneau JF (1975) Mobilization of heavy metals by organic acids in the soils of a lead mining and smelting district. In: Proceedings of the IXth Annual

Conference on Trace Substances in Environmental Health, Columbia, Missouri, 10-12 June 1975, pp 107-112.

Bondarenko GP (1968) An experimental study of the solubility of galena in the presence of fulvic acids. Geochem Int, **5**: 525-531.

Bornschein RL (1985) Influence of social factors on lead exposure and child development. Environ Health Perspect, **62**: 343-351.

Bornschein RL & Rabinowitz MB (1985) Proceedings of the Second International Conference on Prospective Lead Studies. Environ Res, **38**: 1-210.

Bornschein RL, Succop P, Dietrich KN, Clark CS, Que Hee S, & Hammond PB (1985) The influence of social and environmental factors on dust lead, hand lead, and blood lead levels in young children. Environ Res, **38**: 108-118.

Bornschein RL, Succop PA, Krafft KM, Clark CS, Peace B, & Hammond PB (1986) Exterior surface dust lead, interior house dust lead and childhood lead exposure in an urban environment. In: Hemphill DD ed. Trace substances in environmental health II. Columbia, Missouri, University of Missouri, pp 322-332.

Bornschein RL, Succop PA, Krafft, KM, Clark CS, Peace B, & Hammond PB (1987) Exterior surface dust lead, interior house dust lead and childhood lead exposure in an urban environment. Trace Subst Environ Health, **20**: 322-332.

Bornschein RL, Grote J, Mitchell T, Succop PA, Dietrich KN, Krafft KM, & Hammond PB (1989) Effects of prenatal lead exposure on infant size at birth. In: Smith MA, Grant LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Publishers, pp 307-319.

Boscolo P & Carmignani M (1988) Neurohumoral blood pressure regulation in lead exposure. Environ Health Perspect, **78**: 101-106.

Boutron CF, Görlach U, Candelone J-P, Bolshov MA, & Delmas RJ (1991) Decrease in anthropogenic lead, cadmium and zinc in Greenland snows since the late 1960s. Nature (Lond), **353**: 153-156.

Braunstein GD, Dahlgren J, & Loriaux DL (1987) Hypogonadism in chronically lead-poisoned men. Infertility, **1**: 33-51.

Brown KW & Black SC (1983) Quality assurance and quality control data validation procedures used for the Love Canal and Dallas lead soil monitoring programs. Environ Monit Assess, **3**: 113-122.

Brunekreef B (1984) The relationship between air lead and blood lead in children: A critical review. Sci Total Environ, **38**: 79-123.

Brunekreef B (1986) Childhood exposure to environmental lead. London, United Kingdom, Monitoring and Assessment Research Centre.

Buchet J-P, Lauwerys R, Roels H, & Hubermont G (1977) Mobilization of lead during pregnancy in rats. Int Arch Occup Environ Health, **40**: 33-36.

Buchet J-P, Roels H, Bernard A, & Lauwerys R (1980) Assessment of renal function of workers exposed to inorganic lead, cadmium, or mercury vapour. J Occup Med, 22: 741-750.

Buchet JP, Lauwerys R, Vandervoorde A, & Pycke JM (1983) Oral daily intake of cadmium, lead, manganese, copper, chromium, mercury, calcium, zinc, and arsenic in Belgium: a duplicate meal study. Food Chem Toxicol, 21: 19-24.

Bull RJ (1980) Lead and energy metabolism. In: Singhal PL & Thomas JA ed. Lead toxicity. Baltimore, Maryland, Urban Schwarzenberg, Inc., pp 119-168.

Bushnell PJ & Bowman RE (1979a) Reversal learning deficits in young monkeys exposed to lead. Pharmacol Biochem Behav, 10: 733-742.

Bushnell PJ & Bowman RE (1979b) Persistence of impaired reversal learning in young monkeys exposed to low levels of dietary lead. J Toxicol Environ Health, 5: 1015-1023.

Bushnell PJ & DeLuca H (1983) The effects of lactose on the absorption and retention of dietary lead. J Nutr, 113: 365-378.

Bushnell PJ & Levin ED (1983) Effects of zinc deficiency on lead toxicity in rats. Neurobehav Toxicol Teratology, 5: 283-288.

Bushnell G, Brockhaus A, & Baltissen R (1977a) Neurobehavioural and system effects of long-term blood lead elevation in rats. Arch Toxicol, 37: 247-263.

Bushnell PJ, Allan JR, & Marlar RJ (1977b) Scotopic vision deficits in young monkeys exposed to lead. Science, 196: 333-335.

Byers RK & Lord EE (1943) Late effects of lead poisoning on mental development. Am J Dis Child, 66: 471-494.

Calder IC, Collings MT, & Heyworth JS (1990) Evaluation of soil lead: blood lead relationship for Port Pirie. Proceedings of the 23rd Annual Conference of Trace Substances in Environmental Health. Environ Geochem Health, 12(Suppl): 81-91.

Campbell BC, Beattie AD, Moore MR, Goldberg A, & Reid AG (1977) Renal insufficiency associated with excessive lead exposure. Br Med J, 1: 482-485.

Cantor KP, Sontag JM, & Held MF (1986) Patterns of mortality among plumbers and pipefitters. Am J Ind Med, 10: 73-89.

Capar SG & Rigsby EJ (1989) Survey of lead in canned evaporated milk. J Assoc Off Anal Chem, 72: 378-381.

Cardenas A, Roels H, Bernard AM, Barbon R, Buchet JP, Lauwerys RR, Rosello J, Ramis I, Mutti A, Franchini I, Fels LM, Stolte H, de Broe ME, Nuyts GD, Taylor SA, & Price RG (1993) Markers of early renal changes induced by industrial pollutants. II. Application to workers exposed to lead. Br J Ind Med, 50: 28-36.

CDC (1985) Preventing lead poisoning in young children. Atlanta, Georgia, US Department of Health and Human Services, Public Health Service, Centers for Disease Control, pp 7-19 (Publication No. 99-2230).

CEC (1981) Directive 77/312/CEE du Conseil du 29 mars 1977 concernant la surveillance biologique de la population vis-à-vis du risque saturnin. Rapport sur la mise en oeuvre de la directive. Luxembourg, Commission des Communautés européennes, Direction Santé et Sécurité (V/E/1/81-17/2).

Cerklewski FL & Forbes RM (1976) Influence of dietary zinc on lead toxicity in the rat. J Nutr, **110**: 689-696.

Chai S & Webb RC (1988) Effects of lead on vascular reactivity. Environ Health Perspect, **78**: 85-89.

Chakravorti S & Bhar S (1978) Chronic occupational exposure to lead: An evaluation of environmental lead levels, lead absorption and intoxication of storage battery workers. Bombay, Central Labour Institute, Industrial Hygiene Division.

Chamberlain AC (1983) Effect of airborne lead on blood lead. Atmos Environ, 17: 677-692.

Chamberlain AC (1985) Prediction of response of blood lead to airborne and dietary lead from volunteer experiments with lead isotopes. Proc R Soc (London), **B224**: 149-182.

Chamberlain AC, Heard MJ, Little P, Newton D, Wells AC, Wiffen RD (1978) Investigations into lead from motor vehicles. Harwell, United Kingdom Atomic Energy Authority (Report No. AERE-R9198).

Chan WH, Tang AJS, Chung DHS, & Lusis MA (1986) Concentration and deposition of trace metals in Ontario - 1982. Water Air Soil Pollut, **29**(4): 373-389.

Charney E, Kessler B, Farfel M, & Jackson D (1983) Childhood lead poisoning: a controlled trial for the effect of dust-control measures on blood lead levels. N Engl J Med, **309**: 1089-1093.

Chau YK, Wong PTS, & Bengert GA (1979) Determination of tetraalkyl-lead compounds in water, sediments, and fish samples. Anal Chem, **51**: 186-188.

Chau YK, Wong PTS, & Kramer O (1980) Occurrence of tetraalkylead compounds in the aquatic environment. Bull Environ Contam Toxicol, **24**: 265-269.

Chettle DR, Scott MC, & Somervaille LJ (1991) Lead in bone: sampling and quantitation using K x-rays excited by ^{109}Cd. Environ Health Perspect, **91**: 49-55.

Chisolm JJ Jr (1962) Aminoaciduria as a manifestation of renal tubular injury in lead intoxication and a comparison with patterns of aminoaciduria seen in other diseases. J Pediatr, **60**: 1-17.

Chisolm JJ & Brown DH (1979) Micromethod for zinc protoporphyrin in erythrocytes: including new data on the absorptivity of zinc protoporphyrin and new observations in neonates and sickle cell disease. Biochem Med, **22**: 214-237.

Chisolm JJ, Thomas DJ, & Hamill TG (1985) Erythrocyte porphobilinogen synthase activity as an indicator of lead exposure to children. Clin Chem, **31**: 601-605.

Choie DD & Richter GW (1972) Cell proliferation in rat kidney induced by lead acetate and effects of uninephrectomy on cell proliferation. Am J Pathol, **66**: 265-275.

Choie DD & Richter GW (1974) Cell proliferation in mouse kidney induced by lead. Synthesis of deoxyribonucleic acid. Lab Invest, **30**: 647-651.

Chowdhury AR, Dewan A, & Gandhi DN (1984) Toxic effect of lead on the testes of rat. Biomed Biochem Acta, **43**: 95-100.

Chowdhury AR, Chinoy NJ, & Gautam AK (1986) Effect of lead on human semen. Adv Contracept Delivery Syst, **2**: 208-211.

Christoffersson JO, Schutz A, Skerfving S, Ahlgren L, & Mattson S (1986) Decrease of skeletal lead after end of occupational exposure. Arch Environ Health, **41**: 312-318.

Clark CS, Bornschein RL, Succop P, Que Hee SS, Hammond PB, & Peace B (1985) Condition and type of housing as an indicator of potential environmental lead exposure and pediatic blood lead levels. Environ Res, **38**: 46-53.

Clausing P, Brunekreef B, & van Wijnen JH (1987) A method for estimating soil ingestion by children. Int Arch Occup Environ Health, **59**: 73-82.

Cohen N, Modai D, Golik A, Weissgarten J, Peller S, Katz A, Averbukh Z, & Shaked U (1989) Increased concanavalin A-induced suppressor cell activity in humans with occupational lead exposure. Environ Res, **48**: 1-6.

Cohn J, Cox C, & Cory-Slechta DA (1993) The effects of lead exposure on learning in a multiple repeated acquisition and performance schedule. Neurotoxicology, **14**: 329-346.

Collins MF, Hrdina PD, & Whittle E (1992) Lead in blood and brain regions of rats chronically exposed to low doses of the metal. Toxicol Appl Pharmacol, **65**: 314-322.

Colombo A (1985) The underdefined nature of the blood lead-air lead relationship from biological and statistical grounds. Atmos Environ, **19**: 1485-1493.

Columbano A, Ledda-Columbano GM, Lee G, Rajalakshmi S, & Sarma DSR (1984) Inability of mitogen-induced liver hyperplasia to support induction of enzyme-altered islands induced by liver carcinogens. Cancer Res, **47**: 5557-5559.

Cookman GR, King W, & Regan CM (1987) Chronic low-level lead exposure impairs embryonic to adult conversion of the neural cell adhesion molecule. J Neurochem, **49**(2): 399-403.

Cookman GR, Hemmens SE, Keane GJ, King WB, & Regan CM (1988) Chronic low level lead exposure precociously induces rat glial development *in vitro* and *in vivo*. Neurosci Lett, **86**: 33-37.

Cools A, Salle HJA, Verberk MM, & Zielhuis RL (1976) Biochemical response of male volunteers ingesting inorganic lead for 49 days. Int Arch Occup Environ Health, **38**: 129-139.

Cooney GH, Bell A, McBride W, & Carter C (1989a) Neurobehavioural consequences of prenatal low level exposures to lead. Neurotoxicol Teratol, **11**: 95-104.

Cooney GH, Bell A, McBride W, & Carter C (1989b) Low level exposures to lead: the Sydney lead study. Dev Med Child Neurol, **31**: 640-649.

Cooney G, Bell A, & Stavron C (1991) Low level exposures to lead and neurobehavioural development: the Sydney study at seven years. In: Heavy metals in the environment. Edinburgh, CEP Consultants, pp 16-19.

Cooper WC (1981) Mortality in employees of lead production facilities and lead battery plants, 1971-1975. In: Environmental lead: Proceedings of the Second International Symposium on Environmental Lead Research, Cincinnati, Ohio, December 1978. New York, London, San Francisco, pp 111-143.

Cooper WC (1988) Deaths from chronic renal disease in US battery and lead production workers. Environ Health Perspect, **78**: 61-63.

Cooper WC & Gaffey WR (1975) Mortality of lead workers. J Occup Med, **17**: 100-107.

Cory-Slechta DA (1990a) Lead exposure during advanced age: alterations in kinetics and biochemical effects. Toxicol Appl Pharmacol, **104**: 67-78.

Cory-Slechta DA (1990b) Exposure duration modifies the effects of low level lead on fixed interval performance. Neurotoxicology, **11**: 427-442.

Cory-Slechta DA & Pokora MJ (1991) Behavioral manifestations of prolonged lead exposure initiated at different stages of the life cycle: I. Schedule-controlled responding. Neurotoxicology, **12**(4): 745-760.

Cory-Slechta DA & Thompson T (1979) Behavioural toxicity of chronic post-weaning lead exposure in the rat. Toxicol Appl Pharmacol, **47**: 151-159.

Cory-Slechta DA & Widzowski DV (1991) Low level lead exposure increases sensitivity to the stimulus properties of dopamine D1 and D2 agonists. Brain Res, **553**: 65-74.

Cory-Slechta DA, Weiss B, & Cox C (1985) Performance and exposure indices of rats exposed to low concentrations of lead. Toxicol Appl Pharmacol, **78**: 291-299.

Coscia GC, Discalzi G, & Ponzetti C (1987) Immunological aspects of occupational lead exposure. Med Lav, **78**: 360-364.

Cramer K, Goyer RA, Jagenburg OR, & Wilson MH (1974) Renal ultrastructure, renal function and parameters of lead toxicity in workers with different length of lead exposure. Br J Ind Med, **31**: 113-127.

Cueto LM, Baer RD, & Gonzalez EM (1989) Three cases of unusual lead poisoning. Am J Gastroenterol, **84**: 1460.

Culbard EB, Thornton L, Watt JM, Wheatley M, Moorcroft S, & Thompson M (1988) Metal contamination in British urban dusts and soils. J Environ Qual, **17**: 226-234.

Cullen MR, Kayne RD, & Robins JM (1984) Endocrine and reproductive dysfunction in men associated with occupational inorganic lead intoxication. Arch Environ Health, **39**: 431-440.

Dabeka RW & McKenzie AD (1987) Lead, cadmium, and fluoride levels in market milk and infant formulas in Canada. J Assoc Off Anal Chem, 70(4):754-757.

Dabeka RW, McKenzie AD, & Lacroix GMA (1987) Dietary intakes of lead, cadmium, arsenic and fluoride by Canadian adults: a 24-hour duplicate diet study. Food Addit Contam, 4(1): 89-102.

Dalpra L, Tibiletti MG, Nocera G, Giulotto P, Auriti L, Carnelli V, & Simoni G (1983) SCE analysis in children exposed to lead emission from a smelting plant. Mutat Res, 120: 249-256.

Danielson BRG, Dencker L, & Lindgren A (1983) Transplacental movement of inorganic lead in early and late gestation in the mouse. Arch Toxicol, 54: 97-107.

David O, Clark J, & Voller K (1972) Lead and hyperactivity. Lancet, 2: 900-903.

Davidson C, Grimm T, & Nasta M (1981) Airborne lead and other elements derived from local fires in the Himalays. Science, 214: 1344-1346.

Davies BE (1983) A graphical estimation of the normal lead content of some British soils. Geoderma, 29: 67-75.

Davies JM (1984) Lung cancer mortality among workers making lead chromate and zinc chromate pigments at three English factories. Br J Ind Med, 41: 158-169.

Davies PH & Everhart WH (1973) Effects of chemical variations in aquatic environments: Volume 3 - Lead toxicity to rainbow trout and testing application factor concept. Washington, DC, US Environmental Protection Agency (EPA Report No. R373011C).

Davies BE, Elwood PC, Gallacher J, & Ginnever RC (1985) The relationships between heavy metals in garden soils and house dusts in an old lead mining area of North Wales, Great Britain. Environ Pollut, B9: 255-266.

Davies DJ, Thornton I, Watt JM, Culbard EB, Harvey PG, Delves HT, Sherlock JC, Smart GA, Thomas JFA, & Quinn MJ (1987a) Lead intake and blood lead in 2 year olds UK urban children. Sci Total Environ, 90: 13-29.

Davies DJ, Watt JM, & Thornton I (1987b) Lead levels in Birmingham dusts and soils. Sci Total Environ, 67: 177-185.

Davis JM & Grant LD (1992) The sensitivity of children to lead. In: Guzelian PS, Henry CJ, & Olin S ed. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC, ILSI Press, pp 15-27.

Davis JM & Svendsgaard DJ (1990) Nerve conduction velocity and lead: A critical review and meta-analysis. In: Johnson BL, Anger WK, Durao A, & Xinteras C ed. Advances in neurobehavioural toxicology: Applications in environmental and occupational health. Chelsea, Michigan, Lewis Publishers, pp 353-376.

Davis S, Waller P, Buschbom R, Balfour J, & White P (1990a) Quantitative estimates of soil ingestion in normal children between the ages of 2 and 7 years: Populations-based estimates using aluminium, silicon, and titanium as soil tracer elements. Arch Environ Health, 45: 112-122.

Davis JM, Otto DA, Weil DE, & Grant LD (1990b) The comparative developmental neurotoxicity of lead in humans and animals. Neurotoxicol Teratol, 12: 215-229.

Day JP, Hart M, & Robinson MS (1975) Lead in urban street dust. Nature (Lond), **253**: 343-345.

Dees JH, Heatfield BM, Reuben MD, & Trump BF (1980) Adenocarcinoma of the kidney. III. Histogenesis of renal adenocarcinomas induced in rats by N-(4-fluoro-4-biphenyl)acetamide. J Natl Cancer Inst, **64**: 1537-1545.

De La Burde B & Choate MS (1972) Does asymptomatic lead exposure in children have latent sequelae? J Pediatr, **81**: 1088-1096.

De La Burde B & Choate MS (1975) Early asymptomatic lead exposure and development at school age. J Pediatr, **87**: 638-664.

De Leacy EA (1987) Lead-crystal decanters - a health risk? Med J Aust, **147**: 622.

Delumyea R & Kalivretenos A (1987) Elemental carbon and lead content of fine particles from American and French cities of comparable size and industry, 1985. Atmos Environ, **21**: 1643-1647.

Delves HT & Campbell MJ (1988) Measurements of total lead concentrations and of lead isotope ratios in whole blood by use of inductively coupled plasma source mass spectrometry. J Anal At Spectrom, **3**: 343-348.

Desilva PE & Donnan MB (1980) Blood lead levels in Victorian children. Med J Aust, **2**: 315-318.

Diemel JAL, Brunekreef B, Boleu JSM, Biersteker K, & Veenstra SJ (1981) The Arnhem lead study. II. Indoor pollution, and indoor/outdoor relationships. Environ Res, **25**: 449-456.

Dieter M, Mathews HB, Jeffcoate RA, & Moseman RF (1993) Bioavailability of lead found in mine tailings from Alaska. J Toxicol Environ Health, **39**: 79-93.

Dietrich KN, Krafft KM, Bier M, Succop P, Berger O, & Bornschein R (1986) Early effects of fetal lead exposure: neurobehavioural findings at six months. Int J Biosoc Res, **8**: 151-168.

Dietrich KN, Krafft KM, Bornschein RL, Hammond PB, Berger OM, Succop PA, & Bier M (1987) Low-level fetal lead exposure effect on neurobehavioural development in early infancy. Pediatrics, **80**: 721-730.

Dietrich KN, Krafft KM, Bier M, Berger O, Succop PA, & Bornschein RL (1989) Neurobehavioural effects of foetal lead exposure: the first year of life. In: Smith MA, Grant LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Publishers, pp 320-331.

Dietrich KN, Succop PA, Bornschein RL, Krafft KM, Berger O, Hammond PB, & Buncher CR (1990) Lead exposure and neurobehavioural development in later infancy. Environ Health Perspect, **89**: 13-19.

Dietrich KN, Succop PA, Berger OG, Hammond PB, & Bornschein RL (1991) Lead exposure and cognitive development of urban, preschool children: the Cincinnati lead cohort at age 4 years. Neurotoxicol Teratol, **13**: 203-211.

Dietrich KN, Succop PA, Berger OG, & Keith RW (1992) Lead exposure and the central auditory processing abilities and cognitive development of urban children: the Cincinnati lead study cohort at age 5 years. Neurotoxicol Teratol, **14**: 51-56.

Dietrich K, Berger O, Succop P, Hammond P, & Bornschein R (1993a) The developmental consequences of low to moderate prenatal and postnatal lead exposure: Intellectual attainment in the Cincinnati Lead Study Cohort following school entry. Neurotoxicol Teratol, **15**: 37-44.

Dieterich K, Berger O, & Succop P (1993b) Lead exposure and the motor developmental status of urban 6-year-old children in the Cincinnati Prospective Study. Pediatrics, **91**: 301-307.

Djuric D, Kerin Z, Graovac-Leposavic L, Novak L, & Kop M (1971) Environmental contamination by lead from a mine and smelter: A preliminary report. Arch environ Health, **23**: 275-279.

Dolenc P, Staessen JA, Lauwerys RR, & Amery A (1993) Short report: low-level lead exposure does not increase the blood pressure in the general population. J Hypertens, **11**: 589-593.

Dong A, Simsiman GV, & Chesters G (1985) Release of phosphorus and metals from soils and sediments during dispersion. Soil Sci, **139**: 97-99.

Donovan MP, Schein LG, & Thomas JA (1980) Inhibition of androgen-receptor interaction in mouse prostate gland cytosol by divalent metal ions. Mol Pharmacol, **17**: 156-162.

Drasch GA & Ott J (1988) Lead in human bones. Investigations of an occupationally non-exposed population in southern Bavaria (FGR). II. Children. Sci Total Environ, **68**: 61-69.

Drasch GA, Böhm J, & Baur C (1987) Lead in human bones. Investigations of an occupationally non-exposed population in southern Bavaria (FGR). I. Adults. Sci Total Environ, **64**: 303-315.

Dresner DL, Ibrahim NG, Mascarenhas BR, & Levere RD (1982) Modulation of bone marrow heme and protein synthesis by trace elements. Environ Res, **28**: 55-66.

Drill S, Konz J, Mahar H, & Morse M (1979) The environmental lead problem: An assessment of lead in drinking water from a multi-media perspective. Washington, DC, US Environmental Protection Agency (EPA-570/9-79-003, NTIS-PB-296556).

Duggan MJ (1980) Lead in urban dust: An assessment. Water Air Soil Pollut, **14**: 309-321.

Egle P & Shelton KR (1986) Chronic lead intoxication causes a brain specific nuclear protein to accumulate in the nuclei of cells lining kidney tubules. J Biol Chem, **261**: 2294-2298.

Elias R (1985) Lead exposures in the human environment. In: Mahaffey KR ed. Dietary and environmental lead: human health effects. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 79-109.

Ellen G & van Loon JW (1990) Determination of cadmium and lead in foods by graphite furnace atomic absorption spectrometry with Zeeman background correction: test with certified reference materials. Food Addit Contam, **7**: 265-273.

Elwood PC (1986) The sources of lead in blood: A critical review. Sci Total Environ, **52**: 1-23.

Elwood PC, Davey-Smith G, Oldham PD, & Toothill C (1988a) Two Welsh surveys of blood lead and blood pressure. Environ Health Perspect, **78**: 119-121.

Elwood PC, Yarnell JWG, Oldham PD, Catford JC, Nutbeam D, Davey-Smith G, & Toothill C (1988b) Blood pressure and blood lead in surveys in Wales. Am J Epidemiol, **127**: 942-945.

Ernhart B & Morrow-Tlucak M (1987) The caretaking environment and exposure of children to lead. In: Thornton I & Culbard E ed. Lead in the home environment. Northwood, Science Reviews Ltd.

Ernhart CB, Wolf AW, Sokol RJ, Brittenham GM, & Ernhard P (1985) Fetal lead exposure: antenatal factors. Environ Res, **38**: 54-66.

Ernhart CB, Wolf WW, Kennard MJ, Erhard P, Filipovick HF, & Sokol RJ (1986) Intrauterine exposure to low levels of lead: the status of the neonate. Arch Environ Health, **41**: 287-291.

Ernhart CB, Morrow-Tlucak M, Marler MR, & Wolf AW (1987) Low level lead exposure in the prenatal and early preschool periods: early preschool development. Neurotoxicol Teratol, **9**: 259-270.

Ernhart CB, Morrow-Tlucak M, & Wolf AW (1988) Low level lead exposure and intelligence in the preschool years. Sci Total Environ, **71**: 453-459.

Ernhart CB, Morrow-Tlucak M, Worf AW, Super D, & Drotar D (1989a) Low level lead exposure in the prenatal and early preschool periods: intelligence prior to school entry. Neurotoxicol Teratol, **11**: 161-170.

Ernhart CB, Brittenham G, Marler MR, & Sokol RJ (1989b) Lead related birth defects: some methodologic issues. In: Smith MA, Grant LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Publishers, pp 357-370.

Evans RD & Rigler FH (1985) Long distance transport of anthropogenic lead as measured by lake sediments. Water Air Soil Pollut, **24**: 141-151.

Everson J & Patterson CC (1980) "Ultra-clean" isotope dilution/mass spectrometric analyses for lead in human blood plasma indicate that most reported values are artificially high. Clin Chem, **26**: 1603-1607.

Evis MJ, Kane KA, Moore MR, & Parratt JR (1985) The effects of chronic low lead treatment and hypertension on the severity of cardiac arrhythmias induced by coronary artery ligation in anaesthetized rats. Toxicol Appl Pharmacol, **80**: 234-242.

Evis MJ, Dhaliwal K, Kane KA, Moore MR, & Parratt JR (1987) The effects of chronic lead treatment and hypertension on the severity of cardiac arrhythmias induced by coronary artery occlusion or by noradrenaline in anaesthetised rats. Arch Toxicol, **59**: 336-340.

Ewers U, Stiller-Winkler R, & Idel H (1982) Serum immunoglobulin, complement C3, and salivary IgA level in lead workers. Environ Res, **29**: 351-357.

Fanning D (1988) A mortality study of lead workers, 1926-1985. Arch Environ Health, **43**: 247-251.

FAO/WHO (1993) Evaluation of certain food additives and contaminants. Forty-first report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva, World Health Organization (Technical Report Series 837).

Feigl F, Anger V, & Oesper RE (1972) Spot tests in inorganic analysis. London, Elsevier Publishing Company, pp 285-286.

Fergusson DM, Fergusson JE, Horwood LJ, & Kinzett NG (1988a) A longitudinal study of dentine lead levels, intelligence, school performance and behaviour. Part I. Dentine lead levels and exposure to environmental risk factors. J Child Psychol Psychiatr, **29**: 781-792.

Fergusson DM, Fergusson JE, Horwood LJ, & Kinzett NG (1988b) A longitudinal study of dentine levels, intelligence, school performance and behaviour. Part II. Dentine lead and cognitive ability. J Child Psychol Psychiatr, **29**: 793-809.

Fergusson DM, Fergusson JE, Horwood LJ, & Kinzett NG (1988c) A longitudinal study of dentine lead levels, intelligence, school performance and behaviour. Part III. Dentine lead levels and attention/activity. J Child Psychol Psychiatr, **29**: 811-824.

Fergusson JE, Fergusson DM, Horwood LJ, & Kinzett NG (1989) A longitudinal study of dentine lead levels, intelligence, school performance and behaviour: The measurement of dentine lead. Sci Total Environ, **80**: 229-241.

Fernando NP, Healy MA, Aslam M, Davis SS, & Hussein A (1981) Lead poisoning and traditional practices: The consequences for world health. A study in Kuwait. Public Health (Lond), **95**: 250-260.

Fischbein A, Alvares AP, Anderson KE, Sassa S, & Kappas A (1977) Lead intoxication among demolition workers: the effect of lead on the hepatic cytochrome P-450 system in humans. J Toxicol Environ Health, **3**: 431-437.

Fischbein A, Rice C, Sarkozi L, Kon SH, Petrocci M, & Selikoff IJ (1979) Exposure to lead in firing ranges. J Am Med Assoc, **241**: 1141-1144.

Fischbein A, Thornton J, Blumberg WE, Bernstein J, Valciukas JA, Moses M, Davidow B, Kaul B, Sirota M, & Selikoff IJ (1980) Health status of cable splicers with low-level exposure to lead: results of a clinical survey. Am J Public Health, **70**: 697-700.

Flegal AR, Rosman KJR, & Stephenson MD (1987) Isotope systematics of contaminant leads in Monterey Bay. Environ Sci Technol, **21**: 1075-1079.

Flora S-S & Tandon SK (1987) Effect of combined exposure to lead and ethanol on some biochemical indices in the rat. Biochem Pharmacol, **36**: 537-541.

Florence TM, Lilley SG, & Stauber JL (1988) Skin absorption of lead. Lancet, **2**: 157-158.

Fouassin A & Fondu M (1980) Evaluation of the daily intake of lead and cadmium from food in Belgium. Arch Belg Méd Soc Hyg Méd Trav Méd Lég, **38**: 453-467.

Foster WG (1992) Reproductive toxicity of chronic lead-exposure in the female cynomolgus monkeys. J Reprod Toxicol, **16**: 123-131.

Fouts PJ & Page JH (1942) The effect of chronic lead poisoning on arterial blood pressure in dogs. Am Heart J, **24**: 329-331.

Fowler BA, Kimmel CA, Woods JS, McConnell EE, & Grant LD (1980) Chronic low-level lead toxicity in the rat: III. An integrated assessment of long-term toxicity with special reference to the kidney. Toxicol Appl Pharmacol, **56**: 59-77.

Fox DA & Sillman AJ (1979) Heavy metals affect rod, but not cone pholoreceptors. Science, **206**: 78-80.

Fox DA, Lewkowski JP, & Cooper GP (1977) Acute and chronic effects of neonatal lead exposure on developmental of the visual worked response in rats. Toxicol Appl Pharmacol, **40**: 449-461.

Freeman GB, Johnson JD, Killinger JM, Liao SC, Feder PI, Davis AO, Ruby MV, Chaney RL, Lovre SC, & Bergstrom PD (1992) Relative bioavailability of lead from mining waste soils in rats. Fundam Appl Toxicol, **19**: 388-398.

Friberg L (1988) Quality assurance. In: Clarkson TW, Friberg L, Nordstrom GF, & Sager PR ed. Biological monitoring of toxic metals. New York, Plenum Press, pp 103-126.

Friberg L & Vahter M (1983) Assessment of exposure to lead and cadmium through biological monitoring: Results of a UNEP/WHO global study. Environ Res, **30**: 95-128.

Friedman JA & Weinberger HL (1990) Six children with lead poisoning. J Dis Child, **144**: 1039-1044.

Fullmer CS & Rosen JF (1990) Effect of dietary calcium and lead status on intestinal calcium absorption. Environ Res, **51**: 91-99.

Fullmer CS (1990) Intestinal lead and calcium absorption: Effect of 1,25-dihydroxy-cholecalciferol and lead status. Proc Soc Exp Biol Med, **194**: 258-264.

Fulton M, Thomson G, Hunter R, Raab G, Laxen D, & Hepburn W (1987) Influence of blood lead on the ability and attainment of children in Edinburgh. Lancet, **30 May**: 1221-1226.

Galal-Gorchev H (1991a) Dietary intake of pesticide residues, cadmium, mercury and lead. Food Addit Contam, **8**(6): 793-806.

Galal-Gorchev H (1991b) Global overview of dietary lead exposure. Special issue incorporating the Proceedings of the Symposium on the Bioavailability and Dietary Exposure of Lead, Chapel Hill, North Carolina, September 1990. Chem Speciation Bioavailab, **3**(3/4): 5-11.

Garber BT & Wei E (1974) Influence of dietary factors on the gastrointestinal absorption of lead. Toxicol Appl Pharmacol, **27**: 685-691.

Garcia-Miragaya J (1984) Levels, chemical fractionation, and solubility of lead in roadside soils of Caracas, Venezuela. Soil Sci, **138**: 147-152.

Gartrell MJ, Craun JC, Podrebarac DS, & Gunderson EL (1985a) Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1979 - September 1980. J Assoc Off Anal Chem, **68**: 1184-1187.

Gartrell MJ, Craun JC, Podrebarac DS, & Gunderson EL (1985b) Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1979 - September 1980. J Assoc Off Anal Chem, **81**: 1163-1183.

Gartside PS (1988) The relationship of blood lead levels and blood pressure in NHANES II: additional calculations. Environ Health Perspect, **78**: 31-34.

Gartside PS & Buncher CR (1982) Relationship of air lead and blood lead for workers at an automobile battery factory. Int Arch Occup Environ Health, **50**: 1-10.

GEMS (1985) Global Environmental Monitoring System: Assessment of human exposure to lead: Comparison between Belgium, Malta, Mexico and Sweden. Stockholm, Karolinska Institute.

Gennart JP, Bernard A, & Lauwerys R (1992) Assessment of thyroid, testes, kidney and autonomic nervous system function in lead-exposed workers. Int Arch Occup Environ Health, **64**: 49-57.

Gerhardsson L, Lundstrom N-G, Nordbery G, & Wall S (1986) Mortality and lead exposure: a retrospective cohort study of Swedish smelter workers. Br J Ind Med, **43**: 707-712.

Getz LL, Haney AW, Larimore RW, McNurney JW, Leland HV, Price PW, Rolfe GL, Wortman RL, Hudson JL, Solomon RL, & Reinbold KA (1977) Transport and distribution in a watershed ecosystem. In: Boggess WR ed. Lead in the environment. Springfield, Virginia, National Technical Information Service, pp 105-133 (National Science Foundation report No. NSF/RA-770214).

Gibson JL (1904) A plea for painted railings and painted walls of rooms as the source of lead poisoning amongst: Queensland children. Aust Med Gaz, **23**: 149.

Gilbert SG & Rice DC (1987) Low-level lifetime lead exposure produces behavioral toxicity (spatial discrimination reversal) in adult monkeys. Toxicol Appl Pharmacol, **91**: 484-490.

Gmerek DE, McCofferty MR, O'Neill KJ, Melamed BR, & O'Neill JJ (1981) Effect of inorganic lead on rat brain mitochondrial respiration and energy production. J Neurochem, **36**: 1109-1113.

Goldstein GW (1990) Lead poisoning and brain cell function. Environ Health Perspect, **89**: 91-94.

Gould JH, Capar SG, Jacobs RM, & Plunkett R (1988) A quick color test to detect lead release from glazed ceramic and enameled metalware. Anal Lett, **21**: 2145-2154.

Goyer RA (1985) Renal changes associated with lead exposure. In: Mahaffey KR ed. Dietary and environmental lead: Human health effects. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 315-335.

Goyer RA (1992) Nephrotoxicity and carcinogenicity of lead - An update on exposure and effects of lead. Fundam Appl Toxicol, **18**: 1-16.

Goyer RA (1993) Lead toxicity: current concerns. Environ Health Perspect, **100**: 177-187.

Goyer RA & Rhyne BC (1973) Pathological effects of lead. Int Rev Exp Pathol, **12**: 1-77.

Goyer RA & Wilson MH (1975) Lead induced inclusion bodies: results of ethylenediamine-tetra-acetic acid treatment. Lab Invest, **32**: 149-156.

Goyer RA, Leonard DL, Moore JF, Rhyne B, & Krigman MR (1970) Lead dosage and the role of the intranuclear inclusion body. Arch Environ Health, **20**: 705-711.

Goyer RA, Falk HL, Hogan M, Feldman DD, & Richter W (1981) Renal tumors in rats given trisodium nitrilotriacetic acid in drinking water for 2 years. J Natl Cancer Inst, **66**: 869-880.

Goyer RA, Weinberg CR, Victery WM, & Miller CR (1989) Lead induced nephrotoxicity: kidney calcium as an indicator of tubular injury. In: Bach PH & Lock EA ed. Nephrotoxicity. New York, London, Plenum Press, pp 11-20.

Grandjean P (1979) Occupational lead poisoning in Denmark: screening with the haematofluorometer. Br J Ind Med, **36**: 52-58.

Grandjean P & Olsen B (1984) Lead. In: Vercruysse A ed. Techniques and instrumentation in analytical chemistry. Volume 4: Evaluation of analytical methods in biological systems, Part B: Hazardous metals in human toxicology. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 153-169.

Grandjean P, Wulf HC, & Niebuhr E (1983) Sister chromatid exchange in response to variations in occupational lead exposure. Environ Res, **32**: 199-204.

Grandjean P, Hansen ON, & Lyngbye K (1984) Analysis of lead in circumpulpal dentin of deciduous teeth. Ann Clin Lab Sci, **14**: 270-275.

Grandjean P, Hansen ON, & Lyngbye K (1986) Lead concentration in deciduous teeth: variation related to tooth type and analytical technique. J Toxicol Environ Health, **19**: 437-445.

Grandjean P, Jensen BM, Sando SH, Jorgensen PJ, & Antonsen S (1989a) Delayed blood regeneration in lead exposure: an effect on reserve capacity. Am J Public Health, **79**: 1385-1388.

Grandjean P, Hollnagel H, Hedegaard L, Christensen JM, & Larsen S (1989b) Blood lead-blood pressure relations: alcohol intake and haemoglobin as confounders. Am J Epidemiol, **129**: 732-739.

Grandjean P, Lyngbye T, & Hansen ON (1991) Lessons from a Danish study on neuropsychological impairment related to lead exposure. Environ Health Perspect, **94**: 111-115.

Granick JL, Sassa S, Granick S, Levere RD, & Kappas A (1973) Studies in lead poisoning. II. Correlation between the ratio of activated to inactivated aminolevulinic acid dehydratase of whole blood and the blood lead level. Biochem Med, **8**: 149-159.

Grant LD & Davis JM (1989) Effects of low-level lead exposure on paediatric neurobehavioural development: Current findings and future directions. In: Smith MA, Grand LD, & Sors AI ed. Lead exposure and child development: An international Assessment. Dordrecht, London, Kluwer Academic Publishers, pp 49-115.

Grant LD, Kimmel CA, West GL, Martinez-Vargas CM, & Howard JL (1980) Chronic low-level lead toxicity in the rat. II. Effects on postnatal physical and behavioral development. Toxicol Appl Pharmacol, **56**: 42-58.

Graziano JH & Blum C (1991) Lead exposure from lead crystal. Lancet, **337**: 141-142.

Graziano JH, Popovac D, Factor-Litvak P, Shrout P, Kline J, Murphy MJ, Zhao Y, Mehmeti A, Ahmedi X, Rajovic B, Zvicer Z, Nenezic U, Lolacono NJ, & Steun Z (1990) Determinants of elevated blood lead during pregnancy in a population surrounding a lead smelter in Kosova, Yugoslavia. Environ Health Perspect, **89**: 95-100.

Graziano JH, Slavkovic V, Factor-Litvak P, Popovac D, Ahmedi X, & Mehmeti A (1991) Depressed serum erythropoietin in pregnant women with elevated blood lead. Arch Environ Health, **46**: 347-350.

Greene T, Ernhart CB, & Boyd TA (1992) Contributions of risk factors to elevated blood and dentine levels in preschool children. Sci Total Environ, **115**: 239-260.

Griffith JQ & Landaver MA (1944) The effect of chronic lead poisoning on arterial blood pressure in rats. Am Heart J, **28**: 295-297.

Gulson B & Wilson D (1994) History of lead exposure in children revealed from isotopic analyses of teeth. Arch Environ Health, **49X**: 279-283.

Gupta AK, Sehgal SK, Mohan M, & Anand NK (1990) Cosmetic plumbism. Indian Paediatr, **27**: 760-761.

Gustafson A, Hedmer P, Schutz A, & Skerfving S (1989) Occupational lead exposure and pituitary function. Int Arch Occup Environ Health, **61**: 277-281.

Haeger-Aronsen B (1960) Studies on urinary excretion of δ-aminolaevulic acid and other haem precursors in lead workers and lead-intoxicated rabbits. Scand J Clin Lab Invest, **12**(47): 1.

Haenninen H, Mantere P, Hernberg S, Seppalainen AM, & Kock B (1979) Subjective symptoms in low-level exposure to lead. Neurotoxicology, **1**: 333-347.

Hakim RB, Stewart WF, Canner JK, & Tielsch JM (1991) Occupational lead exposure and strabismus in offspring: A case control study. Am J Epidemiol, **133**: 351-356.

Hammond PB, O'Flaherty EJ, & Gartside PS (1981) The impact of air-lead on blood-lead in man: A critique of the recent literature. Food Cosmet Toxicol, **19**: 631-638.

Hammond PB, Bornschein RL, & Succop P (1985) Dose-effect and dose-response relationships of blood lead to erythrocytic protoporphyrin in young children. Environ Res, **38**: 187-196.

Hansen ON, Trillingsgaard A, Beese I, Lyngbye T, & Grandjean P (1989) A neuropsychological study of children with elevated dentine lead level: assessment of the effect of lead in different socio-economic groups. Neurotoxicol Teratol, **11**: 205-213.

Harlan WR (1988) The relationship of blood lead levels to blood pressure in the US population. Environ Health Perspect, **78**: 9-13.

Harlan WR, Landis JR, Schmouder RL, Goldstein NG, & Harlan LC (1985) Blood lead and blood pressure: relationship in the adolescent and adult US population. J Am Med Assoc, **253**: 530-534.

Harvey PG, Hamlin MW, Kumar R, & Delves HT (1984) Blood lead, behaviour and intelligence test performance in preschool children. Sci Total Environ, **40**: 45-60.

Harvey PG, Hamlin MW, Kumar R, Morgan J, Spurgeon A, & Delves HT (1988) Relationships between blood lead, behaviour, psychometric and neuropsychological test performance in young children. Br J Dev Psychol, **6**: 145-156.

Hatzakis A, Kokkevi A, Maravelias C, Katsouyanni K, Salaminios F, Kalandidi A, Koutselinis A, Stefanis C, & Trichopoulos D (1989) Psychometric intelligence deficits in lead-exposed children. In: Smith MA, Grand LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Publishers, pp 211-223.

Hawk BA, Schroeder SR, Robinson G, Otto D, Mushak P, Kleinbaum D, & Dawson G (1986) Relation of lead and social factors to IQ of low-SES children: a partial replication. Am J. Ment Defic, **91**: 178-183.

Heard MJ & Chamberlain AC (1982) Effects of minerals and food on uptake of lead from the gastrointestinal tract in humans. Hum Toxicol, **1**: 411-416.

Hem JD & Durum WH (1973) Solubility and occurrence of lead in surface water, J An Water Works Assoc, **65**: 562-568.

Henning SJ & Cooper LC (1988) Intestinal accumulation of lead salts and milk lead by suckling rats (42645). Proc Soc Exp Biol Med, **187**: 110-116.

Hernberg S (1973) Prevention of occupational poisoning from inorganic lead. Work Environ Health, **10**: 53-61.

Hernberg S & Nikkanen J (1970) Enzyme inhibition by lead under normal urban conditions. Lancet, **1**(7637): 63-64.

Hilderbrand DC, Der R, Griffin WT, & Fahim MS (1973) Effect of lead acetate on reproduction. Am J Obstet Gynecol, **115**: 1058-1065.

Hogstedt C, Hane M, Agrell A, & Bodin L (1983) Neuropsychological test results and symptoms among workers with well-defined long term exposure to lead. Br J Ind Med, **49**: 99-105.

Holness DL & Nethercott JR (1988) Acute lead intoxication in a group of demolition workers. Appl Ind Hyg, **3**: 338-341.

Holtzman D, Shen Hgu J, & Montell P (1978) *In vitro* effects of inorganic lead on isolated rat brain mitochondrial respiration. Neurochem Res, **3**: 195-206.

Holtzman D, Shen Hgu J, & Desautel M (1981) Absence of effects of lead feedings and growth retardation on mitochondrial and microsomal cytochrome in the developing brain. Toxicol Appl Pharmacol, **58**: 48-56.

Holtzman D, Devries C, Nguyan H, Olson J, & Bensch K (1984) Maturation of resistance to lead encephalopathy: cellular and subcellular mechanisms. Neurotoxicology, 5: 97-124.

Hopper JL, Balderas A, & Mathews JO (1982) Analysis of variation in blood lead levels in Melbourne families. Med J Aust, 2: 573-576.

Huang J, He F, Yigun W, & Zhang S (1988a) Observations on renal function in workers exposed to lead. Sci Total Environ, 71: 535-537.

Huang XP, Feng ZY, Zhai WL, & Xu JH (1988b) Chromosomal aberrations and sister chromatid exchanges in workers exposed to lead. Biomed Environ Sci, 1: 382-387.

Huber F & Schmidt U (1976) Methylation of organolead and lead (II) compounds to C^2 ^{4}Pb by microorganisms. Nature (Lond), 259: 157-158.

Hutton M, Wadge A, & Milligan PJ (1988) Environmental levels of cadmium and lead in the vicinity of a major refuse incinerator. Atmos Environ, 22: 411-416.

IAEA (1987) Co-ordinated research programme on human daily dietary intakes of nutritionally important trace elements as measured by nuclear and other techniques. IAEA Newl, 2: 6-15.

IARC (1980) Lead and lead compounds. In: Some metals and metallic compounds. Lyon, International Agency for Research on Cancer, pp 325-416 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 23).

IARC (1987a) Genetic and related effects: An updating of selected IARC Monographs from Volumes 1 to 42. Lyon, International Agency for Research on Cancer (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 6).

IARC (1987b) Lead and lead compounds. In: Overall evaluations of carcinogenicity: an updating of IARC Monographs, Volumes 1 to 42. Lyon, International Agency for Research on Cancer, pp 230-232 (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Supplement 7).

Ibels LS & Pollock CA (1986) Toxicology management review. Lead intoxication. Med Toxicol, 1: 387-410.

Ichiba M & Tomokuni K (1990) Studies on erythrocyte pyrimidine 5'-nucleotidase test and its evaluation in workers occupationally exposed to lead. Int Arch Occup Environ Health, 62: 305-310.

ILZSG (International Lead and Zinc Study Group) (1992) Lead and zinc statistics. Int Lead Zinc Study Group Bull, 32: 3.

IPCS (1977) Environmental health criteria 3: Lead. Geneva, World Health Organization, 160 pp.

IPCS (1989) Environmental health criteria 85: Lead - Environmental effects. Geneva, World Health Organization, 106 pp.

IPCS (1994) Environmental health criteria 155: Biomarkers and risk assessment: Concepts and principles. Geneva, World Health Organization, 82 pp.

IRPC (International Radiological Protection Commission), Task Group on Lung Dynamics (1966) Deposition and retention models for internal dosimetry of the human respiratory trace. Health Phys, 12: 173-207.

IRPTC (1987) IRPTC legal file 1986. Geneva, International Register of Potentially Toxic Chemicals, United Nations Environment Programme, vol 1.

Irwig LM, Harrison WO, Rocks P, Webster I, & Andrew M (1978) Lead and morbidity: a dose response relationship. Lancet, 2(8079): 4-7.

Jaakkola J & Anttila A (1992) [Occupational exposures to chemical agents in Finland.] Helsinki, Institute of Occupational Health and Finnish Work Environmental Fund (in Finnish).

James AC (1978) Lung deposition of submicron aerosols calculated as a function of age and breathing rate. In: National Radiological Protection Board Annual Report. Harwell, UK, National Radiological Protection Board, pp 71-75.

Jaremin B (1983) Blast lymphocyte transformation (LTT), rosette (E-RFC) and leukocyte migration inhibition (MIF) tests in persons exposed to the action of lead during work. Report II. Bull Inst Marit Trop Med (Gdynia), 34: 187-197.

Jensen AA (1984) Metabolism and toxicokinetics. In: Grandjean P ed. Biological effects of organolead compounds. Boca Raton, Florida, CRC Press, chapter 8, pp 97-115.

Johnson NE & Tenuta K (1979) Diets and lead blood levels of children who practice pica. Environ Res, 18: 369-376.

Jorhem L & Slorach S (1988) Lead, chromium, tin, iron, and cadmium in foods in welded cans. Food Addit Contam, 4: 309-316.

Jorhem L, Mattsson P, & Slorach S (1988) Lead in table wines on the Swedish market. Food Addit Contam, 5: 645-649.

Kaminsky P, Leone J, & Duc M (1988) Incidence du saturnisme hydrique dans un service de médecine interne en région de sols acides. Presse Méd, 17: 419-422.

Kampe W (1983) Lead and cadmium in food - is there an actual danger? Forum Staedte-Hyg, 34: 236-241.

Kang HK, Infante PF, & Carra JS (1980) Occupational lead exposure and cancer (letter). Science, 207: 935-936.

Katagiri Y, Toriumi H, & Kawai M (1983) Lead exposure among 3-year-old children and their mothers living in a pottery-producing area. Int Arch Occup Environ Health, 52: 223-229.

Kaye WE, Novotny TE, & Tucker M (1987) New ceramics-related industry implicated in elevated blood lead levels in children. Arch Environ Health, 42: 161-164.

Kazantzis G (1989) Lead: ancient metal - modern menace. In: Smith MA, Grant LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Press, pp 119-128.

Kehoe RA (1961) The metabolism of lead in man in health and disease: The normal metabolism of lead (The Harben Lectures, 1960). J R Inst Public Health Hyg, 24: 81-97.

Kehoe RA (1987) Studies of lead administration and elimination in adult volunteers under natural and experimentally induced conditions over extended periods of time. Food Chem Toxicol, 25: 425-493.

Keller CA & Doherty RA (1980a) Distribution and excretion of lead in young and adult female mice. Environ Res, 21: 217-228.

Keller CA & Doherty RA (1980b) Bone lead mobilization in lactating mice and lead transfer to suckling offspring. Toxicol Appl Pharmacol, 55: 220-228.

Kerin Z (1973) Lead in new-fallen snow near a lead smelter. Arch Environ Health, 26: 256-260.

Kholil-Manesh F, Gonich HC, Cohen AH, Alinovi R, Berganaschi E, Mutti A, & Rosen VJ (1992) Experimental model of lead nephrotoxicity. I. Continuous high-dose lead administration. Kidney Int, 41: 1192-1203.

Kimber I, Stonard MD, Gidlow DA, & Niewola Z (1986) Influence of chronic low-level exposure to lead on plasma immunoglobulin concentration and cellular immune function in man. Int Arch Occup Environ Health, 57: 117-125.

King E & Conchie D (1979) Industrial lead absorption. Ann Occup Hyg, 22: 213-239.

Kirkby H & Gyntelberg F (1985) Blood pressure and other cardiovascular risk factors of long term exposure to lead. Scand J Work Environ Health, 11: 15-19.

Kocak R, Anarat A, Altintas G, & Evilyaoglu N (1989) Lead poisoning from contaminated flour in a family of 11 members. Hum Toxicol, 8: 385-386.

Kolbye AC, Mahaffey R, Fiorino A, Corneliussen PC, & Jelinek CF (1974) Food exposures to lead. Environ Health Perspect, 7(Exp Issue): 65-75.

Koller LD (1985) Immunological effects of lead. In: Mahaffey KR ed. Dietary and environmental lead: Human health effects. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 339-354.

Koller LD & Roan JG (1980) Effect of lead, cadmium and methylmercury on immunologic memory. J Environ Pathol Toxicol, 4: 47-52.

Koo WWK, Succop PA, Bornschein RL, Krug-Wispe SK, Steichen JJ, Tsang RC Hammond PB, & Berger OG (1991) Serum vitamin D metabolites and bone mineralization in young children with chronic to moderate lead exposure. Pediatrics, 87: 680-687.

Kopp SJ, Barron JT, & Tow JP (1988) Cardiovascular actions of lead and relationship to hypertension: a review. Environ Health Perspect, 89: 91-99.

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 & Kello D (1979) Bioavailability of lead in rats fed "human" diets. Bull Environ Contam Toxicol, 21: 312-314.

Kostial K, Kello D, & Jugo S (1978) Influence of age on metal metabolism and toxicity. Environ Health Perspect, 25: 81-86.

Kovar IZ, Strehlow CD, Richmond J, & Thompson MG (1984) Perinatal lead and cadmium burden in a British urban population. Arch Dis Child, 59: 36-39.

Krueger JA & Duguay KM (1989) Comparative analysis of lead in Maine urban soils. Bull Environ Contam Toxicol, 42: 574-581.

Kusell M, Lake L, Anderson M, & Gerschenson LE (1978) Cellular and molecular toxicology of lead. II. Effect of lead on d-aminolevulinc acid synthelase of cultured cells. J Toxicol Environ Health, 4: 515-525.

Kutbi II, Ahmed M, & Saber A (1989) Measurement of blood-lead levels in school children of Jeddah Saudi Arabia and assessment of sub-toxic levels of lead on some sensitive hematological parameters. J Environ Sci Health, A24: 943-955.

Lacey RF, Moore MR, & Richards WN (1985) Lead in water, infant diet and blood: The Glasgow duplicate diet study. Sci Total Environ, 41: 235-257.

Lai CS (1972) Lead poisoning as an occupational hazard in Chinese opera actors: a case report. Singap Med J, 13: 115-117.

Landis JR & Flegal KM (1988) A generalized Mantel-Haenszel analysis of the regression of blood pressure on blood lead using NHANES II data. Environ Health Perspect, 78: 35-41.

Landrigan PJ, Gehlbach SH, Rosenblum BF, Shoults JM, Cancelaria RM, Barthel WF, Liddle JA, Smrek AL, Staehling NW, & Sanders JF (1975) Epidemic lead absorption near an ore smelter; The role of particulate lead. N Engl J Med, 292: 123-129.

Lansdown RG, Shepherd J, Clayton BE, Delves HT, Graham PJ, & Turner WC (1974) Blood-lead levels, behaviour, and intelligence: a population study. Lancet, 1(7857): 538-541.

Lansdown R, Yule W, Urbanowicz MA, & Hunter J (1986) The relationship between blood-lead concentrations, intelligence, attainment and behaviour in a school population: the second London study. Int Arch Occup Environ Health, 57: 225-235.

Laurs AJ (1976) Review of European test methods for measuring lead and cadmium release. In: Proceedings of the International Conference on Ceramic Foodware Safety, Geneva, 1974. New York, Lead Industries Association Inc., pp 27-36.

Lauwerys R, Buchet JP, Roels HA, & Materne DD (1974) Relationship between urinary δ-aminolevulinic acid excretion and the inhibition or red cell δ-aminolevulinate dehydratase by lead. Clin Toxicol, 7: 383-388.

Lavelle JM, Poppenga RH, Thacker BJ, Geisy JP, Weis C, Othoudt R, & Vandervoort C (1991) Bioavailability of lead in mining wastes: An oral intubation study in young swine. Chem Speciation Bioavailab, 3: 105-111.

Laxen DPH, Raab GM, & Fulton M (1987) Children's blood lead and exposure to lead in household dust and water - a basis for an environmental standard for lead in dust. Sci Total Environ, 66: 235-244.

Lee RE & Goranson S (1972) National air surveillance cascade impact or network. I. Size distribution measurements of suspended particulate matter in air. Environ Sci Technol, 6: 1019-1024.

Leeming RJ & Blair JA (1980) The effect of pathological and normal physiological processes on biopterin levels in man. Clin Chim Acta, 108: 102-111.

Lepow ML, Bruckman L, Rubino RA, Markowitz S, Gillette M, & Kapish J (1974) Role of airborne lead in increased body burden of lead in Hartford children. Environ Health Perspect, 7: 99-102.

Lerda D (1992) Study of sperm characteristics in persons occupationally exposed to lead. Am J Ind Med, 22: 567-571.

Levin ED & Bowman RE (1983) The effect of pre- or postnatal lead exposure on Hamilton search task in monkeys. Neurobehav Toxicol Teratol, 5: 391-394.

Levin ED & Bowman RE (1986) Long-term lead effects on the Hamilton Search Test and delayed alternation in monkeys. Neurobehav Toxicol Teratol, 8: 219-224.

Levin ED & Bowman RE (1989) Long-term effects of chronic post-natal lead exposure on delayed spatial alternation in monkeys. Neurotoxicol Teratol, 10: 505-510.

Lilienthal H, Winneke G, Brockhaus A, & Molik B (1986) Pre- and postnatal lead-exposure in monkeys: Effects on activity and learning set formation. Neurobehav Toxicol Teratol, 8: 265-272.

Lilienthal H, Winneke G, & Ewert T (1990) Effects of lead on neurophysiological and performance measures: animal and human data. Environ Health Perspect, 89: 21-25.

Lilis R (1981) Long-term occupational lead exposure, chronic nephropathy, and renal cancer: a case report. Am J Ind Med, 2: 293-297.

Lilis R, Fischbein A, Eisinger J, Blumberg WE, Diamond S, Anderson HA, Rom W, Rice C, Sarkozi L, Kon S, & Selikoff IJ (1977) Prevalence of lead disease among secondary lead smelter workers and biological indicators of lead exposure. Environ Res, 14: 255-285.

Lilley SG, Florence TM, & Stauber JL (1988) The use of sweat to monitor lead absorption through the skin. Sci Total Environ, 76: 267-278.

Lind B, Vahter M, Rahnster B, & Björs U (1988) Quality control samples for the determination of lead and cadmium in blood, feces, air filters, and dust. Fresenius Z Anal Chem, 332: 741-743.

Lindholm ML, Sallmen M, Anttila A, Taskinen H, & Hemminki K (1991) Paternal occupational lead exposure and spontaneous abortion. Scand J Work Environ Health, 17(2): 95-103.

Lin-Fu JS (1985) Historical perspective on health effects of lead. In: Mahaffey KR ed. Dietary and environmental lead: Human health effects. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 43-64.

Lovering TG ed. (1976) Lead in the environment. Washington, DC, US Department of the Interior, Geological Survey (Geological Survey Professional Paper No. 957).

Lyngbye T, Hansen OL, Trillingsgaard A, Beese I, & Grandjean P (1990a) Learning disabilities in children: significance of low-level lead-exposure and confounding factors. Acta Paediatr Scand, **79**: 352-360.

Lyngbye T, Jorgensen PJ, & Grandjean P (1990b) Validity and interpretation of blood lead levels: a study of Danish school-children. Scand J Clin Lab Invest, **50**: 441-449.

McGrath SP (1986) The range of metal concentrations in top soils of England and Wales in relation to soil protection guidelines. In Hemphill DD ed. Trace substances in environmental health, vol 20. Columbia, Missouri, University of Missouri, pp 242-252.

McGregor AJ & Mason MJ (1990) Chronic occupational lead exposure and testicular endocrine function. Hum Exp Toxicol, **9**: 371-376.

McIntosh MJ, Meredith PA, Moore MR, & Goldberg A (1985) Neurotoxic action of lead: effect on tetrahydrobiopterin metabolism in the rat. Comp Biochem Physiol, **81C**(1): 227-231.

McIntosh MJ, Meredith PA, Moore MR, & Goldberg A (1989) Action of lead on neurotransmission in rats. Xenobiotica, **19**(1): 101-113.

McKhann CF & Vogt EC (1933) Lead poisoning in children. J Am Med Assoc, **101**: 1131-1135.

McMichael AJ & Johnson HM (1982) Long-term mortality profile of heavily-exposed lead smelter workers. J Occup Med, **24**: 375-378.

McMichael AJ, Vimpani GV, Robertson EF, Baghurst PA, & Clark PD (1986) The Port Pirie cohort study: maternal blood lead and pregnancy outcome. J Epidemiol Community Health, **41**: 18-25.

McMichael AJ, Baghurst PA, Wigg NR, Vimpani GV, Robertson EF, & Roberts RJ (1988) Port Pirie cohort study: environmental exposure to lead and children's abilities at the age of four years. N Engl J Med, **319**: 468-475.

Maenhaut W, Zoller WH, Duce RA, & Hoffman GL (1979) Concentration and size distribution of particulate trace elements in the south polar atmosphere. J Geophys Res, **84**: 2421-2431.

Mahaffey KR (1985) Factors modifying susceptibility to lead toxicity. In: Mahaffey KR ed. Dietary and environmental lead: Human health effects. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 373-419.

Mahaffey KR & Annest JL (1986) Association of erythrocyte protoporphyrin with blood lead level and iron status in the Second National Health and Nutrition Examination Survey, 1976-1980. Environ Res, **41**: 327-338.

Mahaffey-Six KR & Goyer RA (1972) The influence of iron deficiency on tissue content and toxicity of ingested lead in the rat. J Lab Clin Med, **79**: 128-136.

Mahaffey KR, Rosen JF, Chesney RW, Peeler JT, Smith CM, & Debuca HF (1982) Association between age, blood lead concentration, and serum 1,25-dihydroxy-cholecalciferol levels in children. Am J Clin Nutr, **35**: 1327-1331.

Maines MD (1992) Haem oxygenase-clinical applications and functions. Boca Raton, Florida, CRC Press.

Maki-Paakkanen J, Sorsa M, & Vainio H (1981) Chromosome aberrations and sister chromatid exchanges in lead-exposed workers. Hereditas, **94**: 269-275.

Manton WI (1985) Total contribution of airborne lead to blood lead. Br J Ind Med, **42**: 168-172.

Manton WI & Cook JD (1984) High accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid. Br J Ind Med, **41**: 313-319.

Manton WI & Thal ER (1986) Lead poisoning from retained missiles: an experimental study. Ann Surg, **204**: 594-599.

Mao P & Molnar JJ (1967) The fine structure and histochemistry of lead-induced renal tumors in rats. Am J Pathol, **50**: 571-603.

Maranelli G & Apostoli P (1987) Assessment of renal function in lead poisoned workers. In: Occupational and environmental chemical hazards: Cellular and biochemical indices for monitoring toxicity. Chichester, Ellis Horwood Ltd, chapter 42, pp 344-348.

Marcus AH (1985a) Testing alternative nonlinear kinetic models in compartmental analysis. In: Eisenfield J & Delisi C ed. Mathematics and computers in biomedical applications. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 259-267.

Marcus AH (1985b) Multicompartment kinetic models for lead: Part I. bone kinetics and variable absorption in humans without excessive lead exposures. Environ Res, **36**: 441-458.

Marcus AH (1985c) Multicompartment kinetic models for lead: Part II. linear kinetics and variable absorption in humans without excessive lead exposures. Environ Res, **36**: 459-472.

Marcus AH & Schwartz J (1987) Dose-response curves for erythrocyte protoporphyrin vs blood lead: effects of iron status. Environ Res, **44**: 221-227.

Marino PE, Franzblau A, Lilis R, & Landrigan PJ (1989) Acute lead poisoning in construction workers: the failure of protective standards. Arch Environ Health, **44**: 140-145.

Marks SC & Popoff SN (1988) Bone cell biology: the regulation of development, structure, and function in the skeleton. Am J Anat, **183**: 1-44.

Marlowe M & Errrera J (1982) Low lead levels and behaviour problems in children. Behav Disord, **7**: 163-172.

Matte TD, Figueroa JP, Ostrowski S, Burr G, Jackson-Hunt L, Kennylside RA, & Baker EL (1989a) Lead poisoning among household members exposed to lead-acid battery repair shops in Kingston, Jamaica. Int J Epidemiol, **18**: 874-881.

Matte TD, Figueroa JP, Burr G, Flesch JP, Keenlyside RA & Baker EL (1989b) Lead exposure among lead-acid battery workers in Jamaica. Am J Ind Med, **16**: 167-177.

Meredith PA & Moore MR (1979) The influence of lead on haem biosynthesis and biodegradation in the rat. Biochem Soc Trans, 7: 637-639.

Meredith PA, Moore MR, Campbell BC, Thompson GG, & Goldberg A (1978) Delta-aminolevulinic acid metabolism in normal and lead-exposed humans. Toxicology, **9**: 1-9.

Merwin BW (1976) Review of US standards on test methods for lead and cadmium release. In: Proceedings of the International Conference on Ceramic Foodware Safety, Geneva, 1974. New York, Lead Industries Associate Inc., pp 36-40.

Meyer BR, Fishbein A, Rosemann K, Lerman Y, Drayer DE, & Reidenberg MM (1984) Increased urinary enzyme excretion in workers exposed to nephrotoxic chemicals. Am J Med, **76**: 989-998.

Michaelson A & Sauerhoff MW (1974) An improved model of lead induced brain dysfunction in the suckling rat. Toxicol Appl Pharmacol, **28**: 88-96.

Mielke H, Blake B, Burroughs S, & Hassinger N (1984) Urban lead levels in Minneapolis: the case of the Hmong children. Environ Res, **34**: 64-76.

Mitchell DG, Aldous KM, & Ryan FJ (1974) Mass screening for lead poisoning, capillary blood sampling and automated Delves cup atomic absorption analysis. NY State J Med, **74**: 1599-1603.

Mitchell-Heggs CAW, Conway M, & Cassar J (1990) Herbal medicine as a cause of combined lead and arsenic poisoning. Hum Exp Toxicol, **9**: 195-196.

Molina-Ballesteros G, Zuniga-Charles MA, Ortega AC, & Solis-Camara P (1983) Lead concentrations in the blood of children from pottery-making families exposed to lead salts in a Mexican village. Bull Panam Health Organ, **17**: 35-41.

Möller L & Kristensen TS (1992) Blood lead as a cardiovascular risk factor. Am J Epidemiol, **136**: 1091-1100.

Moore MR (1983) Lead exposure and lead plumbosolvency. In: Rutter M & Jones RR ed. Lead versus health. London, John Wiley and Sons, pp 79-106.

Moore MR & Meredith PA (1979) The carcinogenicity of lead. Arch Toxicol, **42**: 87-94.

Moore MR, Meredith PA, Campbell BC, & Watson SW (1979) The gastrointestinal absorption of lead 203 chlorine in man. In: Hemphill DD ed. Trace substances in environmental health - XIII. Proceedings of the 13th Annual Conference on Trace Substances in Environmental Health, Columbia, June 1979. Columbia, Missouri, University of Missouri, pp 368-373.

Moore MR, Meredith PA, & Goldberg A (1980) Lead and heme biosynthesis. In: Singhal PL & Thomas JA ed. Lead toxicity. Baltimore, Maryland, Urban and Schwarzenberg, Inc., pp 79-118.

Moore MR, Goldberg A, & Pocock SJ (1982) Some studies of maternal and infant lead exposure in Glasgow. Scott Med J, 27: 113-122.

Moore MR, Bushnell IWR, & Goldberg A (1989) A prospective study of the results of changes in environmental lead exposure in children in Glasgow. In: Smith MA, Grant LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Publishers, pp 371-378.

Moore MR, Goldberg A, & Young-Laiwah AAC (1987) Lead effects on the haem-biosynthetic pathway. Relationship to toxicity. Ann NY Acad Sci, 514: 191-203.

Mooty J, Ferrand CF, & Harris P (1975) Relationship of diet to lead poisoning in children. Pediatrics, 55: 636-639.

Moreau T, Orssaud G, Juguet B, & Busquet G (1982) Plombémie et pression artérielle: premiers résultats d'une enquête transversale de 431 sujets de sexe masculin. Rev Epidemiol Santé Publique, 30: 395-397.

Morgan A & Holmes A (1978) The fate of lead in petrol-engine exhaust particulates inhaled by the rat. Environ Res, 15: 44-56.

Muijser H, Hoogendijk EMG, Hooisma J, & Twisk DAM (1987) Lead exposure during demolition of a steel structure coated with lead-based paints. II. Reversible changes in the conduction velocity of the motor nerves in transiently exposed workers. Scand J Work Environ Health, 13: 56-61.

Munoz C, Garbe K, Lilienthal H, & Winneke G (1986) Persistence of retention deficit in rats after neonatal lead exposure. Neurotoxicology, 7(2): 569-580.

Muramatsu Y & Parr RM (1985) Survey of currently available reference materials for use in connection with the determination of trace elements in biological and environmental materials. Vienna, International Atomic Energy Agency (Report No. IAEA/RL/128).

Murata K & Araki S (1991) Autonomic nervous system dysfunction in workers exposed to lead, zinc, and copper in relation to peripheral nerve conduction: a study of R-R interval variability. Am J Ind Med, 20: 663-671.

Murphy MJ, Graziano JH, Popovac D, Kline JK, Mehmeti A, Factor-Litvak P, Ahmadi G, Shrout P, Rajovic B, Nenezic DU, & Stein ZA (1990) Past pregnancy outcomes among women living in the vicinity of a lead smelter in Kosovo, Yugoslavia. Am J Public Health, 80: 33-35.

Mushak P (1989) Biological monitoring of lead exposure in children: overview of selected biokinetic and toxicological issues. In: Smith MA, Grant LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Publishers, pp 129-145.

Mushak P & Crocetti AF (1989) Determination of numbers of lead-exposed American children as a function of lead source: Integrated summary of a report to the U.S. Congress on childhood lead poisoning. Environ Res, 50: 210-299.

Mussalo-Rauhamaa H, Salmela SS, Leppanen A, & Pyysalo H (1986) Cigarettes as a source of some trace and heavy metals and pesticides in man. Arch Environ Health, 41: 49-55.

NAS-NRC (1972) Airborne lead in perspective. Washington, DC, National Academy of Sciences.

Needleman HL & Gatsonis CA (1990) Low-level lead exposure and the IQ of children: a meta-analysis of modern studies. J Am Med Assoc, **263**: 673-678.

Needleman HL, Tuncay OC, & Shapiro IM (1972) Lead levels in deciduous teeth of urban and suburban children. Nature (Lond), **235**: 111-112.

Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, & Barrett P (1979) Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med, **300**: 689-695.

Needleman HL, Schell A, Bellinger D, Leviton A, & Allred EN (1990) The long-term effects of childhood exposure to low doses of lead: An 11-year follow-up report. N Engl J Med, **322**: 83-88.

Neri LC, Hewitt D, & Orser B (1988) Blood lead and blood pressure: analysis of cross-sectional and longitudinal data from Canada. Environ Health Perspect, **78**: 123-126.

Nerin C, Olavide S, & Cacho J (1989) Determination of lead in airborne particulate by hydride generation. Water Air Soil Pollut, **44**: 339-345.

Neubecker TA & Allen HE (1983) The measurement of complexation capacity and conditional stability constants for ligands in natural waters. Water Res, **17**: 1-14.

NFA (Australian National Food Authority, National Health and Medical Council) (1991) The 1990 Australian market basket survey report. Canberra, Commonwealth of Australia, Australian Government Publishing Service.

Ng A & Patterson CC (1982) Changes of Pb and Ba with time in California offshore basin sediments. Geochim Cosmochim Acta, **46**: 2307-2322.

Ng TP, Goh HH, Ng YL, Ong CN, Chia KS, Chia SE, & Jeyaratnam J (1991) Male endocrine functions in workers with moderate exposure to lead. Br J Ind Med, **48**: 485-491.

Nielsen T (1984) Atmospheric occurrence of organolead compounds. In: Grandjean P ed. Biological effects of organolead compounds. Boca Raton, Florida, CRC Press, pp 43-62.

Nilsson U, Attewell R, Christoffersson J-O, Schütz A, Ahlgren L, Skerfving S, & Mattsson S (1991) Kinetic of lead in bone and blood after end of occupational exposure. Pharmacol Toxicol, **69**: 477-484.

NIOSH (1977a) Method No. P&CAM 102. In: Manual of analytical methods, vol 1, 2nd ed. Cincinnati, Ohio, National Institute for Occupational Safety and Health.

NIOSH (1977b) Method No. P&CAM 191. In: Manual of analytical methods, vol 1, 2nd ed. Cincinnati, Ohio, National Institute for Occupational Safety and Health, pp 191/1-191/9.

NIOSH (1977c) Method No. P&CAM 195. In: Manual of analytical methods, vol 1, 2nd ed. Cincinnati, Ohio, National Institute for Occupational Safety and Health.

NIOSH (1977d) Method No. P&CAM 200. In: Manual of analytical methods, vol 1, 2nd ed. Cincinnati, Ohio, National Institute for Occupational Safety and Health, pp 200/1-200/8.

NIOSH (1977e) Method No. P&CAM 214. In: Manual of analytical methods, vol 1, 2nd ed. Cincinnati, Ohio, National Institute for Occupational Safety and Health, pp 214/1-214/6.

NIOSH (1981) Method No. P&CAM 351. In: Manual of analytical methods, vol 7. Cincinnati, Ohio, National Institute for Occupational Safety and Health, pp 351/1-351/11.

Nordenson I, Beckman G, Beckman L, & Nordstrom S (1978) Occupational and environmental risks in and around a smelter in northern Sweden: IV. Chromosomal aberrations in workers exposed to lead. Hereditas, **88**: 263-267.

Nordstrom S, Beckman L, & Nordenson I (1978a) Occupational and environmental risks in and around a smelter in northern Sweden: I. Frequencies in birth weight. Hereditas, **88**: 43-46.

Nordstrom S, Beckman L, & Nordenson I (1978b) Occupational and environmental risks in and around a smelter in northern Sweden: III. Frequencies of spontaneous abortion. Hereditas, **88**: 51-54.

Nordstrom S, Beckman L, & Nordenson I (1979) Occupational and environmental risks around a smelter in northern Sweden: V. Spontaneous abortion among female employees and decreased birth weight in their offspring. Hereditas, **90**: 291-296.

Nosal RM & Wilhelm WJ (1990) Lead toxicity in the shipbreaking industry: the Ontario experience. Can J Public Health, **81**: 259-262.

Novotny T, Cook M, Hughes J, & Lee SA (1987) Lead exposure in a firing range. Am J Public Health, 77: 1225-1226.

Nriagu J (1979) Global inventory of natural and anthropogenic emissions of trace metals to the atmosphere. Nature (Lond), 279: 409-411.

Nriagu J (1989) A global assessment of natural sources of atmospheric trace metals. Nature (Lond), **338**: 47-49.

Nriagu J & Pacyna JM (1988) Quantitative assessment of worldwide contamination of air, water, and soils by trace metals. Nature (Lond), **333**: 134-139.

OCTEL (1991) Worldwide survey of motor gasoline quality. London, Associated Octel Company Ltd (Octel Promotional Publication No. 4).

OECD (1993) Risk Reduction Monograph No. 1: Lead background and national experience with reducing risk. Paris, Organisation for Economic Co-operation and Development, 277 pp (Report No. OCDE/GD(93)67).

O'Flaherty EJ (1991) Physiologically based lead kinetics. Trace Subst Environ Health, **24**: 44-54.

O'Flaherty EJ (1993) Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans. Toxicol Appl Pharmacol, **118**: 16-29.

O'Flaherty EJ, Hammond PB, Lerner SI, Hanenson IB, & Roda SMB (1980) The renal handling of δ-aminolevulinic acid in the rat and in the human. Toxicol Appl Pharmacol, **55**: 423-432.

O'Flaherty EJ, Hammond PB, & Lerner SI (1982) Dependence of apparent blood lead half-life on the length of previous lead exposure in humans. Fundam Appl Toxicol, 2: 49-54.

Olejnik D, Walkowska A, Wisnilwska J, & Ziembinski R (1985) [Evaluation of the daily dose of mercury, lead and cadmium in the diet of certain population groups.] Roczn Pzh, XXXVI: 9-21 (in Polish, with English abstract).

Olson KW & Skogerboe RK (1975) Identification of soil lead compounds from automotive sources. Environ Sci Technol, 9: 227-230.

Ong CN & Lee WR (1980) High affinity of lead for fetal hemoglobin. Br J Ind Med, 37: 292-298.

Ong CN, Phoon WO, Law HY, Tye CY, & Lim HH (1985) Concentration of lead in maternal blood, cord blood, and breast milk. Arch Dis Child, 60: 576-759.

Ong CN, Endo G, & Chia KS (1987) Evaluation of renal function in workers with low blood lead levels. In: Occupational and environmental chemical hazards: Cellular and biochemical indices for monitoring toxicity. Chichester, Ellis Horwood Ltd, chapter 39, pp 327-333.

Orfila MP (1814) Traité des poisons. Paris, Crochard, vol 2.

Orssaud G, Claude JR, Moreau T, Lellouch J, Juguet B, & Festy B (1985) Blood lead concentration and blood pressure. Br Med J, 290: 244.

Padilla F, Shapiro AP, & Jensen WN (1969) Effect of chronic lead intoxication on blood pressure in the rat. Am J Med Sci, 258: 359-365.

Paglia DE, Valentine WN, & Dahlgren JG (1975) Effects of low-level lead exposure on pyrimidine 5'-nucleotidase and other erythrocyte enzymes: possible role of pyrimidine 5'-nucleotidase in the pathogenesis of lead-induced anaemia. J Clin Invest, 56: 1164-1169.

Pagliuca A, Mufti GJ, Baldwin D, Lestas AN, Wallis RM, & Bellingham AJ (1990) Lead poisoning: clinical, biochemical, and haematological aspects of a recent outbreak. J Clin Pathol, 43: 277-281.

Parfitt AM (1990) Pharmacologic manipulation of bone remodelling and calcium homeostasis: Calcium metabolism. Prog Basic Clin Pharmacol, 4: 1-27.

Parkinson DK, Ryan C, Brommet EJ, & Connell MM (1986) A psychiatric epidemiologic study of occupational lead exposure. Am J Epidemiol, 123: 261-269.

Parkinson DK, Ryan C, Bromet J, & Connell MM (1987) A psychiatric epidemiological study of occupationally exposure. Am J Epidemiol, 123: 261-269.

Patterson C (1965) Contaminated and natural lead environments of man. Arch Environ Health, 11: 344-360.

Patterson CC (1983) Criticism of "flow of metals into the global atmosphere". Geochim Cosmochim Acta, 47: 1163-1168.

Patterson CC & Settle DM (1976) The reduction of orders of magnitude errors in lead analyses of biological materials and natural waters by evaluating and controlling the extent and source of industrial lead contamination introduced during sample collecting, handling, and analyses. In: LaFleur PD ed. Accuracy in trace analysis: Sampling, sample handling and analysis. Volume 1. Proceedings of the 7th Materials Research Symposium, Gaithersburg, Maryland, October, 1974. Washington, DC, US Department of Commerce, National Bureau of Standards, pp 321-352 (NBS Special Publication No. 422).

Pekkarinen M (1970) Methodology in the collecting of food consumption data. World Rev Nutr Diet, 12: 145-170.

Pentschew A (1965) Morphology and morphogenesis of lead encephalopathy. Acta Neuropathol, 5: 133-160.

Pentschew A & Garro F (1966) Lead encephalo-myelopathy of the suckling rat and its implications on the porphyrinopathic nervous diseases with special reference to the permeability/disorders of the nervous system's capillaries. Acta Neuropathol, 6: 266-278.

Perino J & Ernhart CB (1974) The relation of subclinical lead level to cognitive and sensorimotor impairment in black preschoolers. J Learn Disabil, 7: 616-620.

Pickston L, Brewerton HV, Drysdale JM, Hughes JT, Smith JM, Love JL, Sutcliffe ER, & Davidson F (1985) The New Zealand diet: a survey of elements, pesticides, colours and preservatives. N Z J Technol, 1: 81-89.

Piomelli S, Seaman C, Zullow D, Curran A, & Davidow B (1982) Threshold for lead damage to heme synthesis in urban children. Proc Natl Acad Sci (USA), 79: 3335-3339.

Piper W & Tephly T (1974) Differential inhibition of erythrocyte and hepatic uroporphyrinogen. I. Synthelase activity by lead. Life Sci, 14: 873-876.

Pirkle JL, Schwartz J, Lamdis JR, & Harlan WR (1985) The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am J Epidemiol, 121: 246-258.

Pocock SJ, Shaper AG, Walker M, Wale CJ, Clayton B, Delves T, Lacey RF, Packham RF, & Powell P (1983) Effects of tap water lead, water hardness, alcohol, and cigarettes on blood lead concentrations. J Epidemiol Community Health, 37: 1-7.

Pocock SJ, Shaper AG, Ashby D, Delves T, & Whitehead TP (1984) Blood lead concentration, blood pressure, and renal function. Br Med J, 289: 872-874.

Pocock S, Ashby D, & Smith MA (1987) Lead exposure and children's intellectual performance. Int J Epidemiol, 16: 57-67.

Pocock SJ, Shaper AG, Ashby D, Delves HT, & Clayton BE (1988) The relationship between blood lead, blood pressure, stroke and heart attacks in middle-aged British men. Environ Health Perspect, 78: 23-30.

Pocock SJ, Ashby D, & Smith MA (1989) Lead exposure and children's intellectual performance. The Institute of Child Health/Southampton Study. In: Smith M, Grant LD, & Sors A ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Press, pp 149-165.

Pollock CA & Ibels LS (1986) Lead intoxication in paint removal workers on the Sydney Harbour Bridge. Med J Aust, **145**: 635-639.

Ponka A, Salminen E, & Ahonen S (1991) Lead in the ambient air and blood specimens of children in Helsinki. Sci Total Environ, **138**(1-3): 301-308.

Pontifax AH & Garg AK (1985) Lead poisoning from an Asian Indian folk remedy. Can Med Assoc J, **133**: 1227-1228.

Poole C, Smythe LE, & Alpers M (1980) Blood lead levels of Papua New Guinea children living in a remote area. Sci Total Environ, **15**: 17-24.

Pounds JG (1984) Effect of lead intoxication on calcium homeostasis and calcium-mediated cell function: a review. Neurotoxicology, **5**: 295-332.

Pounds JG, Marlar RJ, & Allen JR (1978) Metabolism of lead-210 in juvenile and adult rhesus monkeys Macaca mulatta. Bull Environ Contam Toxicol, **19**: 684-691.

Pounds JG, Long GJ, & Rosen JF (1991) Cellular and molecular toxicity of lead in bone. Environ Health Perspect, **91**: 17-32.

Purchase NG & Fergusson JE (1986) Lead in teeth: the influence of the tooth type and the sample within a tooth on lead levels. Sci Total Environ, **52**: 239-250.

Qazi QH, Madahar C, & Huceoglu AM (1980) Temporary increase in chromosome breakage in an infant prenatally exposed to lead. Hum Genet, **53**: 201-203.

Qian ZM & Morgan EH (1990) Effect of lead on the transport of transferrin-free and transferrin-bound iron into rabbit reticulocytes. Biochem Pharmacol, **40**: 1049-1054.

Quarterman J & Morrison JN (1975) The effects of dietary calcium and phosphorus on the retention and excretion of lead in rats. Br J Nutr, **34**: 351-362.

Que Hee SS & Boyle JR (1988) Simultaneous multielemental analysis of some environmental and biological samples by inductively coupled plasma atomic emission spectrometry. Anal Chem, **60**: 1033-1042.

Que Hee SS, MacDonald TJ, & Bornschein RL (1985a) Blood lead by furnace-Zeeman atomic absorption spectrophotometry. Microchem J, **32**: 55-63.

Que Hee SS, Peace B, Clark CS, Boyle JR, Bornschein RL, & Hammond PB (1985b) Evolution of efficient methods to sample lead sources, such as house dust and hand dust in the homes of children. Environ Res, **38**: 77-95.

Raab GM, Laxen DPH, & Fulton M (1987) Lead from dust and water as exposure sources for children. Environ Geochem Health, **9**: 80.

Rabinowitz MB (1991) Toxicokinetics of bone lead. Environ Health Perspect, **91**: 33-37.

Rabinowitz M & Needleman HL (1982) Temporal trends in the lead concentrations of umbilical cord blood. Science, **216**: 1429-1431.

Rabinowitz MB, Wetherill G, & Kopple J (1975) Absorption, storage and excretion of lead by normal humans. In: Proceedings of the Ninth Annual Conference on Trace Substances in Environmental Health. Columbia, Missouri, University of Missouri, pp 361-368.

Rabinowitz MB, Wetherill GM, & Kopple JD (1976) Kinetics analysis of lead metabolism in healthy humans. J Clin Invest, **58**: 260-270.

Rabinowitz MB, Wetherill GW, & Kopple JD (1977a) Magnitude of lead intake from respiration by normal man. J Lab Clin Med, **90**: 238-248.

Rabinowitz MB, Wetherill GW, & Kopple JD (1977b) Effect of food intake and fasting on gastrointestinal lead absorption in humans. Am J Clin Nutr, **33**: 1784-1788.

Rabinowitz MB, Kopple JD, & Wetherill GW (1980) Effect of food intake and fasting on gastrointestinal lead absorption in humans. Am J Clin Nutr, **33**: 1784-1788.

Rabinowitz MB, Leviton A, & Needleman HL (1986) Occurrence of elevated protoporphyrin levels in relation to lead burden in infants. Environ Res, **39**: 253-257.

Rabinowitz M, Bellinger D, Leviton A, Needleman H, & Schoenbaum S (1987) Pregnancy hypertension, blood pressure during labor, and blood lead levels. Hypertension, **10**: 447-451.

Rabinowitz MB, Leviton A, & Bellinger D (1989) Blood lead-tooth lead relationship among Boston children. Bull Environ Contam Toxicol, **43**: 485-492.

Rabinowitz MB, Wang J-D, & Soong WT (1991) Dentine lead and child intelligence in Taiwan. Arch Environ Health, **46**: 351-360.

Ragan HA (1977) Effect of iron deficiency on the absorption of lead and cadmium in the rat. J Lab Clin Med, **90**: 700-706.

Reaves GA & Berrow ML (1984) Total lead concentrations in Scottish soils. Geoderma, **32**: 1-8.

Reisinger K, Stoeppler M, & Nurnberg HW (1981) Evidence for the absence of biological methylation of lead in the environment. Nature (Lond), **281**: 228-230.

Reuter JH & Perdue EM (1977) Importance of heavy metal-organic matter interactions in natural waters. Geochim Cosmochim Acta, **41**: 325-334.

Rhagavan SRV, Dwight Culver B, & Gonick HC (1981) Erythrocyte lead-binding protein after occupational exposure. II. Influence of lead inhibition of membrane Na+, K+-adenosinetriphosphatase. J Toxicol Environ Health, **7**: 561-568.

Rice DC (1984a) Behavioural deficit (delayed matching to sample) in monkeys exposed from birth to low level lead. Toxicol Appl Pharmacol, **75**: 337-345.

Rice DC (1984b) Effect of lead on schedule-controlled behavior in the monkey. In: Seiden LS & Balster RL ed. Behavioral pharmacology: The current status. New York, Alan R. Liss, pp 473-486.

Rice DC (1985) Chronic low-lead exposure from both produces deficits in discrimination reversal monkey's. Toxicol Appl Pharmacol, **77**: 201-210.

Rice DC & Karpinski KF (1988) Lifetime dow level lead exposure produces deficits in delayed alternation in adult monkeys. Neurotoxicol Teratol, **10**: 207-214.

Roberts J, Mahaffey KR, & Annest JL (1985) Blood lead levels in general populations. In: Mahaffey KR ed. Dietary and environmental lead: Human health effects. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 355-372.

Robins JM, Cullen MR, Connors BB, & Kayne RD (1983) Depressed thyroid indexes associated with occupational exposure to inorganic lead. Arch Intern Med, **143**: 220-224.

Robinson TR (1974) Delta-aminolevulinic acid and lead in urine of lead antiknock workers. Arch Environ Health, **28**: 133-138.

Rodamilans M, Osaba MJM, To-Figueras J, Fillat FR, Marques JM, Perez P, & Corbella J (1988) Lead toxicity on endocrine testicular function in an occupationally exposed population. Hum Toxicol, 7: 125-128.

Rodney BS & Lee MG (1985) Environmental lead hazard in a high-risk Jamaican population. West Indian Med J, **34**: 176-179.

Roels HA & Lauwerys R (1987) Evaluation of dose-effect and dose-response relationships for lead exposure in different Belgian population groups (foetus, child, adult men and women). Trace Elem Med, **4**: 80-87.

Roels HA, Buchet J-P, Lauwerys R, Hubermont G, Bruaux P, Claeys-Thoreau F, Lafontaine A, & van Overschelde J (1976) Impact of air pollution by lead on the haem biosynthetic pathway in school-age children. Arch Environ Health, **31**: 310-316.

Roels HA, Buchet JP, Lauwerys RR, Bruaux P, Claeys-Thoreau F, Lafontaine A, & Verduyn G (1980) Exposure to lead by the oral and the pulmonary routes of children living in the vicinity of a primary lead smelter. Environ Res, **22**: 81-94.

Rosen JF & Chesney RW (1983) Circulating calcitriol concentration in health and disease. J Pediatr, **103**: 1-7.

Rosen JF, Chesney RW, Hamstra AJ, Deluca HF, & Mahaffey KR (1980) Reduction in 1,25-dihydroxyvitamin D in children with increased lead absorption. N Engl J Med, **302**: 1128-1131.

Rosen JF, Markowitz ME, Bijur PE, Jenks ST, Wielopolski L, Kalef-Ezra JA, & Slatkin DN (1991) Sequential measurements of bone lead content by L x-ray fluorescence in $CaNa_2EDTA$-treated lead-toxic children. Environ Health Perspect, **91**: 57-62.

Rosner D & Markowitz G (1985) A "gift of God": The public health controversy over leaded gasoline during the 1920s. Am J Public Health, 75(4): 344.

Rossouw J, Offermeier J, & van Rooyen J (1987) Apparent central neurotransmitter receptor changes induced by low-level lead exposure during different developmental phases in the rat. Toxicol Appl Pharmacol, **91**: 132-139.

Routh DK, Mushak P, & Boone L (1979) A new syndrome of elevated blood lead and microcephaly. J Pediatr Psychol, **4**: 67-76.

Rundle SA & Duggan MJ (1986) Lead pollution from the external redecoration of old buildings. Sci Total Environ, **57**: 181-190.

Ryu JE, Ziegler EE, Nelson SE, & Fomon SJ (1983) Dietary intake of lead and blood lead concentration in early infancy. Am J Dis Child, **137**: 886-891.

Ryu JE, Ziegler EE, Nelson SE, & Fomon SJ (1985) Dietary and environmental exposure to lead and blood lead during early infancy. In: Mahaffey KR ed. Dietary and environmental lead: Human health effects. Amsterdam, Oxford, New York, Elsevier Science Publishers, pp 187-209.

Saenger P, Markowitz MR, & Rosen JF (1984) Depressed excretion of 6β-hydroxycortisol in lead-toxic children. J Clin Endocrinol Metab, **58**: 363-367.

SAHC (1993) Proceedings of the International Meeting on Non-Occupational Exposure to Lead, Melbourne, Australia, 5-9 October 1992. Adelaide, South Australian Health Commission, 56 pp.

Sarto F, Stella M, & Acqua A (1978) [Cytogenic studies in 20 workers occupationally exposed to lead.] Med Lav, **69**: 172-180 (in Italian).

Satzger RD, Clow CS, & Bonnin E (1982) Determination of background levels of lead and cadmium in raw agricultural crops by using differential pulse anodic stripping voltammetry. J Assoc Off Anal Chem, **65**: 987-991.

Sauk J & Somerman MJ (1991) Physiology of bone: mineral compartment proteins as candidates for environmental perturbation by lead. Environ Health Perspect, **91**: 9-16.

Schlegel H & Kufner G (1979) Long-term observation of biochemical effects of lead in human experiments. J Clin Chem Clin Biochem, **17**: 225-233.

Schmid E, Bauchinger M, Pietruk S, & Hall G (1972) [Cytogenic action of lead in human peripheral lymphocytes *in vitro* and *in vivo*.] Mutat Res, **16**: 401-406 (in German).

Schmidt U & Huber F (1976) Methylation of organolead and lead(II) compounds $(CH_3)_4$ Pb by microorganisms. Nature (Lond), **259**: 157-158.

Schmitt MDC, Trippler DL, & Wachtler JN (1988) Soil lead concentrations in residential Minnesota as measured by ICP AES. Water Air Soil Pollut, **39**: 157-168.

Schneitzer L, Osborn HH, Bierman A, Mezey A, & Kaul B (1990) Lead poisoning in adults from renovation of an older home. Ann Emerg Med, **19**: 415-420.

Schroeder SR, Hawk B, Otto DA, Mushak P, & Hicks RE (1985) Separating the effects of lead and social factors on IQ. Environ Res, **38**: 144-154.

Schutz AS, Skerfving S, Ranstam J, & Christoffersson JO (1987) Kinetics of lead in blood after the end of occupational exposure. Scand J Work Environ Health, **13**: 221-231.

Schutz A, Ranstam J, Skerfving S, & Tejning S (1989) Blood-lead levels in school children in relation to industrial emission and automobile exhausts. Ambio, **13**: 115-117.

Schwartz J (1988) The relationship between blood lead and blood pressure in the NHANES II survey. Environ Health Perspect, **78**: 15-22.

Schwartz J (1993) Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. Environ Res, **65**: 42-55.

Schwartz J & Otto D (1987) Blood lead, hearing thresholds, and neurobehavioral development in children and youth. Arch Environ Health, **42**: 153-160.

Schwartz J & Otto D (1991) Lead and minor hearing impairment. Arch Environ Health, **46**: 300-305.

Schwartz J, Angle C, & Pitcher H (1986) Relationship between childhood blood lead levels and stature. Pediatrics, 77: 281-288.

Schwartz J, Landrigan PL, & Baker EL (1990) Lead-induced anemia: dose-response relationships and evidence for a threshold. Am J Public Health, **80**: 165-168.

Scott DR, Hemphill DC, & Holboke LE (1976) Atomic absorption and optical emission analysis of NASN atmospheric particulate samples for lead. Environ Sci Technol, **9**: 877-880.

Selander S & Cramer K (1970) Interrelationships between lead in blood, lead in urine and ALA in urine during lead work. Br J Ind Med, 27: 28-39.

Selevan SG, Landrigan PJ, Stern FB, & Jones JH (1985) Mortality of lead smelter workers. Am J Epidemiol, **122**: 673-683.

Selevan SG, Landrigan PJ, Stern FB, & Jones JH (1988) Brief report: lead and hypertension in a mortality study of lead smelter workers. Environ Health Perspect, **78**: 65-66.

Seppäläinen AM & Hernberg S (1980) Subclinical lead neuropathy. Am J Ind Med, **1**: 413-420.

Seppäläinen AM, Hernberg S, Vesanto R, & Kock B (1983) Early neurotoxic effects of occupational lead exposure: a prospective study. Neurotoxicology, **4**(2): 181-192.

Settle DM & Patterson CC (1980) Lead in albacore: guide to lead pollution in Americans. Science, **207**: 1167-1176.

Shaltout A, Yaish SA, & Fernando N (1981) Lead encephalopathy in infants in Kuwait. Ann Trop Paediatr (London), **1**: 209-215.

Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, & Thompson AG (1981) British regional heart study: cardiovascular risk factors in middle-aged men in 24 towns. Br Med J, **283**: 179-186.

Sharma RR, Chandy MJ, & Lad SD (1990) Transient hydrocephalis and acute lead encephalopathy in neonates and infants. Report of two cases. Br J Neurosurg, 4: 141-146.

Sherlock J, Smart G, Forbes GI, Moore MR, Patterson WJ, Richards WN, & Wilson TS (1982) Assessment of lead intakes and dose-response for a population in Ayr exposed to a plumbsolvent water supply. Hum Toxicol, **1**: 115-122.

Sherlock JC, Pickford CJ, & White GF (1986) Lead in alcoholic beverages. Food Addit Contam, **3**: 347-354.

Siegel M, Forsyth B, Siegel L, & Cullen MR (1989) The effect of lead on thyroid function in children. Environ Res, **49**: 190-196.

Silbergeld EK (1991) Lead in bone: implications for toxicology during pregnancy and lactation. Environ Health Perspect, **91**: 63-70.

Silbergeld EK, Schwartz J, & Mahaffey KR (1988) Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. Environ Res, **47**: 79-94.

Silva PA, Hughes P, Williams S, & Faed JM (1988) Blood lead, intelligence, reading attainment, and behaviour in eleven year old children in Dunedin, New Zealand. J Child Psychol Psychiatry Appl Discipl, **29**: 43-52.

Sinclair DF & Dohnt BR (1984) Sampling and analysis techniques used in a blood lead survey of 1341 children in Port Pirie, South Australia. Clin Chem, **30**(10): 1616-1619.

Skerfving S (1988) Biological monitoring of exposure to inorganic lead. In: Clarkson TW, Friberg L, Nordberg GF, & Sager PR ed. Biological monitoring of toxic metals. New York, Plenum Press, pp 169-197 (Rochester Series on Environmental Toxicity).

Skerfving S, Schutz A, & Ranstam J (1986) Decreasing lead exposure in Swedish children. Sci Total Environ, **58**: 225-229.

Skogerboe RK, Hartley AM, Vogel RS, & Koirtyohann SR (1977) Monitoring for lead in the environment. In: Boggess WR ed. Lead in the environment. Washington, DC, National Science Foundation, pp 33-70 (NSF Report No. NSF/RA-770214; PB-278278).

Slorach SA, Gustafsson I-B, Jorhem L, & Mattsson P (1983) Intake of lead, cadmium and certain other metals via a typical Swedish weekly diet. Var Föda, **35**(Suppl 1): 3-16.

Smith MA (1989) The effects of low-level lead exposure on children. In: Smith MA, Grant LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dorcrecht, London, Kluwer Academic Publishers, pp 3-47.

Smith F & Hursh J (1977) Bone storage and release. In: Field J ed. Handbook of physiology: Reaction to environmental agents. Bethesda, Maryland, American Physiological Society, section 9, pp 469-482.

Smith M, Delves T, Lansdown R, Clayton B, & Graham P (1983) The effects of lead exposure on urban children: the Institute of Child Health/Southampton Study. Dev Med Child Neurol, **47**(Suppl): 1-54.

Snee RD (1981) Evaluation of studies of the relationship between blood lead and air lead. Int Arch Occup Environ Health, **48**: 219-242.

Sobel AE, Yuska H, Peters DD, & Kramer B (1940) The biochemical behaviour of lead. I. Influence of calcium phosphorus and vitamin D on lead in the blood and bone. J Biol Chem, **132**: 239-265.

Sokol RZ (1987) Hormonal effects of lead acetate in the male rat: Mechanism of action. Biol Reprod, **37**: 1135-1138.

Sokol RZ, Madding CE, & Swerdloff RS (1985) Lead toxicity and the hypothalamic-pituitary-testicular axis. Biol Reprod, **33**: 722-728.

Spivey GH, Baloh RW, Brown CP, Browdy BL, Campion DS, Valentine JL, Morgan DE, & Culver BD (1980) Subclinical effects of chronic increased lead absorption - a

prospective study: III. Neurologic findings at follow-up examination. J Occup Med, **22**: 607-612.

Staessen J, Yeoman WB, Fletcher AE, Markowe HLJ, Marmot MG, Rose G, Semmence A, Shipley MJ, & Bulpitt CJ (1990) Blood lead concentration, renal function, and blood pressure in London civil servants. Br J Ind Med, **47**: 442-447.

Staessen JA, Lauwerys RA, Buchet J-P, Bulpitt CJ, Rondia D, Vanrenterghem Y, Amery A, & The Cadmibel Study Group (1992) Impairment of renal function with increasing blood lead concentrations in the general population. N Engl J Med, **327**: 151-156.

Staessen JA, Christopher JB, Fagard R, Lauwerys RR, Roels H, Thijs L, & Amery A (1994) Hypertension caused by low-level lead exposure: myth or fact? J Cardiovasc Risk, **1**: 87-97.

Steelink C (1977) Humates and other natural organic substances in the aquatic environment. J Chem Ed, **54**: 599-603.

Steenhout A (1987) How clean is clean? An exotoxicological method for getting guidelines (air, dust, deposition, water) for lead, keeping tooth and blood lead levels in the normal range. In: Proceedings of the International Conference on Heavy Metals in the Environment. Edinburgh, CEP Consultants, pp 283-285.

Steenhout A & Pourtois M (1981) Lead accumulation in teeth as a function of age with different exposures. Br J Ind Med, **38**: 297-303.

Stiles KM & Bellinger DC (1993) Neuropsychological correlates of low-level lead exposure in school-age children: A prospective study. Neurotoxicol Teratol, **15**(1): 27-35.

Stollery BT, Banks HA, Broadbent DE, & Lee WR (1989) Cognitive functioning in lead workers. Br J Ind Med, **46**: 698-707.

Stollery BT, Broadbent DE, Banks HA, & Lee WR (1991) Short term prospective study of cognitive functioning in lead workers. Br J Ind Med, **48**: 739-749.

Stone CH & Soares JH (1976) The effect of dietary selenium level of lead toxicity in the Japanese quail. Poult Sci, **55**: 341-349.

Stone C, Fox MRS, & Hogye KS (1981) Bioavailability of lead in oysters fed to young Japanese quail. Environ Res, **26**: 409-421.

Stuik EJ (1974) Biological response of male and female volunteers to inorganic lead. Int Arch Arbeitsmed, **33**: 83-97.

Succop PA, O'Flaherty EJ, Bornschein RL, Roba SB, & Greenland RD (1989) Recent observations concerning the relationship of blood lead to erythrocytic protoporphyrin. In: Smith MA, Grant LD, & Sors AE ed. Lead exposure and child development: An international Assessment. Dordrecht, London, Kluwer Academic Publishers, pp 477-484.

Talbot RW & Andren AW (1983) Relationships between Pb and ^{210}Pb in aerosol and precipitation at a semiremote site in northern Wisconsin. J Geophys Res, **88**: 6752-6760.

Taskinen H, Nordman H, Engstrom K, & Hernberg S (1981) [Blood lead levels in Finnish children.] Duodecim, **97**(10): 663-670 (in Finnish).

Teruya K, Sakurai H, Omae K, Higashi T, Muto T, & Kaneko Y (1991) Effect of lead on cardiac parasympathetic function. Int Arch Occup Environ Health, **62**: 549-553.

Thornton I & Webb JS (1975) Trace elements in soils and surface waters contaminated plast metaliferous mining part of England. In: Proceedings of the IXth Annual Conference on Trace Substances in Environmental Health, Columbia, Missouri, 10-12 June, pp 77-88.

Thornton I, Culbard E, Moorcroft S, Watt J, Wheatley M, & Thompson M (1985) Metals in urban dusts and soils. Environ Technol Lett, **6**: 137-144.

Todd AC, McNeill FE, Palethorpe JE, Peach DE, Chettle DR, Tobin MJ, Strosko SJ, & Rosen JC (1992) *In vivo* x-ray fluorescence of lead in bone using K x-ray excitation with ^{109}Cd sources; radiation dosimetry studies. Environ Res, **57**: 117-132.

Triebig G, Weltle D, & Valentin H (1984) Investigations on neurotoxicity of chemical substances at the workplace. V. Determination of the motor and sensory nerve conduction velocity in persons occupationally exposed to lead. Int Arch Occup Environ Health, **53**: 189-204.

Trotter RT (1990) The cultural parameters of lead poisoning: A medical anthropologist's view of intervention in environmental lead exposure. Environ Health Perspect, **89**: 79-84.

Tuppurainen M, Wagar G, Kurppa K, Sakari W, Wambugu A, Froseth B, Alho J, & Nykyri E (1988) Thyroid function as assessed by routine laboratory tests of workers with long-term lead exposure. Scand J Work Environ Health, **14**: 175-180.

UK (1982) The Glasgow duplicate diet study (1979/1980): A joint survey for the Department of the Environment and the Ministry of Agriculture, Fisheries and Food. London, Her Majesty's Stationery Office (Pollution Report No. 11).

US Department of the Treasury (1991) Report of analyses of wines and related products to determine lead content. Washington, DC, US Department of the Treasury, Bureau of Alcohol, Tobacco and Firearms.

US EPA (1986a) Air quality criteria for lead. Washington, DC, Environmental Protection Agency (EPA-600/8-83/028aF-dF).

US EPA (1986b) Test methods for evaluating solid waste SW-846 - Physical/chemical methods. Method No. 7420 and 7421. Washington, DC, US Environmental Protection Agency, Office of Solid Waste and Emergency Response.

US EPA (1989) Evaluation of the potential carcinogenicity of lead and lead compounds. Washington, DC, US Environmental Protection Agency, Office of Health and Environmental Assessment (EPA/600/8-89/045A).

US EPA (1990) Supplement to the 1986 EPA air quality criteria for lead. Volume 1, Addendum: Relationship of blood pressure to lead exposure. Washington, DC, US Environmental Protection Agency, Office of Health and Environmental Assessment (EPA/600/8-89/0 49F).

US EPA (1991) National air quality and emission trends report. Research Triangle Park, North Carolina, US Environmental Protection Agency (EPA-450/4-91-023).

US NCI (1979) Bioassay of lead dimethylditho-carbamate for possible carcinogenicity. Washington, DC, National Cancer Institute, Carcinogenesis Testing Program, Division of Cancer Cause and Prevention (Technical Report Series No. 151 - NTIS PB-85-134663).

Vahter M & Friberg L (1988) Quality control in integrated human exposure monitoring of lead and cadmium. Fresenius Z Anal Chem, **332**: 726-731.

Vahter M & Slorach S (1990) GEMS - Global Environment Monitoring System. Exposure monitoring of lead and cadmium: an international pilot study within the WHO/UNEP Human Exposure Assessment Location (HEAL) Programme. Nairobi, United Nations Environment Programme, 82 pp.

Vahter M, Berglund M, Friberg L, Jorhem L, Lind B, Slorach S, & Åkesson A (1990) Dietary intake of lead and cadmium in Sweden. Var Föda, **42**(2): 1-16.

Vahter M, Berglund M, Slorach S, Friberg L, Saric M, Xingquan Z, & Fujita M (1991a) Methods for integrated exposure monitoring of lead and cadmium. Environ Res, **56**: 78-79.

Vahter M, Berglund M, Lind B, Jorhem L, Slorach S, & Friberg L (1991b) Personal monitoring of lead and cadmium exposure - a Swedish study with special reference to methodological aspects. Scand J Work Environ Health, 17: 65-74.

Van Esch GJ & Kroes R (1969) The induction of renal tumors by feeding basic lead acetate to mice and hamsters. Br J Cancer, **23**: 765-771.

Varo P & Kovistoinen P (1983) Mineral element composition of Finnish foods. XII. General discussion and nutritional evaluation. Acta Agric Scand, **22**: 165.

Vatsala S & Ramakrishna T (1985) "Tinning" of brass utensils: Possibility of lead poisoning. Indian J Environ Health, **27**: 140-141.

Verrula GR & Noah PK (1990) Clinical manifestations of childhood lead poisoning. J Trop Med Hyg, **93**: 170-177.

Verschoor M, Wibowo A, & Herber R (1987) Influence of occupational low level lead exposure on renal parameters. Am J Ind Med, **12**: 341-351.

Victery W (1988) Evidence for effects of chronic lead exposure on blood pressure in experimental animals: An overview. Environ Health Perspect, **78**: 71-76.

Victery W, Vander AJ, Markel H, Katzman L, Shulak JM, & Germain C (1982a) Lead exposure, begun in-utero, decreases renin and angiotensin II in adult rats. Proc Soc Exp Biol Med, **170**: 63-67.

Victery W, Vander AJ, Shulak JM, Schoeps P, & Julius S (1982b) Lead, hypertension and the renin-angiotensin system in rats. J Lab Clin Med, **99**: 354-362.

Volkening J, Baumann H, & Heumann KG (1988) Atmospheric distribution of particulate lead over the Atlantic Ocean from Europe to Antarctica. Atmos Environ, **22**: 1169-1174.

Wadge A & Hutton M (1987) The leachability and chemical speciation of selected trace elements in fly ash from coal combustion and refuse incineration. Environ Pollut, **48**: 85-99.

Winneke G, Beginn U, Ewert T, Havestadt C, Kraemer U, Krause C, Thron HL, & Wagner HM (1985) Comparing the effects of perinatal and later childhood lead exposure on neuropsychological outcome. Environ Res, **38**: 155-167.

Winneke G, Collet W, Krämer U, Brockhaus A, Ewert T, & Krause C (1989) Follow-up studies in lead-exposed children. In: Smith MA, Grant LD, & Sors AI ed. Lead exposure and child development: An international assessment. Dordrecht, London, Kluwer Academic Publishers, pp 260-270.

Winneke G, Brockhaus A, Ewers U, Kramer U, & Neuf M (1990) Results from the European multicenter study on lead neurotoxicity in children: implications for risk assessment. Neurotoxicol Teratol, **12**: 553-559.

Wong PTS, Chau YK, & Luxon PL (1975) Methylation of lead in the environment. Nature (Lond), **253**: 263-264.

Wooler K & Melamed S (1978) Simple tests for monitoring excessive lead absorption. Med J Aust, 1: 163-169.

World Bureau of Metal Statistics (1992) World metal statistics, July, **45**(7): 75-78.

Worley PF, Barabon JM, Desouza EB, & Snyder SH (1986) Mapping second messenger systems in the brain: differential localizations of adenylate cyclase and protein kinase. C. Proc Natl Acad Sci (USA), **83**: 4053-4057.

Worth D, Matranga A, Lieberman M, Devos E, Karelekas P, Ryan C, & Kraun G (1981) Lead in drinking water: The contribution of household tap water to blood lead levels. In: Lynam DR, Piantanida LG, & Cole JF ed. Environmental lead. Proceedings of the Second International Symposium on Environmental Lead Research. New York, London, San Francisco, Academic Press, pp 199-225.

Yankel AJ, von Lindern IH, & Walter SD (1977) The Silver Valley lead study: The relationship between childhood blood lead levels and environmental exposure. J Air Pollut Control Assoc, **27**: 763-767.

Yip R & Dallman PR (1984) Developmental changes in erythrocyte protoporphyrin: Roles of iron deficiency and lead toxicity. J Pediatr, 710-713.

Yule W, Lansdown R, Millar IB, & Urbanowicz M-A (1981) The relationship between blood lead concentrations, intelligence and attainment in a school population: a pilot study. Dev Med Child Neurol, **23**: 567-576.

Zelikoff JT, Li JH, Hartwig A, Wang XW, Costa M, & Rossman TG (1988) Genetic toxicology of lead compounds. Carcinogenesis, **9**: 1727-1732.

Zerez CR, Wong MD, & Tanaka KR (1990) Partial purification and properties of nicotinamide adenine dinucleotide synthetase from human erythrocytes: evidence that enzyme activity is a sensitive indicator of lead exposure. Blood, **75**: 1576-1582.

Zhu BG (1984) Study of chronic lead-poisoning from using tea kettles. Chung-Hua Yu Fang I Hsueh Tsa Chih, **18**: 328-330.

Ziegler EE, Edwards BB, Jensen RL, Mahaffey KR, & Fomon SJ (1978) Absorption and retention of lead by infants. Pediatr Res, 12: 29-34.

Zuckerman MA, Savory D, & Rayman G (1989) Lead encephalopathy from an imported Toby mug. Postgrad Med J, **65**: 307-309.

RESUME

La présente monographie est consacrée aux risques pour la santé humaine découlant de l'exposition au plomb et aux dérivés minéraux du plomb. On y insiste sur les données dont on a eu connaissance depuis la publication du No 3 de la Série des Critères de l'environnement: Plomb (OMS, 1977). Quant aux effets du plomb au niveau de l'environnement, ils sont étudiés dans le No 85 de cette série: Lead - Environmental Aspects (Le plomb dans l'environnement) (WHO, 1989, en anglais seulement).

1. Identité, propriétés physiques et chimiques et méthodes d'analyse

Le plomb est un métal mou, gris argent, qui fond à 327,5 °C. Il est très résistant à la corrosion mais se dissout à chaud dans l'acide nitrique et l'acide sulfurique. La valence habituelle du plomb dans ses dérivés minéraux est de +2. La solubilité dans l'eau de ses composés est variable, le sulfure et les oxydes étant peu solubles et le nitrate, le chlorate et le chlorure assez solubles à chaud. Le plomb forme également des sels avec des acides organiques tels que l'acide lactique et l'acide acétique ainsi que des composés organiques stables tels que le plomb-tétraéthyle et le plomb-tétraméthyle.

Les méthodes d'analyse les plus couramment utilisées pour doser le plomb à faible concentration dans les produits biologiques et dans l'environnement sont la spectrométrie d'absorption avec atomisation en flamme, en four à cellules de graphite et en plasma induit par haute fréquence (ICP/PIHF), ainsi que la coulométrie avec redissolution anodique. Selon le traitement préalable subit par l'échantillon et les techniques d'extraction et l'instrumentation utilisées, la limite de détection peut être de 0,12 µmoles de plomb par litre de sang (2,49 µg/dl). Toutefois, on n'obtient de résultats fiables qu'en se conformant à une marche à suivre bien codifiée pour réduire au minimum le risque de contamination au cours du prélèvement des échantillons, de leur conservation, de leur traitement et de leur analyse.

2. Sources d'exposition humaine

La proportion du plomb dans la croûte terrestre est d'environ 20 mg/kg. Le plomb présent dans l'environnement peut être d'origine naturelle ou artificielle. Le plomb naturellement présent

dans l'atmosphère provient, entre autres, de l'altération des roches et des éruptions volcaniques, et on l'estime à 19 000 tonnes/an, contre 126 000 tonnes/an provenant des mines et des fonderies, la consommation annuelle totale étant supérieure à 3 millions de tonnes.

On a trouvé des concentrations de plomb atmosphérique de 50 pg/m^3 dans des zones reculées. La concentration de fond du plomb dans le sol varie de 10 à 70 mg/kg et on a relevé à proximité de routes une teneur moyenne de 138 mg/kg. Actuellement la teneur de l'eau en plomb dépasse rarement quelques microgrammes/litre; la concentration naturelle du plomb dans les eaux de surface est estimée à 0,02 μg/litre.

Le plomb et ses dérivés peuvent pénétrer dans l'environnement par une porte d'entrée quelconque lors de l'extraction minière, des opérations de fonte et du traitement, de l'utilisation, du recyclage ou du rejet du plomb. Le plomb est principalement utilisé dans les batteries, les câbles, les pigments, les additifs pour essence, la brasure et les aciers. Le plomb et ses dérivés entrent également dans la composition de la brasure que l'on utilise pour souder les conduites d'eau et les boites de conserve alimentaire; il sert également à la confection de certains remèdes traditionnels, des capsules de bouteilles contenant des boissons alcoolisées, des vernis pour céramique et de la verrerie de cristal. Dans les pays où l'on utilise encore de l'essence au plomb, les principales émissions dans l'atmosphère proviennent de sources de combustion de produits pétroliers, sources qui peuvent être mobiles ou fixes (en agglomération). Les émissions dans l'atmosphère sont également très importantes à proximité des mines et des fonderies de plomb.

Le plomb en suspension dans l'air peut se déposer sur le sol et dans l'eau et il parvient ainsi jusqu'à l'homme par l'intermédiaire de la chaîne alimentaire et de l'eau de boisson. Le plomb atmosphérique contribue également pour une part importante au plomb présent dans la poussière domestique.

3. Transport, distribution et transformation dans l'environnement

Le transport et la distribution du plomb à partir de sources fixes, mobiles ou naturelles, s'effectue principalement par l'intermédiaire de l'air. La majeure partie du plomb émis dans l'air se redépose à proximité de la source d'émission, même si quelques particules (de diamètre < 2 μm) dont transportées sur de longues distances et provoquent la contamination de sites aussi

reculés que les glaciers arctiques. Le plomb aéroporté peut contribuer à l'exposition humaine par contamination des aliments, d l'eau et de la poussière, ainsi que par inhalation directe. L'élimination du plomb aéroporté dépend des conditions atmosphériques et de la taille des particules en suspension. De grandes quantités de plomb peuvent être déversées dans le sol et l'eau. Cependant, ces produits ont tendance à rester sur place du fait de la médiocre solubilité dans l'eau des dérivés du plomb.

Le plomb qui s'est déposé dans l'eau, que ce soit à partir de l'air ou par lessivage des sols, se répartit rapidement entre les sédiments et la phase aqueuse, selon la valeur du pH, la teneur en sels et la présence éventuelle d'agents chélateurs organiques. Lorsque le pH dépasse 5,4, l'eau dure peu contenir environ 30 μg de plomb/litre et l'eau douce environ 500 μg/litre. Une très faible quantité du plomb déposé sur le sol passe dans les eaux de surface ou les eaux souterraines sauf en cas d'érosion ou d'altération des roches; il est normalement fortement lié par chélation aux matières organiques.

Le plomb en suspension dans l'air peut passer dans les êtres vivants soit directement, soit par fixation à partir du sol. Les animaux peuvent être exposés au plomb de manière directe par broutage de l'herbe, ingestion de terre ou par inhalation. Le plomb minéral ne subit qu'une faible bioamplification le long de la chaîne alimentaire.

4. Concentrations dans l'environnement et exposition humaine

Dans la population générale adulte des non-fumeurs, la principale voie d'exposition est la consommation de nourriture et d'eau. Le plomb est suspension dans l'air peut jouer un rôle important dans l'exposition, en fonction de facteurs tels que le tabagisme, la profession, la proximité d'une autoroute, d'une fonderie, etc. ou de certains lieux de loisirs (par exemple, ateliers d'artisanat, stands de tir, etc.). Pour les nourrissons et les enfants en bas âge, la nourriture, l'air, l'eau et la poussière ou la terre sont les principales voies d'exposition potentielles. Pour les nourrissons jusqu'à quatre ou cinq mois, les principales sources d'exposition au plomb sont l'air, le lait et les laits maternisés ainsi que l'eau.

Les concentrations de plomb observées dans l'air, les aliments, l'eau et le sol ou la poussière varient largement d'une région à l'autre du monde et dépendent du degré d'industrialisation,

d'urbanisation ainsi que du mode de vie. Dans l'air ambiant, des concentrations supérieures à 10 $\mu g/m^3$ ont été signalées en milieu urbain à proximité d'une fonderie, alors que dans les villes où l'on n'utilise plus d'essence au plomb, ces concentrations peuvent tomber en-dessous de 0,2 $\mu g/m^3$. Dans ces conditions, la dose de plomb absorbée à partir de l'air peut varier de moins de 4 μg/jour à plus de 200 μg/jour.

Dans des échantillons d'eau potable prélevés à la source, on trouve généralement des concentrations de plomb inférieures à 5 μg/litre. Cependant, lorsque l'eau est prélevée au robinet dans les maisons dont les canalisations sont en plomb, les teneurs peuvent dépasser 100 μg/litre, en particulier lorsque l'eau a séjourné dans la tuyauterie pendant plusieurs heures.

L'exposition au plomb par la voie alimentaire dépend de nombreux facteurs tenant au mode de vie et notamment à la nature des aliments consommés, au mode de préparation, au fait que l'on utilise ou non de la brasure au plomb, à la teneur de l'eau en plomb et à l'utilisation de vaisselle recouverte d'un vernis au plomb.

Les nourrissons et les enfants peuvent souvent être très exposés au plomb présent dans la poussière et dans la terre. La teneur de la poussière en plomb dépend de facteurs tels que la vétusté et l'état de la maison, l'utilisation de peintures à base de plomb, la présence de plomb dans l'essence et la densité urbaine. La dose de plomb absorbée dépendra également de l'âge et du comportement de l'enfant ainsi que de la biodisponibilité du plomb dans le produit où il est présent.

Chez les ouvriers des industries où l'on produit, raffine, utilise ou rejette du plomb ou des dérivés du plomb, la principale voie d'exposition est l'inhalation. Au cours d'un poste de travail de 8 heures, les ouvriers peuvent en absorber des quantités atteignant 400 μg, qui s'ajoutent aux 20 ou 30 μg absorbés quotidiennement à partir de la nourriture, de l'eau et de l'air ambiant; l'ingestion de grosses particules peut également contribuer de façon importante à cet apport.

5. Cinétique et métabolisme chez les animaux de laboratoire et l'homme

L'homme et les animaux résorbent le plomb qu'ils ingèrent ou inhalent; la résorption percutanée est minime chez l'homme. Selon

sa granulométrie, sa forme chimique et sa solubilité dans les liquides biologiques, un dérivé du plomb peut être résorbé jusqu'à hauteur de 50% après avoir été inhalé. Certaines grosses particules (plus de 7 μm) sont avalées après avoir été rejetées des voies respiratoires par l'action de l'ascenseur muco-ciliaire. Chez l'homme et les animaux d'expérience, l'absorption du plomb dans les voies digestives dépend de la nature physico-chimique du produit ingéré, de l'état nutritionnel du sujet ainsi que du type d'aliments consommés. Chez l'homme adulte, le plomb contenu dans les aliments est absorbé à peu près à hauteur de 10%; la proportion est plus élevée lorsque le sujet est à la diète. Toutefois, chez les nourrissons et les enfants en bas âge, le plomb d'origine alimentaire peut être absorbé à hauteur de 50%, encore que le taux d'absorption du plomb provenant des poussières ou de la terre ainsi que des écailles de peinture puisse être plus faible, selon sa biodisponibilité. Les régimes alimentaires pauvres en calcium, phosphates, sélénium ou zinc peuvent accroître l'absorption du plomb. Le fer et la vitamine D influent également sur l'absorption du plomb.

Le taux de plomb dans le sang ou plombémie est utilisé pour évaluer la charge en plomb de l'organisme ainsi que les doses de plomb (internes) absorbées. La relation entre la plombémie et la concentration du plomb dans les diverses sources d'exposition n'est pas linéaire (corrélation curviligne).

Une fois absorbé, le plomb ne se répartit pas de manière homogène dans l'organisme. Après être rapidement passé dans le sang et les tissus mous, il se redistribue lentement des les os. La plomb s'accumule dans les os pendant une longue période de la vie humaine et peut servir de source endogène de plomb. La demi-vie du plomb dans le sang et les tissus mous est d'environ 28 à 36 jours mais elle peut être beaucoup plus longue dans les diverses parties de l'os. Le taux de rétention du plomb dans l'organisme est plus élevé chez l'enfant que chez l'adulte. Pendant toute la durée de la gestation, le plomb passe facilement de la mère au foetus.

La plombémie est la mesure la plus couramment utilisée pour évaluer l'exposition au plomb. Toutefois, on dispose aujourd'hui de techniques permettant de doser le plomb dans les dents et les os, encore que la cinétique du phénomène ne soit pas parfaitement élucidée.

6. Effets sur les animaux de laboratoire et les systèmes d'épreuves *in vitro*

Chez toutes les espèces d'animaux de laboratoire étudiées, y compris des primates non-humains, on a constaté que le plomb produisait des effets indésirables au niveau de plusieurs organes et systèmes, notamment le système haematopoïétique, le système nerveux, les reins, le système cardio-vasculaire, l'appareil reproducteur et le système immunitaire. Le plomb est également nocif pour les os et on a montré qu'il avait des effets cancérogènes sur le rat et la souris.

Malgré les différences d'ordre cinétique qui existent entre les animaux d'expérience et l'homme, ces études apportent des arguments biologiques de poids à la plausibilité de tels effets chez l'homme. Chez le rat, on a observé une diminution de la capacité d'apprentissage et de mémorisation lorsque la plombémie était de l'ordre de 0,72 à 0,96 µmol/litre (soit 15 à 20 µg/dl), les mêmes effets étant observés chez des primates non-humains pour une plombémie ne dépassant pas 0,72 µmol/litre (15 µg/dl). En outre, l'expérimentation animale a également permis d'observer des troubles de la vision et de l'audition.

Chez le rat, une plombémie supérieure à 2,88 µmol/litre (60 µg/dl), soit une valeur analogue à celle qui, selon les observations, constitue le seuil d'apparition des effets chez l'homme, est à même de provoquer l'apparition d'effets néphrotoxiques. Des effets cardio-vasculaires ont été également observés chez des rats après exposition chronique à de faibles doses de plomb entraînant une plombémie de l'ordre de 0,24 à 1,92 µmol/litre (5 à 40 µg/dl). A des doses inférieures à la dose maximale tolérée qui est de 200 mg de plomb (sous forme d'acétate) par litre d'eau potable, on a observé l'apparition de tumeurs. Cette dose constitue la dose maximale qui n'entraîne pas d'autres effets morphologiques ou fonctionnels.

7. Effets sur l'homme

Chez l'homme, le plomb peut produire des effets biologiques très divers selon l'intensité et la durée de l'exposition. On a ainsi observé des effets au niveau infracellulaire ainsi que des effets s'exerçant sur les fonctions générales de l'organisme, effets qui vont de l'inhibition de certaines enzymes jusqu'à l'apparition d'altérations morphologiques marquées et à la mort. Ces altérations se produisent dans de larges limites de doses,

l'organisme humain en développement étant généralement plus sensible que l'organisme adulte.

On a montré que le plomb avait des effets sur nombre de processus biochimiques; en particulier on a largement étudié les effets qu'il produit sur la synthèse hémique, tant chez l'adulte que chez l'enfant. Lorsque la plombémie est élevée, on observe une augmentation du taux de protoporphyrine érythrocytaire sérique ainsi qu'une augmentation de l'excrétion urinaire de coproporphyrine et d'acide δ-aminolévulinique. A des valeurs plus faibles de la plombémie, on observe l'inhibition d'enzymes comme la δ-aminolévulinique acide-déshydratase et la dihydrobioptérine-réductase.

Les effets du plomb sur le système haématopoïétique se traduisent par une diminution de la synthèse de l'hémoglobine et l'on a observé une anémie chez des enfants lorsque la plombémie dépassait 1,92 μmol/litre (40 μg/dl).

Pour des raisons d'ordre neurologique, métabolique et compartementale, les enfants sont plus sensibles aux effets du plomb que les adultes. Des études épidémiologiques tant prospectives que transversales ont été effectuées pour déterminer dans quelle mesure une exposition au plomb présent dans l'environnement affecte les fonctions psychologiques dépendant du système nerveux central. On a ainsi montré qu'il existait une association entre l'exposition au plomb et les troubles des fonctions neurocomportementales chez l'enfant.

On a également constaté des anomalies des fonctions psychologiques et neurocomportementales chez des ouvriers longtemps exposés au plomb. Il a été montré que les paramètres électrophysiologiques étaient d'utiles indicateurs des effets infracliniques du plomb sur le système nerveux central.

On sait depuis longtemps que la neuropathie périphérique est due à une exposition prolongée à de fortes concentrations de plomb sur le lieu de travail. A plus faibles concentrations, on a observé une diminution de la vitesse de conduction nerveuse. Ces effets se révèlent souvent réversibles, en fonction de l'âge et de la durée de l'exposition, après cessation de l'exposition.

Les effets que le plomb exerce sur le coeur sont indirects et s'opèrent par l'intermédiaire du système neuro-végétatif; il n'y a pas d'effets directs sur le myocarde. L'ensemble des faits tirés des

études sur des populations d'adultes indiquent qu'il existe une très faible association entre la plombémie et la tension artérielle systolique ou diastolique. Etant donné la difficulté qu'il y a à tenir compte des facteurs de confusion, il n'a pas été possible d'établir, à partir des résultats de ces études, une relation de cause à effet. Rien n'indique non plus que l'association qui pourrait exister entre la plombémie et la tension artérielle constitue un problème médical majeur.

On sait que le plomb peut entraîner des lésions tubulaires proximales qui se caractérisent par une aminoacidurie généralisée, une hypophosphatémie avec d'une hyperphosphaturie relative et une glycosurie accompagnée d'inclusions nucléiques, d'altérations des mitochondries et d'une hypertrophie des cellules de l'épithélium tubulaire proximal. Ces effets sur les tubules s'observent après une exposition relativement brève et sont généralement réversibles. En revanche, les altérations scléreuses et les fibroses interstitielles qu'on observe lors d'une exposition chronique à de fortes concentrations de plomb, entraînent des problèmes fonctionnels qui peuvent déboucher sur une insuffisance rénale. On a observé une augmentation du risque de néphropathie chez les travailleurs dont la plombémie dépassait 3,0 μmol/litre (soit environ 60 μg/dl). En utilisant des indicateurs fonctionnels plus sensibles, on a récemment découvert l'existence d'effets rénaux dans la population générale.

Les effets du plomb sur la fonction de reproduction, ne concernent, chez l'homme, que la morphologie et le nombre des spermatozoïdes. Chez la femme, on a attribué au plomb un certain nombre de grossesses à issue défavorable.

Il ne semble pas que le plomb ait des effets nocifs sur la peau, les muscles ou le système immunitaire. Si l'on excepte le cas du rat, le plomb ne paraît pas non plus être à l'origine de l'apparition de tumeurs.

8. Evaluation des risques pour la santé humaine

Le plomb a des effets nocifs sur plusieurs organes et systèmes, les effets les plus sensibles étant relevés au niveau infracellulaire ainsi que sur le développement du système nerveux. On a fait état d'une association entre la plombémie et l'hypertension. En outre, le plomb entraîner une cascade d'effets sur les réserves hémiques de l'organisme et il perturbe également la synthèse hémique. Cependant, certains de ces effets ne sont pas véritablement

considérés comme délétères. Il y a également perturbation de l'homéostase du calcium avec des contre-coups sur d'autres processus cellulaires.

a) Les preuves les plus substantielles sont on dispose à propos de l'action nocive du plomb proviennent d'études transversales et prospectives sur des populations dont la plombémie est généralement inférieure à 1,2 µmol/litre (25 µg/dl) et concernent une diminution du quotient d'intelligence (QI). Il importe cependant de noter que ces observations ne constituent pas une preuve définitive d'une relation de cause à effet entre ce phénomène et l'exposition au plomb. Cependant la mesure de ce QI à partir de l'âge de 4 ans fait ressortir un déficit qui se situe entre 0 et 5 points (sur une échelle avec un écart-type de 15) pour une augmentation de la plombémie de 0,48 µmol/litre (10 µg/dl), l'ampleur de l'effet étant vraisemblablement de 1 à 3 points. Lorsque la plombémie dépasse 1,2 µmol/litre (25 µg/dl), on peut avoir une relation différente entre cette plombémie et le QI. Les estimations de l'ampleur de l'effet observé sont des moyennes calculées sur des groupes et ne représentent qu'une probabilité pour un individu en particulier.

   Les études épidémiologiques dont on dispose ne donnent pas de preuves définitives de l'existence d'un seuil. Lorsque la plombémie se situe en-dessous de l'intervalle 0,48-0,72 µmol/litre (10-15 µg/dl), l'incertitude qui entache toute estimation de l'effet s'accroît, du fait des facteurs de confusion et des limites dans la précision des dosages et des tests psychométriques. Il n'en reste pas moins qu'en-dessous de cet intervalle de valeurs, certains éléments incitent à penser à l'existence d'une association.

b) L'expérimentation animale milite en faveur de l'existence d'une relation de cause à effet entre l'exposition au plomb et certains effets neurologiques, puisqu'elle fait ressortir des déficits dans les fonctions cognitives pour une plombémie ne dépassant pas 0,53 à 0,72 µmol/litre (11-15 µg/dl), déficits qui peuvent persister bien après la cessation de l'exposition au plomb.

c) Pour une plombémie ne dépassant pas 1,44 µmol/litre (30 µg/dl), il peut y avoir réduction de la vitesse de conduction nerveuse périphérique chez l'homme. En outre, pour des valeurs de la plombémie de dépassant pas 1,92 µmol/litre (40 µg/dl), il peut également y avoir perturbation des fonctions moto-sensorielles et la fonction du système nerveux

neurovégétatif (variabilité de l'intervalle R-R sur l'électrocardiogramme) peut être affectée pour une valeur moyenne de la plombémie d'environ 1,68 µmol/litre (35 µg/dl). Chez les travailleurs dont la plombémie dépasse 2,88 µmol/litre (60 µg/dl), il y a accroissement du risque de néphropathie saturnienne. Toutefois, des études récentes basées sur des indicateurs plus sensibles de la fonction rénale incitent à penser que des effets peuvent se produire à des valeurs plus faibles de l'exposition au plomb.

d) Il semblerait que l'exposition au plomb soit associée à une légère augmentation de la tension artérielle. L'ordre de grandeur probable de cette augmentation est le suivant: pour un doublement de la plombémie (par exemple lorsqu'elle passe de 0,8 à 1,6 µmol/litre, soit de 16,6 à 33,3 µg/dl), il y a une augmentation moyenne de 1 mmHg de la systolique. L'association avec la diastolique est analogue mais d'ampleur plus faible. Toutefois, on se demande si ces associations statistiques résultent réellement de l'exposition au plomb ou s'il s'agit d'un artefact imputable à des facteurs de confusion.

e) Certaines études épidémiologiques - mais pas toutes - font état d'une association liée à la dose entre les accouchements avant terme et certains indices de la croissance et de la maturation foetales à des valeurs de la plombémie supérieures ou égales à 0,72 µmol/litre (15 µg/dl).

f) Les données relatives à la cancérogénicité pour l'homme du plomb et de plusieurs de ses dérivés minéraux, sont insuffisantes.

g) On a mis en évidence des effets que le plomb exerce sur un certain nombre de systèmes enzymatiques et de paramètres biochimiques. Les valeurs de la plombémie au-dessus desquelles on peut mettre en évidence des effets avec les techniques actuelles, pour ce qui est des paramètres susceptibles d'avoir une importance clinique, sont toutes supérieures à 0,96 µmol/litre (20 µg/dl). Certains effets sur les enzymes peuvent être mis en évidence à des valeurs plus faibles de la plombémie, mais leur signification clinique demeure incertaine.

RESUMEN

La presente monografía se centra en los riesgos para la salud humana asociados a la exposición al plomo y a los compuestos inorgánicos de plomo. Se han destacado los datos disponibles desde la publicación de Criterios de Salud Ambiental No. 3: Plomo (OMS, 1977). Los efectos ambientales del plomo se examinan en Environmental Health Criteria 85: Lead - Environmental Aspects (OMS, 1989).

1. Identidad, propiedades físicas y químicas y métodos analíticos

El plomo es un metal blando, gris plateado, que se funde a 327,5 °C. Es muy resistente a la corrosión, pero es soluble en ácido nítrico y en ácido sulfúrico caliente. Su valencia corriente en los compuestos inorgánicos es +2. Su solubilidad en agua varía; el sulfito de plomo y los óxidos de plomo son poco solubles, mientras que las sales de nitrato, clorato y cloruro son razonablemente solubles en agua fría. El plomo también forma sales con ácidos orgánicos tales como el láctico y el acético, y compuestos orgánicos estables tales como el tetraetilo de plomo y el tetrametilo de plomo.

Los métodos utilizados más corrientemente para el análisis de bajas concentraciones de plomo en materias biológicas y ambientales son la llama, el horno de grafito y la espectroscopia de absorción atómica de plasma acoplado inductivamente y la voltimetría de separación anódica. Según sean el tratamiento previo de la muestra, las técnicas de extracción y la instrumentación analítica, pueden alcanzarse niveles de detección de 0,12 μmoles de plomo por litro de sangre (2,49 μg/dl). Sin embargo, se obtienen resultados fiables sólo cuando se siguen procedimientos específicos para reducir al mínimo el riesgo de contaminación durante la recogida, el almacenamiento, procesamiento y análisis de la muestra.

2. Fuentes de exposición humana

El nivel de plomo en la corteza terrestre es de aproximadamente 20 mg/kg. El plomo del medio ambiente puede provenir de fuentes naturales o antropogénicas. Las fuentes naturales de plomo atmosférico comprenden el desgaste geológico y las emisiones volcánicas y se han estimado en 19 000 toneladas por

año, frente a unas 126 000 toneladas por año emitidas en el aire como resultado de la minería, la fundición y el consumo de más de 3 millones de toneladas de plomo por año.

Se han encontrado concentraciones atmosféricas de plomo de 50 pg/m^3 en zonas remotas. Los niveles básicos de plomo en el suelo oscilan entre 10 y 70 mg/kg y se ha comunicado un nivel medio de 138 mg/kg en las proximidades de las carreteras. Los niveles de plomo presentes en las aguas rara vez exceden de unos pocos microgramos por litro; la concentración natural de plomo en las aguas superficiales se ha estimado en 0,02 μg/litro.

El plomo y sus compuestos pueden entrar en el medio ambiente en cualquier punto durante las actividades de minería, fundición, elaboración, utilización, reciclado o eliminación. Se utiliza principalmente en la fabricación de pilas, cables, pigmentos, aditivos de la gasolina, productos para soldar y de acero. El plomo y los compuestos de plomo también se utilizan para soldar las tuberías de distribución de agua y las latas de conserva, en algunos remedios tradicionales, en las tapas de las botellas de bebidas alcohólicas y en los esmaltes cerámicos y la cristalería de mesa. En los países donde todavía se utiliza gasolina con plomo, la principal emisión en el aire proviene de fuentes móviles y estacionarias de combustión de gasolina (centros urbanos). Las zonas próximas a las minas y funderías de plomo están expuestas a la emisión de niveles elevados en el aire.

El plomo del aire puede depositarse en el suelo y el agua, desde donde llega al ser humano por conducto de la cadena alimentaria y del agua de bebida. El plomo atmosférico también es una fuente importante del plomo presente en el polvo de las viviendas.

3. Transporte, distribución y transformación en el medio ambiente

El transporte y la distribución del plomo procedente de fuentes fijas, móviles y naturales tienen lugar principalmente a través del aire. La mayor parte de las emisiones de plomo se depositan cerca de la fuente, aunque algunas partículas de materia (< 2 μm de diámetro) recorren largas distancias y contaminan lugares remotos tales como los glaciares árticos. El plomo del aire puede contribuir a la exposición humana mediante la contaminación de los alimentos, del agua y del polvo, así como por inhalación directa. La eliminación del plomo del aire depende de las condiciones atmosféricas y del tamaño de las partículas. Pueden descargarse

grandes cantidades de plomo en el suelo y en el agua. Sin embargo, ese material tiende a permanecer localizado debido a la escasa solubilidad de los compuestos de plomo en el agua.

El plomo depositado en el agua, ya provenga del aire o de la escorrentía del suelo, se distribuye rápidamente entre el sedimento y la fase acuosa, según el pH, el contenido de sales y la presencia de agentes quelantes orgánicos. Con un pH superior a 5,4, las aguas duras pueden contener aproximadamente 30 μg de plomo por litro y las aguas blandas aproximadamente 500 μg de plomo por litro. Muy poco plomo depositado en el suelo se transporta a las aguas superficiales o a las subterráneas, salvo mediante la erosión o el desgaste geoquímico; normalmente está ligado a la materia orgánica de forma bastante estrecha (por quelación).

El plomo del aire puede transferirse a la biota directamente o por absorción del suelo. Los animales pueden encontrarse expuestos al plomo directamente mediante la ingestión de hierba y de tierra o por inhalación. Hay poca biomagnificación del plomo inorgánico a través de la cadena alimentaria.

4. Niveles ambientales y exposición humana

En la población general que no fuma, la principal vía de exposición son los alimentos y el agua. El plomo del aire puede contribuir apreciablemente a la exposición, lo que depende de factores tales como el consumo de tabaco, la ocupación, la proximidad de caminos transitados por vehículos automotores, de funderías de plomo, etc., y ciertas actividades de esparcimiento (por ejemplo, artesanía, tiro con armas de fuego). Los alimentos, el aire, el agua y el polvo/suelo son las principales vías potenciales de exposición de los niños pequeños. Para los niños de hasta 4 ó 5 meses de edad, el aire, la leche, las preparaciones para lactantes y el agua son fuentes notables de exposición al plomo.

Los niveles de plomo presentes en el aire, los alimentos, el agua, y el suelo/polvo varían ampliamente en el mundo y dependen del grado de desarrollo industrial y de urbanización y de factores relacionados con el modo de vida. Se han comunicado niveles superiores a 10 $\mu g/m^3$ presentes en el aire ambiental en zonas urbanas próximas a funderías, mientras que en ciudades donde ha dejado de usarse la gasolina con plomo se han detectado niveles inferiores a 0,2 $\mu g/m^3$. La absorción de plomo del aire puede, pues, variar de menos de 4 μg/día a más de 200 μg/día.

Los niveles de plomo en muestras de agua de bebida extraídas de los manantiales suelen ser inferiores a 5 μg/litro. Sin embargo, el agua del grifo de viviendas cuyas tuberías tienen plomo contiene niveles que exceden de 100 μg/litro, en particular después de haber reposado el agua en las tuberías durante algunas horas.

El nivel de exposición al plomo a través de la dieta depende de muchos factores relacionados con el modo de vida, entre ellos los alimentos que se consumen, la tecnología de elaboración, el empleo de soldadura de plomo, los niveles de plomo en el agua y la utilización de cerámica con barniz de plomo.

Para los niños, el plomo presente en el polvo y en el suelo suele ser la principal vía de exposición. Los niveles de plomo en el polvo dependen de factores tales como la antigüedad y el estado de la vivienda, la utilización de pinturas a base de plomo, el plomo de la gasolina y la densidad urbana. La absorción de plomo dependerá de la edad y de las características comportamentales del niño así como de la biodisponibilidad de plomo en la fuente material.

La inhalación es la vía principal de exposición al plomo para los trabajadores de industrias que producen, refinan, utilizan o desechan plomo y compuestos de plomo. Durante un turno de ocho horas, los trabajadores pueden absorber nada menos que 400 μg de plomo, además de los 20-30 μg/día que absorben de los alimentos, del agua y del aire ambiental; puede haber una absorción notable como resultado de la inhalación de partículas grandes.

5. Cinética y metabolismo en animales de laboratorio y en el ser humano

Los seres humanos y los animales absorben plomo por inhalación o por ingestión; la absorción percutánea es mínima en el ser humano. Según la especiación química, el tamaño de las partículas y la solubilidad de los líquidos corporales, puede absorberse hasta un 50% de los compuestos de plomo inhalados. Algunas partículas de materia inhaladas (de más de 7 μm) se degluten después de la eliminación mucociliar del aparato respiratorio. En los animales experimentales y en el ser humano, la absorción de plomo del aparato gastrointestinal está influenciada por la naturaleza fisicoquímica del material ingerido, el estado nutricional y el tipo de alimentación. En los seres humanos adultos, se absorbe aproximadamente el 10% del plomo contenido en la alimentación; la proporción es más elevada en condiciones de

ayuno. Sin embargo, los lactantes y los niños pequeños absorben nada menos que el 50% del plomo presente en la alimentación, pero la absorción de plomo del polvo/suelo y de desconchones de pintura puede ser menor y depende de su biodisponibilidad. Las dietas pobres en calcio, fosfato, selenio o zinc pueden dar lugar a una mayor absorción de plomo. El hierro y la vitamina D también influyen en la absorción de plomo.

Los niveles de plomo en la sangre (Pb-H) se utilizan para medir la carga corporal y las dosis absorbidas (internas) de plomo. La relación entre el plomo presente en la sangre y la concentración de plomo en las fuentes de exposición es curvilínea.

Una vez absorbido, el plomo no se distribuye de manera homogénea en todo el cuerpo. Hay una absorción rápida en la sangre y en los tejidos blandos, seguida de una redistribución más lenta a los huesos. Los huesos acumulan plomo durante gran parte de la vida humana y pueden actuar como fuente endógena de plomo. La semivida del plomo en la sangre y en otros tejidos blandos es de aproximadamente 28-36 días, pero es mucho más larga en los diversos compartimentos óseos. La retención porcentual de plomo en los depósitos corporales es más elevada en los niños que en los adultos. La transferencia de plomo al feto humano se efectúa fácilmente durante la gestación.

El nivel de plomo en la sangre es la medida más utilizada para determinar la exposición al plomo. Sin embargo, ya se dispone de técnicas para determinar la cantidad de plomo presente en los dientes y en los huesos, aunque aún no se conoce del todo su cinética.

6. Efectos en los animales de laboratorio y en los sistemas *in vitro*

En todas las especies de animales de experimentación estudiadas, inclusive en primates no humanos, se ha observado que el plomo tiene efectos adversos en varios órganos y sistemas de órganos, inclusive los sistemas hematopoyético, nervioso, renal, cardiovascular, reproductivo e inmunitario. El plomo también afecta a los huesos y se ha demostrado que es carcinógeno en ratas y ratones.

Pese a diferencias cinéticas entre las especies de animales experimentales y la humana, dichos estudios apoyan firmemente y justifican desde un punto de vista biológico los hallazgos

realizados en seres humanos. Se han comunicado deficiencias del aprendizaje y de la memoria en ratas con niveles de Pb-H de 0,72-0,96 μmoles/litro (15-20 μg/dl) y en primates no humanos con niveles de Pb-H de no más de 0,72 μmoles/litro (15 μg/dl). Además, se han comunicado deficiencias visuales y auditivas en estudios realizados en animales de experimentación.

La toxicidad renal en las ratas parece presentarse a partir de un nivel de Pb-H de 2,88 μmoles/litro (60 μg/dl); este valor es semejante al que, según se ha comunicado, comienza a tener efectos renales en el ser humano. Se han observado efectos cardiovasculares en ratas después de exposiciones crónicas a niveles bajos que dan lugar a niveles de Pb-H de 0,24-1,92 μmoles/litro (5-40 μg/dl). Se ha demostrado que aparecen tumores con dosis inferiores a la dosis máxima tolerada, de 200 mg de plomo (como acetato de plomo) por litro de agua de bebida. Esta es la dosis máxima no asociada a otros cambios morfológicos o funcionales.

7. Efectos en el ser humano

En el ser humano, el plomo puede tener una amplia variedad de efectos biológicos según el nivel y la duración de la exposición. Se han observado efectos en el plano subcelular y efectos en el funcionamiento general del organismo que van desde la inhibición de las enzimas hasta la producción de acusados cambios morfológicos y la muerte. Dichos cambios se producen a dosis muy diferentes; en general, el ser humano que se está desarrollando es más sensible que el adulto.

Se ha mostrado que el plomo tiene efectos en muchos procesos bioquímicos; en particular, se han estudiado mucho los efectos en la síntesis del hemo en adultos y niños. Se observan niveles más altos de porfirina eritrocitaria sérica y mayor excreción urinaria de coproporfirina y de ácido δ-aminolevulínico cuando las concentraciones de Pb-H son elevadas. Con niveles más bajos se observa inhibición de las enzimas dehidratasa del ácido δ-aminolevulínico y reductasa de la dihidrobiopterina.

Como resultado de los efectos del plomo en el sistema hematopoyético disminuye la síntesis de hemoglobina y se ha observado anemia en niños a concentraciones de Pb-H superiores a 1,92 μmoles/litro (40 μg/dl).

Por razones neurológicas, metabólicas y comportamentales, los niños son más vulnerables a los efectos del plomo que los adultos.

Se han efectuado estudios epidemiológicos prospectivos y transversales para evaluar la medida en que la exposición al plomo ambiental afecta a las funciones psicológicas regidas por el sistema nervioso central (SNC). Se ha mostrado que el plomo está asociado a deficiencias neurocomportamentales en los niños.

Se han observado deficiencias psicológicas y neurocomportamentales en trabajadores que habían estado expuestos al plomo durante un tiempo prolongado. Los parámetros electrofisiológicos han demostrado ser indicadores útiles de los efectos subclínicos del plomo en el SNC.

Desde hace tiempo se sabe que la exposición prolongada a niveles elevados de plomo en el medio laboral provoca neuropatías periféricas. Con niveles más bajos se ha observado una reducción de la velocidad de conducción nerviosa. Se ha observado a menudo que dichos efectos son reversibles después de cesar la exposición, según la edad del sujeto y la duración de la exposición.

Los efectos del plomo en el corazón son indirectos y se producen por conducto del sistema nervioso autónomo; el plomo no tiene efectos directos en el miocardio. Datos colectivos procedentes de estudios de poblaciones adultas indican asociaciones muy débiles entre la concentración de Pb-H y la presión arterial sistólica o diastólica. Dada la dificultad de evaluar el influjo de los factores de confusión pertinentes, no puede establecerse una relación causal sobre la base de esos estudios. No hay indicios de que la relación entre la concentración de Pb-H y la presión arterial tenga mucha importancia para la salud.

Se sabe que el plomo provoca en los tubos proximales del riñón lesiones que se caracterizan por aminoaciduria generalizada, hipofosfatemia con hiperfosfaturia relativa y glucosuria acompañada de cuerpos de inclusión nuclear, modificaciones mitocondriales y citomegalia de las células epiteliales de los tubos proximales. Los efectos tubulares se manifiestan después de una exposición relativamente breve y suelen ser reversibles, mientras que los cambios escleróticos y la fibrosis intersticial, que dan lugar a una disminución de la función renal y a una posible insuficiencia renal, requieren una exposición crónica a niveles elevados de plomo. Se ha advertido un mayor riesgo de nefropatía en los trabajadores que tienen niveles de Pb-H superiores a 3,0 μmoles/litro (aproximadamente 60 μg/dl). Recientemente se han observado efectos renales en la población general tras haberse utilizado indicadores de función más sensibles.

Los efectos del plomo en la función reproductora masculina se limitan a la morfología y el número de los espermatozoides. En cuanto a la femenina, se han atribuido al plomo algunos efectos adversos en el embarazo.

El plomo no parece tener efectos nocivos en la piel, en los músculos ni en el sistema inmunitario. Salvo en la rata, el plomo no parece estar relacionado con el desarrollo de tumores.

8. Evaluación de los riesgos para la salud humana

El plomo tiene efectos adversos en varios órganos y sistemas de órganos; los más delicados parecen ser los cambios subcelulares y los efectos en el desarrollo del sistema nervioso. Se ha observado una asociación entre el nivel de Pb-H y la hipertensión (presión arterial). El plomo produce una serie de efectos en la reserva corporal de hemo y afecta a la síntesis de éste. Sin embargo, algunos de estos efectos no se consideran adversos. Está afectada la homeostasia del calcio, lo que interfiere en otros procesos celulares.

a) Los datos más importantes de los estudios transversales y prospectivos de poblaciones con niveles de Pb-H generalmente inferiores a 1,2 μmoles/litro (25 μg/dl) se relacionan con una disminución del coeficiente de inteligencia (CI). Es importante señalar que esas observaciones no pueden constituir una prueba concluyente de una relación causal con la exposición al plomo. Sin embargo, la magnitud del efecto aparente en el CI, determinado desde los 4 años en adelante, es un déficit de 0 a 5 puntos (en una escala con una desviación estándar de 15) por cada 0,48 μmoles/litro (10 μg/dl) de aumento del nivel de Pb-H, con una magnitud probable del efecto aparente de 1 a 3 puntos. Con niveles de Pb-H superiores a 1,2 μmoles/litro (25 μg/dl), la relación entre el Pb-H y el CI puede ser diferente. Las estimaciones de la magnitud del efecto constituyen promedios grupales y sólo se aplican a cada niño de manera probabilística.

   Los estudios epidemiológicos existentes no prueban de modo concluyente la existencia de un umbral. Por debajo de unos niveles de Pb-H de 0,48-0,72 μmoles/litro (10-15 μg/dl), los efectos de las variables de confusión y los límites de la precisión de las mediciones analíticas y psicométricas aumentan la incertidumbre inherente a toda estimación de un efecto. Sin embargo, hay algunos indicios de una asociación por debajo de dichos niveles.

b) Los estudios realizados en animales respaldan la idea de una relación causal entre el plomo y ciertos efectos en el sistema nervioso; se señalan deficiencias cognitivas a niveles de Pb-H de sólo 0,53-0,72 μmoles/litro (11-15 μg/dl), deficiencias que pueden persistir mucho después de haber terminado la exposición al plomo.

c) Puede producirse una reducción de la velocidad de conducción nerviosa periférica en el ser humano con niveles de Pb-H de sólo 1,44 μmoles/litro (30 μg/dl). Además, las funciones sensitivomotrices pueden verse disminuidas con niveles de Pb-H de sólo 1,92 μmoles/litro (40 μg/dl) aproximadamente y las funciones del sistema nervioso autónomo (variabilidad del intervalo R-R electrocardiográfico) pueden verse afectadas a un nivel promedio de Pb-H de aproximadamente 1,68 μmoles por litro (35 μg/dl). El riesgo de nefropatía plúmbica aumenta en los trabajadores que tienen niveles de Pb-H superiores a 2,88 μmoles/litro (60 μg/dl). Sin embargo, estudios recientes que utilizan indicadores más sensibles de la función renal sugieren la aparición de efectos renales a niveles más bajos de exposición al plomo.

d) La exposición al plomo está asociada a un pequeño aumento de la presión arterial. El orden de magnitud probable es que por cada duplicación del nivel de Pb-H (por ejemplo, de 0,8 a 1,6 μmoles/litro, es decir, de 16,6 a 33,3 μg/dl) hay un aumento medio de 1 mmHg de presión arterial sistólica. La relación con la presión diastólica es de una magnitud semejante pero más pequeña. Sin embargo, no se sabe bien si estas asociaciones estadísticas obedecen realmente a un efecto de la exposición al plomo o son un resultado ficticio debido a factores de confusión.

e) Algunos estudios epidemiológicos, no todos, muestran una relación, dependiente de la dosis, con el parto prematuro y algunos índices de crecimiento y maduración fetales a niveles de Pb-H de 0,72 μmoles/litro (15 μg/dl) o más.

f) Los indicios de carcinogenicidad del plomo y de varios compuestos inorgánicos de plomo en el ser humano son insuficientes.

g) Se ha demostrado que el plomo tiene efectos en cierto número de sistemas enzimáticos y de parámetros bioquímicos. Los niveles de Pb-H por encima de los cuales las técnicas vigentes

pueden demostrar la presencia de efectos en relación con los parámetros de importancia clínica posible son todos superiores a 0,96 μmoles/litro (20 μg/dl). Algunos efectos en enzimas pueden demostrarse con niveles de Pb-H más bajos, pero su importancia clínica es incierta.

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