Chapter 6.7 Lead

General description

Lead (Pb), with atomic number 82, atomic weight 207.19 and a specific gravity of 11.34, is a bluish or silvery-grey metal with a melting point of 327.5 °C and a boiling point at atmospheric pressure of 1740 °C. It has four naturally occurring isotopes with atomic weights 208, 206, 207 and 204 (in decreasing order of abundance). The isotopic ratios may differ for different mineral sources, and this property has been exploited in non-radioactive tracer studies to investigate environmental and metabolic pathways of lead.

Despite the fact that lead has four electrons on its valence shell, its typical oxidation state is +2 rather than +4, since only two of the four electrons ionize easily. Apart from nitrate, chlorate and, to a much lesser degree, chloride, most of the inorganic salts of lead (II) have poor solubility in water.

Stable organic lead compounds, such as tetraethyllead and tetramethyllead, are formed by direct binding of lead to a carbon atom. These compounds are colourless liquids with boiling points of 110 °C and 200 °C, respectively. They are decomposed at boiling point as well as by ultraviolet light and trace chemicals in air, such as halogens, acids and oxidizing agents. Owing to their use as fuel additives for anti-knock purposes, they are sources of environmental lead Nevertheless, their environmental impact has fallen during the past 15 years in most industrialized countries owing to legislation aimed at reducing and replacing lead in petrol.

Sources

Lead is a ubiquitous pollutant in the ecosystem. On a global scale the combustion of alkyl lead additives in motor fuels accounts for the major part of all lead emissions into the atmosphere, thus influencing all compartments of the environment. This has been hypothesized from mass balance studies *(1)* and has been confirmed by the changes in environmental lead levels subsequent to the reductions in worldwide use of alkylleads in petrol since the early 1980s.

Point sources, such as primary or secondary lead smelters, may create local pollution problems. The level of contamination of the surrounding air and soil depends on the amount of lead emitted, the height of the stack, the presence of fugitive sources, topography and other local features. In addition, the refining and manufacture of lead-containing compounds and goods and refuse incineration also give rise to lead emissions.

Since coal, like many minerals, rocks and sediments, usually contains low concentrations of lead, a number of other industrial activities such as iron and steel production, copper smelting and coal combustion must be regarded as additional sources of lead emissions into the atmosphere.

The presence of lead water-pipes in old houses can be an important source of lead exposure for humans, particularly in areas with soft water. In certain areas, lead-containing paint in old

houses can be an additional source of exposure, as are diverse uses such as lead solders, ceramic glazes, cosmetics and folk medicines.

Occurrence in air

It has been estimated that some 0.33 $\times 10^9$ kg of lead per year are directly emitted into the atmosphere *(2)*, and that pre industrial levels of lead in air from natural origins are about 0.6 ng/m^3 *(3)*. Spot measurements in five French and four United States cities in 1984–1985 reported air lead levels ranging from 0.005 μg/m^3 to 0.44 μg/m^3, the highest value being from Paris *(4)*. Air lead concentrations in industrial areas and in urban areas with high traffic density have decreased steadily over the past 15 years, subsequent to abatement of industrial emissions and to reductions in the lead content of petrol or to the increasing use of lead-free petrol. A typical example are annual means of air lead concentrations reported for the industrialized urban Rhine–Ruhr region in Germany. Whereas annual means were 0.81–1.37 μg/m^3 in 1974, they were only 0.17–0.19 μg/m^3 in 1988; for traffic-dominated cities (Cologne and Düsseldorf) the decrease was from 0.81 and 0.96 μg/m^3 to 0.17 and 0.18 μg/m^3, respectively, whereas for more industrialized areas (Essen and Dortmund) it was from 1.30 and 1.37 μg/m^3 to 0.17 and 0.19 μg/m^3, respectively *(5)*. Even more pronounced downward trends from above 3 μg/m^3 in 1974 to about 0.5 μg/m^3 in 1988 have been reported for areas with high traffic density in Belgium *(6)*. Higher air lead concentrations may still be found in the vicinity of primary or secondary lead smelters.

Most of the lead in the air is in the form of fine particles with a mass median equivalent diameter of less than 1 μm. The fraction of organic lead (predominantly lead alkyls that escaped combustion) is generally below 10% of the total atmospheric lead, the majority (>90%) of lead from leaded petrol emissions being inorganic particles such as PbBrCl. In the immediate vicinity of smelters, the particle size distribution usually shows a predominance of larger particles. However, these particles settle at distances of a few hundred metres or 1–2 km, so that further away the particle size distribution is indistinguishable from that of other urban sites.

Lead is removed from the atmosphere by dry or wet deposition. The residence time of lead-containing particles in the atmosphere varies according to a number of factors, such as particle size, wind currents, rainfall and height of emission. Soil and water pollution from car emission fallout is predominantly limited to the immediate urban area. Fallout from the emissions of industrial sources, such as smelters, is likewise limited mainly to the immediate vicinity. However, strong evidence indicates that a fraction of airborne lead is transported over long distances. As a result, a long-term global accumulation of lead has occurred in recent decades. This has been demonstrated convincingly by analyses of glacial ace and snow deposits in remote areas, such as the Greenland ice cap, until about 1960 *(7)*; however, subsequent measurements revealed a marked downward trend in the same glacial strata *(8)*, corresponding to the global fall in the use of alkyl lead additives in petrol.

Conversion factors

Mass concentrations are typically used to express lead concentrations in environmental media such as air, soil or water, so that conversion factors are not necessary. Different units, such as μg/dl, μg/l and μmol/l, are used, however, to characterize lead concentrations in blood. Multiplication by 0.048 gives the μg/dl equivalent in μmol/l. Blood lead concentrations are expressed here as μg/l.

Analytical methods (in air)
Methods typically used for the measurement of particulate lead in air *(9)* include flame atomic absorption spectometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS), anodic stripping voltammetry (ASV), inductively coupled plasma-atomic emission spectroscopy (ICP-AES), and isotope dilution mass spectometry (IDMS). Different preparation methods after collection on membrane or cellulose-acetate filters are summarized by WHO *(9)*. Reported detection limits range between 0.1 ng/m^3 and 0.34 µg/m^3, and recoveries are typically given as 90–110%

Routes of exposure

Air
Most of the lead in ambient air is in the form of sub-micron-sized particles. Some 30–50% of these inhaled particles are retained in the respiratory system. Virtually all of this retained lead is absorbed into the body. Particles in the size range of 1–3 µm are also efficiently deposited in the lungs. Larger particles are deposited with variable efficiency, mainly in the upper respiratory tract with incomplete absorption. All lead particles that are cleared by the lung can be swallowed and result in further lead absorption from the gastrointestinal tract.

Drinking-water
Lead concentrations in drinking-water and groundwater vary from 1 µg/l to 60 µg/l. In most European countries, the levels of lead in domestic tap water are relatively low, i.e. normally 20 µg/l. Consequently, exposure to lead through water is generally low compared with exposure through food . Nevertheless, in old houses with lead pipes used for the domestic drinking-water supply, blood lead levels in six-year-old children were found to be elevated by about 30% relative to houses without lead pipes *(10)*. In areas with soft water, where lead water pipes and lead plumbing are common, the contribution of lead in drinking-water to the total lead intake may even be more pronounced *(11)*.

Food
Most people receive the largest portion of their daily lead intake via food. Most lead enters food during storage and manufacture, e.g. in canned food and in alcoholic drinks. The most important pathway whereby atmospheric lead enters the food chain is thought to be direct foliar contamination of plants. This contamination depends on the rate of fallout of lead in the districts where food is grown; it tends to be higher in heavily industrialized areas. Additionally, air deposits raise the level of lead in soil, which, in the course of decades and centuries, may result in an increased uptake of lead through the roots.

The concentrations of lead in various food items are highly variable. Several studies have reported average lead intakes in the range of 100–500 µg/day for adults, with individual diets covering a much greater range. More recent data indicate total daily intakes of about 100 µg or less *(12)*. For young children, estimates of total daily intake are about one half the figures for adults. Recent duplicate diet data from children aged 5–8 years in Germany amount to median daily intakes of 0.79 µg/kg body weight and a 90th percentile of 1.49 µg/kg body weight *(13)*, corresponding to daily intakes of about 17 µg and 33 µg, respectively.

Weekly dietary intake for adults between 1981 and1988 has been reported to vary widely between different countries. In Europe the highest average value has been given for Italy, at 60 µg/kg body weight, and the lowest for Finland and Sweden at about 2–3 µg/kg *(14)*.

According to the US Food and Drug Administration's total diet study, there was a steady fall in daily dietary intake in adults, infants and children in the period 1979–1988, from about 90 µg/day to below 10 µg/day for adult males, and from about 30 µg/day to below 5 µg/day for infants *(15)*. A comparable decline has not been reported, however, for other countries such as Hungary, Japan and the United Kingdom *(14)*.

Other routes of exposure

An individual's lead exposure may be increased by choice, habit or unavoidable circumstances, in addition to the "normal" environmental exposure through food, drinking-water and air.

These additional exposures can be categorized either as being due to lead in the ambient air or as being independent of lead in the ambient air. The former category includes high lead levels in dust and soil in residential areas near smelters or refineries, high-density traffic, and the consumption of vegetables and fruit grown on high-lead soils or near sources of lead emissions (smelters or roads with high traffic density). The latter category includes occupational exposures; secondary occupational exposures of members of the families of lead workers; contamination of house dust in houses with interior lead paint; contamination of tap water in houses with lead water pipes or lead plumbing; the use of improperly glazed earthenware vessels; tobacco smoke *(16)* and alcohol consumption (particularly wine) *(17)*.

Lead in dust, indoors as well as outdoors, is an important potential source of intake by ingestion, particularly for young children living in contaminated areas, such as near lead smelter areas and in central urban areas (18,19).

Relative significance of different routes of exposure

Exposure to lead from water, food, air and other sources can vary significantly for different individuals and population groups. Since the relative contribution of each of these sources can also vary substantially, comprehensive information covering a wide range of circumstances cannot be provided. A computer-based integrated exposure uptake biokinetic model for lead in children has been developed, however, to estimate the uptake of lead from different environmental media over a wide range of conditions and its compartmental distribution within the body *(20)*.

An important group is that of infants (children up to 1 year of age). At present, insufficient information is available on the lead content of their diet and its absorption for reasonable estimates to be made. Nevertheless, the contribution of drinking-water in this group is likely to be high.

Population groups at higher exposure risk

Children up to 6 years of age are at increased risk for lead exposure, as well as for adverse health effects, because:

1. children have behavioural characteristics (outdoor activity, less concern for hygienic conditions, hand-to-mouth activities or even pica), which increase the risk of lead exposure;
2. children eat and drink more per unit of body weight than adults, so that their relative lead intake is increased;

3. lead absorption in the gastrointestinal tract is substantially higher in children (about 50%, compared with about 10% in adults) *(21)*;
4. there is a greater prevalence of nutritional deficiencies (e.g. iron and vitamin D) among children, which enhance absorption of lead from the gastrointestinal tract;
5. the blood–brain barrier is not yet fully developed in young children; and
6. haematological and neurological effects of lead occur at lower thresholds than in adults.

For this group the contribution of air lead to blood lead by way of inhalation alone underestimates the contribution of environmental lead to blood lead, as air lead can only be taken as a general indicator of lead pollution. Because of the behavioural characteristics of preschool children, outdoor lead deposition is the most important single explanation of differences between inner city and suburban areas in the blood lead of children *(22)*. Lead in dust can make a substantial contribution to absorbed lead in small children, sometimes up to 80% of the total amount.

Since the placenta is no effective biological barrier, pregnant women represent a second group at increased risk because of exposure of the fetus to lead.

Utility of biomarkers
Biomarkers of exposure (such as blood lead concentrations in adults or children, lead concentrations in shed deciduous teeth of children at about 6–9 years of age, and lead concentrations in bones as assessed by non-invasive X-ray fluorescence) are useful in estimating lead body burden. In addition, biomarkers of effect, such as elevated free erythrocyte protoporphyrin (FEP) or inhibition of delta-aminolevulinic acid dehydrase (δ-ALAD), have been used to monitor lead-induced alterations within the haem biosynthetic pathway.

Toxicokinetics

Absorption (bioavailability)
Absorption through the respiratory tract is influenced by the particle size distribution and the ventilation rate. For adults the retention rates of airborne particulates range from 20% to 60%. Although lead salts differ widely in terms of water solubility, the chemical form of lead is not considered an important factor for respiratory absorption.

The proportion of lead absorbed from the gastrointestinal tract is about 10% in adults, whereas levels of 40–50% have been reported in infants *(21)*. Gastrointestinal absorption is highly dependent on dietary or nutritional factors *(23)*: both milk and fasting enhance absorption. Diets with low levels of calcium, vitamin D and iron have been shown to increase lead absorption in laboratory animals. The water solubility of the different lead salts is an important determinant of the gastrointestinal absorption of lead, and hence its bioavailability. This needs to be considered in estimating direct intake of lead from soil by children, taking the pH of the gastrointestinal tract into account.

Distribution
The non-excreted fraction of absorbed lead is distributed among three compartments: blood, soft tissues and the mineralizing tissues (bones and teeth). About 95% of the lead body

burden in adults is located in the bones, compared with about 70% in children *(24)*. Some 99% of the lead in the bloodstream is bound to erythrocytes. The biological half-time of lead in blood can be as short as 20–40 days (isotopic tracer data), although longer half-time values have been reported in lead workers and may depend on the lead body burden *(25,26)*.

Lead concentration in bones increases with age and this increase is more noticeable in males in the more dense tibial bones *(27)*. Lead stored in bones was shown to have a biological half-time of some years *(28)*.

Lead may be released from the bones in decalcification processes related to elderly people, pregnancy, acidosis, thyrotoxicosis or active remodelling processes in the bones of children. Animal experiments have shown mobilization of lead in pregnancy *(29)*. No convincing evidence is as yet available for the human condition at environmental levels of exposure in this respect, except for one isolated case of excessive lead intake prior to pregnancy *(30)*. The evidence for the release of lead from bone in disease states in humans is uncertain, and more information is required. It has, however, been suggested that lead may be released from bone tissue after the menopause *(31)*, and clearly higher blood lead levels have indeed been found in post-menopausal than in pre-menopausal women *(32)*.

Elimination

Nonabsorbed lead passes through the gastrointestinal tract and is excreted in the faeces. Of the absorbed fraction, 50–60% is removed by renal and biliary excretion. Intestinal clearance is about 50% of the renal clearance. (These figures relate to adult subjects.) Surprisingly little information exists on the age dependency of lead retention and excretion. Some data indicate that children, particularly infants, retain a higher amount of lead *(21)*.

Biomarkers of exposure

Lead concentrations in a variety of biological media, such as blood, urine, bone, tooth and hair, have been measured to serve as biomarkers of exposure. These different markers have different validity as surrogate measures of dose. Lead in urine and hair are of only limited value. Bone lead may be measured by noninvasive X-ray fluorescence, but is still limited in sensitivity; it is a useful measure in that it provides retrospective information about integrated lead absorption in the past. This is also true for tooth lead concentrations measured in shed deciduous teeth as an index of lead exposure in early childhood *(33,34)*. Interpretation of the analytical data depends partly on which tooth and which part of this tooth (whole tooth, dentine or circumpulpar dentine) is analysed. Correlations with single blood lead concentrations are typically around 0.60 *(35)*, although correlations with "lifetime integrated blood lead", based on serial blood lead determinations prior to tooth exfoliation, have been reported to be up to 0.79 *(36)*.

Whole blood lead concentration (PbB) is the most widely used and most generally accepted measure of absorbed dose. Blood lead is distributed among plasma and the erythrocytes, with less than 5% being in the plasma; most of the lead is bound to haemoglobin. Although it is likely that plasma lead concentrations may better reflect the "active" fraction of lead in blood and characterize the relationship between blood lead and tissue accumulation (and effect), there is little experimental support because of the analytical problems *(9)*.

Physiologically based pharmokinetic modelling

Absorbed lead is distributed among soft tissues (blood, liver, kidney, brain etc) and mineralizing systems (bone, teeth). Bone is the body's major storage site. Lead accumulates in bones over the lifetime. Knowledge of the kinetics is important because of the possibility of the release of stored lead under appropriate conditions.

Biokinetic movements of lead in the body, based on tracer and balance data, have been characterized by a three-compartment model *(28,37).* Lead within these three compartments, namely blood, bone and soft tissues, was found to have different half-times, with blood being the most labile pool (half-time about 36 days), bone the most stable (half-time about 27 years) and the soft tissues also labile (half-time about 40 days).

Health effects

The toxicity of lead may largely be explained by its interference with different enzyme systems: lead inactivates these enzymes by binding to SH-groups of its proteins or by displacing other essential metal ions. For this reason many organs or organ systems are potential targets for lead, and a wide range of biological effects of lead have been documented. These include effects on haem biosynthesis, the nervous system, the kidneys and reproduction, and also cardiovascular, hepatic, endocrinal and gastrointestinal effects. In conditions of low-level and long-term lead exposure, such as are found in the general population, the most critical effects are those on haem biosynthesis, erythropoiesis, the kidney, the nervous system and blood pressure.

Effects on experimental animals and *in vitro* test systems

Toxicological effects

Effects on both haem biosynthesis and the nervous system have been studied in laboratory animals. Inhibition of the activity of δ-ALAD, an enzyme involved in haem biosynthesis, is among the earliest biological effects of lead. Comparative studies suggest that the brain of the suckling rodent is more vulnerable to lead-induced ALAD inhibition than the adult brain *(38,39).*

Neurobehavioural models of learning and memory, as well as neurophysiological approaches of basic neurobiology, have been used to study the effects of low-level lead exposure on the nervous system of rodents. Much of the pertinent work has been summarized by WHO *(9)*: learning and memory deficit after prenatal and/or early postnatal dietary lead exposure has been reported to occur at blood lead levels of 150–200 μg/l in rats, and in non-human primates at PbB levels not exceeding 150 μg/l. There is some evidence that prenatal/pre-weaning exposure is more effective than post-weaning lead exposure. There is also evidence that neurobehavioural deficit persists into adulthood long after cessation of lead exposure, with concomitant normalization of blood and brain lead levels, if lead is given before weaning *(40).* From a mechanistic point of view there is also accumulating evidence for a possible involvement of lead in the *N*-methyl-D-aspartate receptor complex *(41,42)*.

Carcinogenic effects

Renal tumours have been reported to be associated with lead exposure. In all of the available studies renal carcinogenicity has been found in rats at high dietary doses of lead and long exposure times on a background of cell hyperplasia, cytomegaly and cellular dysplasia *(43).*

Mutagenic effects and effects identified by other in vitro assays
Gene mutations in cultures of mammalian cells have been reported to occur only at concentrations toxic to cells. Some degree of mutagenicity has been found in Chinese hamster cells with lead sulfide and lead nitrate *(44)*. No point mutations have been observed in bacterial systems *(45)*. Mixed results are available on lead-induced chromosome aberrations, sister-chromatid exchanges and micronuclei *(46).*

In vitro studies have also shown that picomolar concentrations of lead significantly activate protein kinase C *(47)* and have been found to generally interfere with calcium second messenger systems, which regulate neurotransmission.

Critical organs, tissues and effects
Brain function appears to be affected at low levels of internal lead exposure in terms of PbB. Neurobiological effects, particularly those related to neurobehaviour, neurochemistry and neurophysiology must, therefore, be considered critical effects for lead.

Effects on humans

Toxicological effects
As far as long-term, low-level lead exposure is concerned, the following effects have to be considered in relation to the general population:

1. effects on haem biosynthesis;
2. effects on the nervous system;
3. effects on blood pressure and cardiovascular effects, and
4. effects on kidney function.

The present discussion is, therefore, limited to these aspects of lead toxicity.

Effects on haem biosynthesis and erythropoiesis
The normal process of haem biosynthesis and its disturbance by lead are well understood. On the cellular level, the initial and final steps of haem formation are mitochondrial, whereas the intermediate steps take place in the cytoplasm. Essentially, lead interferes with the activity of three enzymes:

1. it indirectly stimulates the mitochondrial enzyme delta-aminolaevulinic acid synthetase (ALAS);
2. it directly inhibits the activity of the cytoplasmatic enzyme δ-ALAD; and
3. it interferes with the normal functioning of intramitochondrial ferrochelatase, which is responsible for the insertion of iron(II) into the protoporphyrin ring.

ALAS stimulation has been found in lead workers at PbBs of about 400 µg/l *(48)*. In contrast, ALAD in the erythrocytes is inhibited at very low PbBs. According to Hernberg & Nikkanen *(49)*, activity inhibition in urban adults was 50% at a blood lead level of 160 µg/l. Roels et al. *(50)* were unable to determine a threshold for ALAD inhibition in school-age children with blood lead concentrations of 30–300 µg/l, although first effects appeared to be associated with a PbB of about 100 µg/l.

ALAD inhibition results in an accumulation of its substrate, aminolevulinic acid, in blood, plasma and urine. Although the threshold for urinary ALA elevation is widely accepted as being 400 µg/l, some studies have demonstrated PbB/urinary ALA correlations at lower blood lead values *(48)*.

Interference by lead with the formation of haem from protoporphyrin is apparent from increased levels of FEP or zinc protoporphyrin (ZPP) in blood. Whereas ZPP is likely to be confounded by iron status at lead concentrations below 200 µg/l *(51)*, FEP should be a more valid indicator of lead-induced disruption of haem formation at lower PbB. Based on data from 2004 urban children, a threshold for FEP elevation of 150–180 mg/l was found *(52)*. A reanalysis of the Second National Health and Nutrition Examination Survey (NHANES II) data on 264 children yielded a threshold of 200 µg/l *(51)*.

Effects of lead on erythropoiesis and erythrocyte physiology represent more direct signs of damage to the haemopoietic system than haem precursors in blood or urine. Anaemia is a frequent outcome of chronic lead intoxication. A threshold effect for occupationally exposed adults was estimated at 500 µg/l *(45)*. Impairment of the erythropoietic system to regenerate from phlebotomy was found in lead-exposed workers with an average PbB of 445 µg/l relative to controls *(53)*. A meta-analysis of several studies in children yielded a threshold effect of about 250 µg/l *(54)*. When defining anaemia as a haematocrit < 35%, reanalysis of older data revealed a strong nonlinear dose–response effect at PbB exceeding 200 µg/l in 579 young children living near a lead smelter *(55)*. A threshold level of 500 µg/l has been found in lead workers *(56)*.

In young children, lead exposure is associated with a decrease in the biosynthesis of the important hormonal metabolite of vitamin D, namely 1,25-dihydroxy-vitamin D *(57)*. Associations with blood lead were reported in children with blood lead levels of 120–1200 µg/l *(57,58)*. A threshold has not been determined.

Effects on the nervous system

Encephalopathy has been observed in adults at blood lead levels exceeding 1200 µg/l, and in children at levels of 800–1000 µg/l. The outcome is frequently fatal in children, and those who survive often present with irreversible neurological and neuropsychological sequelae *(59)*.

With regard to the peripheral nervous system, sensory and motor nerve conduction velocity (NCV) measurements have yielded mixed results in many studies. Whereas most studies reported decreased NCVs in lead-exposed workers at PbBs of 300–800 µg/l *(60,61)*, a few others did not show lead-related slowing of NCV. A meta-analysis and critical review of 32 such studies revealed that NCVs are typically reduced in lead workers relative to controls, particularly in the median motor nerve *(62)*. NCV reduction is reversible after cessation of exposure or chelation therapy *(63)*.

With regard to the central nervous system (CNS), neurobehavioural functions have been studied both in lead workers and in environmentally exposed children. Impairment of cognitive and sensorimotor test performance has been found in lead workers relative to controls in many studies. It has been confirmed that such deficit in adults occurs at average PbBs of 500 µg/l but not at 300 µg/l, relative to controls with an average PbB of 100 µg/l *(64,65)*.

Children as a risk group for CNS effects have received particular attention in studies dealing with lead-related neurobehavioural deficit at environmental levels of lead exposure. Both cross-sectional and prospective studies have been performed at blood lead levels below 300 µg/l. Apart from diverse neuropsychological measures covering attentional as well as visual-motor performance aspects, psychometric IQ has received particular attention as a global measure of CNS functioning in such studies, both for its psychometric quality and for the degree of its comparability across studies. Meta-analyses covering cross-sectional and prospective studies have consistently shown that an increase in PbB from100 to 200 µg/l is likely to be associated with a drop in IQ of 1–3 points *(9,66,67).* Although this corresponds to only about 20% of one standard deviation of a typical IQ distribution, societal implications may be substantial if the population-shift hypothesis holds *(68)*; in addition, it is likely that these effects persist.

Existing epidemiological studies do not provide definitive evidence of a threshold. According to a WHO evaluation *(9)* it is concluded that below the PbB range of 100–150 µg/l the effects of confounding variables and limits in the precision of analytical and psychometric measurements increases the uncertainty attached to any estimate of effect. Nevertheless, there is some evidence of an association below this range.

Cardiovascular effects and blood pressure

General population studies did not find associations between blood lead levels and cardiovascular morbidity and mortality *(67,69).* Possible associations between PbB and blood pressure have been studied in several large-scale population studies, such as the British Regional Heart Study and the US NHANES II, as well as studies in Belgium, Canada, Denmark and Wales. A meta-analysis of the available studies by Staessen et al. *(70)*, covering 19 studies with altogether 28 210 subjects, revealed similar associations between both sexes. A two-fold increase in blood lead was associated with a 1-mmHg increase in systolic and a 0.7-mmHg increase in diastolic blood pressure. It is concluded that there is a significant weak positive association, possibly without public health implications for hypertension. A causative role for lead is considered unlikely *(70).*

Effects on kidney function

Occupational studies on lead-related renal dysfunction found a particular sensitivity to lead for *N*-acetyl-ß-D-glucosaminidase (NAG), a lysosomal enzyme present in renal tubular cells and considered a sensitive but nonspecific indicator for early subclinical nephrotoxicity. Excretion of PbB and NAG was found to be associated with PbB levels below 600 µg/l *(71)*, although negative reports exist as well *(72).*

Mixed results have been reported from general population studies *(73–75).* Within a random population group of 965 men (mean PbB = 114 µg/l) and 1016 women (mean PbB = 75 µg/l), Staessen et al. *(75)* found significant inverse associations between PbB and creatinine clearance and significant positive associations between ß2-microglobulin and PbB after adjustment for confounders. The influence of cadmium or elevated blood pressure in explaining lead-related impairment of renal function, but possible reverse causality, could not be excluded.

Carcinogenic effects
According to IARC *(76)*, evidence of the carcinogenicity of lead compounds in humans is inadequate.

Sensory effects
Two cross-sectional studies, based on large samples from the NHANES II survey (N = 4519; age 4–19 years) *(77)* and the Hispanic Health and Nutrition survey (N = 3262; age 6–19 years) *(78)* respectively, found significant linear associations between blood lead levels and elevated pure tone hearing thresholds; there was no discernible threshold for this association. There was an approximate hearing loss of 2 dB within the PbB range of 70–180 µg/l.

Evaluation of human health risks

Exposure evaluation
Average air lead levels are usually below 0.15 µg/m^3 at non-urban sites. Urban air lead levels are typically between 0.15 and 0.5 µg/m^3 in most European cities. Additional routes of exposure must not be neglected, such as lead in dust, a cause of special concern for children.

The relationship between air lead exposure and blood lead has been shown to exhibit downward curvilinearity if the range of exposures is sufficiently large. At lower levels of exposure the deviation from linearity is negligible, and linear models of the relationship between intake and blood lead are satisfactory approximations.

The level of lead in blood is the best available indicator of current and recent past environmental exposure, and may also be a reasonably good indicator of lead body burden with stable exposures. Biological effects of lead will, therefore, be related to blood lead as an indicator of internal exposure.

Table 1. Summary of LOAELs for lead-induced health effects in adults

LOAEL at given blood lead level (µg/l)	Haem synthesis, haematological and other effects	Effects on the nervous system
1000–1200		Encephalopathic signs and symptoms
800	Frank anaemia	
500	Reduced haemoglobin production	Overt subencephalopathic neurological symptoms, cognition impairment
400	Increased urinary ALA and elevated coproporphyrin	
300		Peripherial nerve dys- function (slowed nerve conduction velocities)
200–300	FEP elevation in males	
150–200	FEP elevation in females	

Health risk evaluation
Table 1 summarizes lowest-observed-adverse-effect levels (LOAELs) for haematological and neurological effects in adults. Cognitive effects in lead workers have not been observed at PbB below 400 µg/l. Reductions in nerve conduction velocity were found in lead workers at

PbB as low as 300 µg/l. FEP elevation has been observed at PbB of 200–300 µg/l. ALAD inhibition is likely to occur at PbBs of about 100 µg/l. Because of its uncertain biological significance relative to the functional reserve capacity of the haem biosynthetic system, ALAD inhibition is not treated as an adverse effect here.

Table 2 summarizes LOAELs for haematological, endocrinological and neurobehavioural endpoints in children. Reduced haemoglobin levels have been found at PbBs of around 400 µg/l. Haematocrit values below 35% have not been reported at PbBs below 200 µg/l; this is also true for several enzyme systems, which may be of clinical significance.

CNS effects, as assessed by neurobehavioural endpoints, appear to occur at levels below 200 µg/l. Consistent effects have been reported for global measures of cognitive functioning, such as the psychometric IQ, to be associated with blood lead levels of 100–150 µg/l. Some epidemiological studies have indicated effects at blood lead levels below 100 µg/l. Existing animal studies do provide qualitative support for the claim of lead as the causative agent.

Table 2. Summary of LOAELs for lead-induced health effects in children

LOAEL at given Blood lead level (µg/l)	Haem synthesis, haematological and other effects	Effects on the nervous system
800–1000		Encephalopathic signs and symptoms
700	Frank anaemia	
400	Increased urinary ALA and elevated coproporphyrin	
250–300	Reduced haemoglobin synthesis	
150–200	FEP elevation	
100–150	Vitamin D3 reduction	Cognitive impairment
100	ALAD inhibition	Hearing impairment

Guidelines

Guidelines for lead in air will be based on the concentration of lead in blood. Critical effects to be considered in the adult organism include elevation of FEP, whereas for children cognitive deficit, hearing impairment and disturbed vitamin D metabolism are taken as the decisive effects. All of these effects are considered adverse. A critical level of lead in blood of 100 µg/l is proposed. It should be stressed that all of these values are based on population studies yielding group averages, which apply to the individual child only in a probabilistic manner. Although some lead salts have been found to be carcinogenic in animals, the evidence for a carcinogenic potential in humans is inadequate and will, therefore, not be considered here.

For the derivation of a guideline value the following arguments have been considered.

1. Currently measured “baseline” blood lead levels of minimal anthropogenic origin are probably in the range 10–30 µg/l.

2. Various international expert groups have determined that the earliest adverse effects of lead in populations of young children begin at 100–150 µg/l. Although it cannot be excluded that population effects may occur below this range, it is assumed to be prudent to derive a guideline value based on the lowest value of this range (100 µg/l).
3. It can be assumed that inhalation of airborne lead is a significant route of exposure for adults (including pregnant women) but is of less significance for young children, for whom other pathways of exposure such as ingested lead are generally more important.
4. It appears that 1 µg lead per m^3 air directly contributes approximately 19 µg lead per litre blood in children and about 16 µg per litre blood in adults, although it is accepted that the relative contribution from air is less significant in children than in adults. These values are approximations, recognizing that the relationships are curvilinear in nature and will apply principally at lower blood lead levels.
5. It must be taken into account that, in typical situations, an increase of lead in air also contributes to increased lead uptake by indirect environmental pathways. To correct for uptake by other routes as well, it is assumed that 1 µg lead per m^3 air would contribute to 50 µg lead per litre blood.
6. It is recommended that efforts be made to ensure that at least 98% of an exposed population, including preschool children, have blood lead levels that do not exceed 100 µg/l. In this case, the median blood lead level would not exceed 54 µg/l. On this basis, the annual average lead level in air should not exceed 0.5 µg/m^3. This proposal is based on the assumption that the upper limit of non-anthropogenic lead in blood is 30 µg/l. These estimates are assumed to protect adults also.
7. To prevent further increases of lead in soils and consequent increases in the exposure of future generations, air lead levels should be kept as low as possible.

Since both direct and indirect exposure of young children to lead in air occurs, the air guidelines for lead should be accompanied by other preventive measures. These should specifically take the form of monitoring the lead content of dust and soils arising from lead fallout. The normal hand-to-mouth behaviour of children with regard to dust and soil defines these media as potentially serious sources of exposure. A specific monitoring value is not recommended. Some data indicate that lead fallout in excess of 250 µg/m² per day will increase blood lead levels.

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