

Lead

Toxicological overview

Key Points

Kinetics and metabolism

- Inhalation of fumes, mists or vapours or ingestion of food, drink or soil/dust are the main routes of exposure
- Absorption following inhalation is generally high (50-90%), depending on the particle size and approximately 5-15 % in adults (40 % in children) following ingestion
- Absorbed lead is distributed by blood to liver, kidney, bone and teeth
- The unabsorbed lead is eliminated through the faeces. That what is absorbed is mainly excreted in the urine

Health effects of acute exposure

- Lead is classically a chronic or cumulative toxin, hence few adverse health effects are observed following an acute exposure
- Adverse effects caused by exposure to lead are considered not exhibit a threshold, hence the as low as reasonably practicable principle applies
- May cause GI disturbances (anorexia, nausea, vomiting, abdominal pain), neurological effects (encephalopathy, malaise, drowsiness), hepatic and renal damage or hypertension

Health effects of chronic exposure

- Chronic lead exposure commonly causes haematological effects such as anaemia, basophilic stippling or neurological disturbances including headache, irritability, lethargy, convulsions, muscle weakness, ataxia, tremors and paralysis
- In children, lead exposure may lead to cognitive deficits, such as a decrease in IQ, effects of which do not exhibit a threshold
- Renal and hepatic injury as well as GI disturbances may arise following occupational exposure
- Exposure to lead may cause spontaneous abortion, still birth or decreased birth weight, or cause sperm abnormalities in males
- Inorganic lead compounds are classified as probably carcinogenic to humans (group 2A) by IARC

Toxicological Overview

Summary of health effects

Lead is classically a chronic or cumulative toxin. Few adverse health effects are observed following an acute exposure at low dose levels [1]. Acute effects including GI disturbances (anorexia, nausea, vomiting, abdominal pain), neurological effects (encephalopathy, malaise, drowsiness), hepatic and renal damage and hypertension have been reported [1-3].

Chronic lead exposure may cause anaemia, basophilic stippling and decreased haemoglobin synthesis [4-6]. Neurological effects may also be observed such as fatigue, sleep disturbance, headache, irritability, lethargy, slurred speech, convulsions, muscle weakness, ataxia, tremors and paralysis. Epidemiological studies in children have shown an inverse relationship between blood lead concentrations above 10 $\mu\text{g dL}^{-1}$ and IQ. There is some evidence that even lower exposures are also harmful, and it is therefore assumed that there is no completely harmless level of exposure to lead [2].

Nephropathy and renal tubule dysfunction may arise following chronic lead exposure [5]. Hepatic damage has been reported only in a few cases following occupational exposure to lead [6]. Gastrointestinal disturbances such as nausea, vomiting, anorexia, constipation, abdominal cramps have also been observed in workers [1].

Chronic exposure to lead may cause adverse effects on both male and female reproductive functions [6]. Females may experience spontaneous abortion, stillbirths or low birth weight following occupational exposure before or during pregnancy [5], and in males reduced libido, low semen volume and sperm counts and decreased sperm motility may occur [1, 4].

Occupational exposure to lead has been reported to cause an increase in sister chromatid exchange and chromosomal aberrations, although such increases were not observed in environmentally exposed children [4].

Based on epidemiological and experimental data, the Working Group of the International Agency for Research on Cancer (IARC) concluded that inorganic lead compounds are probably carcinogenic to humans (group 2A) [7].

Kinetics and metabolism

Absorption of lead depends on the physical and chemical state of the metal, and is influenced by age, physiological status, nutritional status and genetic factors [4].

In the general public, exposure to lead occurs primarily through the oral route, with some contribution from inhalation. In contrast, in the occupational setting, inhalation of inorganic lead in the form of fumes, mists, dusts and vapours is a major route of exposure. However, the toxicological effects are the same regardless of the route of exposure [8].

The absorption of particulate lead following inhalation involves the deposition of airborne lead particles in the respiratory tract and the absorption and clearance from the respiratory tract into the circulation [4]. Approximately 35 – 50 % of inhaled lead of particle size less than 1 μm is deposited in the lower respiratory tract, primarily in the alveolar tract, and 50 – 70 % of an inhaled dose is absorbed [2-4]. Higher deposition rates may occur with larger particles but this occurs in the upper respiratory tract and absorption occurs via the ingestion route [4]. Smaller particles of lead, such as those generated in exhaust fumes, are almost completely (>90 %) absorbed [4].

In adults, without occupational exposure, and in older children, lead absorbed by the gastrointestinal tract comes mainly from the intake of lead from food, drink and soil/dust. It has been estimated that children between 2 – 3 years of age ingest approximately 100 mg soil per day [4]. In adults, approximately 5 - 15 % of ingested lead is absorbed in the gut whereas in children and infants absorption may be as high as 40 % [2, 3]. Low levels of calcium, iron, copper, zinc or phosphorus in the diet or high levels of fat can increase lead absorption [2, 7].

Dermal absorption of inorganic lead compounds is generally quite low [4, 7]. One study reported increased levels in saliva and sweat following dermal exposure to inorganic lead, although blood or urine levels remained unchanged. It was postulated that the inorganic lead absorbed through the skin was transported in plasma and rapidly concentrated in sweat and saliva, without significant uptake by erythrocytes [2].

The route of absorption has little effect on the distribution of lead [4, 6]. The distribution of lead appears to be similar in adults and children, although a larger fraction of the body burden of adults appears in bone. Lead is transported primarily in the red blood cells bound to plasma proteins [6]. Absorbed lead is distributed by blood to mineralising systems (bone, teeth) and soft tissues (liver). The half life of lead in blood, soft tissue and bone is approximately 36 days, 40 days and 27 years, respectively [4].

Bone accumulates lead throughout most of the human life span but, at the same time, lead is mobilised from bone by remodelling [4]. In adults, approximately 94 % of the body burden of lead is in the bones, but only 73 % in children. Following chronic exposure, lead becomes deposited, in the form of insoluble lead phosphate, in areas of the skeleton that are rapidly growing, such as the radius, tibia and femur. Characteristic 'lead lines' may be seen on X-ray, and their width is related to duration of exposure [2].

Bone lead is readily mobilised to blood, the effect of which is most apparent in people with a history of occupational exposure and older people. Mobilisation of lead from bone to the more bioavailable maternal blood compartment is of importance in pregnant women and nursing mothers as it poses a risk for the fetus. Lead is readily transferred via the placenta from the mother to the developing fetus during pregnancy and accumulated in the bone. The concentration of lead in cord blood may be 85 – 90 % that of maternal blood, hence posing a risk for the fetus [4].

Inorganic lead is not metabolised, although conjugation with glutathione may occur. Organic lead may be metabolised to inorganic lead [1].

Approximately 90 % of ingested inorganic lead is eliminated unabsorbed through the faeces. Absorbed lead is primarily excreted in the urine (75 %) and faeces (25 %), independent of the route of exposure. The rate of biliary excretion in humans is unknown [2, 6].

Sources and route of human exposure

Lead is a naturally occurring element in the earth's crust, mostly as the sulphide galena. Much of the lead emitted into the atmosphere is in the form of inorganic salts. In addition, combustion of leaded petrol yields predominantly inorganic forms of lead. Hence this report focuses on inorganic lead.

The main route of systemic exposure is predominantly via ingestion or inhalation. Exposure to inorganic lead occurs primarily through ingestion of food and drinking water, although exposure via soil and dust, air, and chipped leaded paint chips significantly contributes to the overall exposure [2-4].

The widespread occurrence of lead in the environment is primarily a result of anthropogenic activities. With the decline in combustion of leaded fuel and the phasing out of lead in pipes and paints, industrial emissions from mining, smelting or recycling are the predominant source of environmental lead [7, 8].

Lead in water may result from industrial sources, but urban runoff significantly contributes to the total burden. Depending on the pH of drinking water, temperature and residence time, lead may be leached from water systems such as from lead solder used for copper pipes as well as from old lead pipes, although this is less frequent due to the upgrading of water pipework [7].

Solid wastes such as ammunition, sewage sludge, leaded paints as well as industrial sources all contribute to the levels of lead found in soil. Measurement of soil samples in England and Wales was carried out and showed lead concentrations of between 3 and 16388 mg kg⁻¹ with a median of 40 mg kg⁻¹ [7].

Flaking, chipped or powdering leaded paint may be a major source of lead exposure in young children. Concentrations of up to 1-5 mg cm⁻² have been reported in chips of lead-based paint. Exposure to lead from paint is usually confined to areas in the immediate vicinity of painted surfaces, and incautious removal of the paint can result in high localised concentrations of lead in indoor air [5]. Domestic sources include the contamination of food and drink from contact with utensils such as earth-glazed pottery or the use of herbal based remedies [1].

Occupational exposure to lead and inorganic lead compounds may occur in a variety of occupations, including steel welding and spray coating, battery manufacturing or recycling, radiator repair shops, plumbing and paint removal associated with building renovation. The Occupational Safety and Health Administration identified over 120 occupations in which workers may be exposed to lead [1].

Health Effects of Acute / Single Exposure

Human Data

General toxicity

The systemic uptake of lead from different sources (air, water, soil, food) contributes to the total body burden of lead. Blood lead (PbB) concentrations are used as a measure of exposure, therefore, effects of lead are not described in terms of route of exposure but rather PbB concentrations [5].

Lead is classically a chronic or cumulative toxin. Few adverse health effects are observed following an acute exposure to relatively low levels [1]. If high enough exposure occurs then the primary symptoms of acute effects include GI disturbances such as anorexia, nausea, vomiting and abdominal pain. Malaise, convulsion, coma, encephalopathy, hepatic and renal damage and hypertension have also been reported [2, 3].

Haematotoxicity

Few haematological effects have been reported following acute lead exposure [6].

Neurotoxicity

In children, the most frequent neurotoxicological effect observed following acute exposure is encephalopathy, which occurs at PbB concentrations exceeding $300 \mu\text{g dL}^{-1}$ although more subtle effects have been reported at $100 \mu\text{g dL}^{-1}$ [1, 9]. Children with acute exposure to lead giving PbB concentrations of $45\text{--}50 \mu\text{g dL}^{-1}$ did not show any deficits in IQ compared to controls [6].

Renal toxicity

Acute exposure to lead may lead to acute nephropathy during early stages of exposure, especially in children. Acute nephropathy is characterised by cytomegaly in proximal tubular epithelial cells and is manifested as aminoaciduria, hypophosphataemia and glycosuria. Morphological changes include the formation of nuclear inclusion bodies, mitochondrial changes and dysfunction of proximal tubules. Most effects are largely reversible [1, 6]. Effects on renal function have been observed at PbB concentrations of $40 \mu\text{g dL}^{-1}$ [1]. Acute interstitial nephritis has also been reported at PbB concentrations of $40\text{--}80 \mu\text{g dL}^{-1}$ [4, 9].

Cardiovascular toxicity

Acute exposure to lead leading to PbB concentrations of $48\text{--}120 \mu\text{g dL}^{-1}$ has been reported to cause hypertension [1-3].

Gastrointestinal toxicity

Following acute lead exposure, gastrointestinal symptoms such as abdominal cramps, diarrhoea with black stools, vomiting and anorexia are most commonly observed in adults at PbB concentrations of 100 – 400 $\mu\text{g dL}^{-1}$ although effects have been observed at concentrations as low as 40 – 60 $\mu\text{g dL}^{-1}$ [1-3, 5]. In children, gastrointestinal disturbances including abdominal pain, constipation, cramps, nausea, vomiting, anorexia and weight loss occur at PbB of 60 - 100 $\mu\text{g dL}^{-1}$ [2, 5].

Hepatotoxicity

Hepatic damage has been reported following acute exposure to lead although PbB concentrations at which this occurs were not stated [2, 3, 9]. The effects of lead on haem synthesis may alter function capacity of hepatic cytochrome P450 enzymes. In children with a urinary excretion of 500 μg per 24 hours, acute exposure to lead has been reported to inhibit hepatic cytochrome P450 enzymes [4, 6].

Delayed effects following an acute exposure

Following an acute exposure, lead-induced encephalopathy may take up to several weeks to occur and includes symptoms such as irritability, poor attention span, memory loss, headache, muscular tremor, ataxia, convulsions, hallucinations, drowsiness, malaise, coma, seizures and death [1, 9].

Health Effects of Chronic / Repeated Exposure

Human Data

Haematotoxicity

Lead exposure may lead to anaemia, due to reduced haemoglobin production and shortened life-span of erythrocytes. Reduced haemoglobin synthesis has occurred in adults and children at PbB of $50 \mu\text{g dL}^{-1}$ or $40 \mu\text{g dL}^{-1}$, respectively [4-6] although inhibition of haemoglobin sufficient to cause clinically observable anaemia has been reported following exposure to $80 - 100 \mu\text{g dL}^{-1}$ lead [1, 3]. Basophilic stippling commonly occurs in erythrocytes due to the aggregation of ribonucleic acid [3].

Lead has a significant effect on haemoglobin synthesis as it inhibits δ -aminolevulinic acid dehydrogenase (ALAD) thereby decreasing haem synthesis, which leads to an increase in δ -aminolevulinic acid synthase. The activity of ALAD may be inhibited at PbB concentrations as low as $3 - 34 \mu\text{g dL}^{-1}$ with no threshold yet apparent. The activity has been reported to inversely correlate with PbB concentrations over the whole dose range [5, 8].

Neurotoxicity

Chronic lead exposure may lead to fatigue, sleep disturbance, headache, irritability, lethargy, slurred speech and convulsions at PbB concentrations of $40 - 120 \mu\text{g dL}^{-1}$ [3]. Muscle weakness, ataxia, tremors and paralysis may also occur [9]. Afferent nerves are not affected hence there is no loss of sensation or pain [3].

Neurobehavioural effects may be observed in lead workers with PbB concentrations of $40 - 80 \mu\text{g dL}^{-1}$, including disturbances in reaction time, visual motor performances, hand dexterity, IQ and cognitive performance, anxiety and mood [1, 6].

Several studies have been carried out to investigate the correlation of behaviour and intelligence with lead exposure in children. Overall, most studies reported an inverse association with PbB and IQ in children, deficits being noted with a PbB concentration of $10 \mu\text{g dL}^{-1}$ and above although the lowest PbB concentration reported to cause such an effect was $5.6 \mu\text{g dL}^{-1}$ [2, 7]. Epidemiological studies suggest that an increase in PbB concentration from 10 to $20 \mu\text{g dL}^{-1}$ is associated with a deficit of 2 IQ points [10]. Children with chronically elevated PbB concentrations of $40 - 60 \mu\text{g dL}^{-1}$ commonly show signs of pallor, pica and irritability [2]. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that it was not possible to establish a threshold for the effect of lead [11].

Renal toxicity

Chronic exposure to lead leading to PbB concentration of $50 - 200 \mu\text{g dL}^{-1}$ may cause chronic nephropathy, characterised as a reduction in glomerular filtration rate, sparse nuclear inclusion bodies and irreversible atrophy of the proximal and distal tubules [5]. Proximal renal tubular dysfunction results in albinuria, aminoaciduria, glycosuria, phosphaturia and renal tubular acidosis [1, 6, 9]. Mortality following chronic nephropathy may occur at PbB concentrations exceeding $60 \mu\text{g dL}^{-1}$ [1].

Cardiovascular toxicity

Meta-analyses of epidemiological data have found a persistent trend in the data that supports a significant, albeit weak, association between PbB and blood pressure. The elevation in blood pressure was more pronounced in middle age rather than in the young [8].

Chronic occupational exposure to lead ($> 30 \mu\text{g dL}^{-1}$) has been reported to cause an elevation in systolic blood pressure, although other studies failed to reveal any significant differences. Diastolic pressures were unaffected by exposure to lead in some studies but others showed an increase in diastolic pressure in workers with PbB concentrations of $50 \mu\text{g dL}^{-1}$ [1, 6]. Reports noted that an increase in PbB concentration of $10 \mu\text{g dL}^{-1}$ produced a systolic increase of 5 mm Hg, whereas others showed that for every doubling of PbB concentration the systolic pressure increases by 1.5 – 3.0 mm Hg or 1.0 – 2.0 mm Hg in males and females, respectively [5].

Gastrointestinal toxicity

Following chronic lead exposure, nausea, vomiting, anorexia, constipation and abdominal cramps have been observed in workers with PbB concentrations of $100 - 400 \mu\text{g dL}^{-1}$ although effects have been observed at concentrations as low as $40 - 60 \mu\text{g dL}^{-1}$ [1, 3, 5, 6, 8]. Individuals may experience a metallic taste and excessive thirst [3].

Gastrointestinal disturbances also occur in children with a PbB of approximately $60 - 100 \mu\text{g dL}^{-1}$ [8].

Hepatotoxicity

Chronic exposure to lead may cause hepatic damage and mild hepatitis, although few cases have been reported. One individual with a PbB concentration of $203 \mu\text{g dL}^{-1}$ following an occupational exposure showed abnormal liver function tests and mild hepatitis upon autopsy, although few data were available [6].

It has been suggested that the effects of lead on haem synthesis may affect the functional capacity of hepatic cytochrome P450 enzymes to metabolise drugs. In children, decreased enzyme activity may occur with PbB concentrations of $44 \mu\text{g dL}^{-1}$. Few data are available in adults [4].

Reproductive and developmental toxicity

Chronic exposure to lead causes adverse effects on both male and female reproductive functions [5].

Occupational exposure to lead before or during pregnancy resulting in a PbB of $> 20 \mu\text{g dL}^{-1}$ has been associated with spontaneous abortion, late fetal death and stillbirth although one study reported a higher incidence of stillbirths in women with PbB concentrations of $10.6 \mu\text{g dL}^{-1}$ [5]. A decreased length of gestation may occur with PbB concentrations $12 - 23 \mu\text{g dL}^{-1}$ [4]. Low birth weight and reduced post-natal growth have also been reported with PbB concentrations of $10.4 \mu\text{g dL}^{-1}$ [1, 4, 9].

Occupational exposure to lead resulting in PbB concentrations of 40 – 50 $\mu\text{g dL}^{-1}$ may be linked with reduced libido, low semen volume and sperm counts, increased abnormal sperm morphology and decreased sperm motility in males, leading to impairment of reproductive function [1, 4].

The most critical effects of lead toxicity occur in children exposed during fetal and/or postnatal development [1]. In children, encephalopathic symptoms and death may occur at PbB concentrations of 80 – 100 $\mu\text{g dL}^{-1}$ [5]. Overt symptoms of the subencephalopathic central nervous system may occur at PbB concentrations of 40 – 60 $\mu\text{g dL}^{-1}$. Peripheral nerve dysfunction, detected by a reduction of nerve conduction velocity, can occur at PbB concentrations of 30 – 50 $\mu\text{g dL}^{-1}$. Non-overt neurotoxicity, such as cognitive (IQ) decreases, electrophysiological and neurophysiological deficits may occur in children at PbB concentrations of $>10 \mu\text{g dL}^{-1}$, although no clear threshold has been demonstrated [1, 5].

Lead may accumulate in areas that are rapidly growing, and in some cases, hypermineralisation of the radius, tibia and femur can be seen on X-ray. Children with PbB concentrations of 60 - 100 $\mu\text{g dL}^{-1}$ showed squint, foot drop and delayed growth [2].

Genotoxicity

Assessment of genotoxicity of lead in humans has focussed on the evaluation of lymphocytes from occupationally or environmentally exposed individuals as well as *in-vitro* studies using mammalian cells or microorganisms. In addition, chromosome aberrations and sister chromatid exchange, the significance of which is unclear, in lymphocytes taken from healthy individuals has been carried out [6].

Increased frequency in sister chromatid exchanges were seen in workers with PbB concentrations of 80 $\mu\text{g dL}^{-1}$ although no change in frequency of sister chromatid exchanges was seen in workers with PbB concentrations of 49 $\mu\text{g dL}^{-1}$ or environmentally exposed children with PbB concentrations of 30 – 63 $\mu\text{g dL}^{-1}$ [4].

An increase in chromosomal aberrations was reported in workers with PbB levels ranging from 22 - 89 $\mu\text{g dL}^{-1}$ although other studies reported that occupationally exposed workers with a PbB of 38 - 120 $\mu\text{g dL}^{-1}$ or environmentally exposed children with PbB concentrations of 12 – 33 $\mu\text{g dL}^{-1}$ did not have an increase in frequency of chromosomal aberrations [4, 6].

Carcinogenicity

The standardised mortality ratios for cancers of the respiratory tract, digestive tract and kidney were increased from 1 to 2.5 in workers in lead production and battery plants who had PbB concentrations of 40 – 100 $\mu\text{g dL}^{-1}$ [1]. A follow-up study did not show a significant elevation in death rate due to cancer [5, 6].

An increase in overall cancer incidence and in the incidence of lung cancer was observed in workers with a PbB concentration of 21 $\mu\text{g dL}^{-1}$. A subsequent study of the same cohort showed an increase in nervous system cancer in workers with a PbB concentration of 29 $\mu\text{g dL}^{-1}$ [6].

A meta-analysis of case control and cohort epidemiological studies of battery or smelter industries found a significant excess risk of overall cancer, lung and bladder cancer. No PbB concentrations were given and no corrections for confounders were made due to lack of available data.

In order to evaluate the potential carcinogenicity of lead, the Working Group of the International Agency for Research on Cancer (IARC) considered epidemiological evidence from occupational studies of highly-exposed workers. Cancers of the lung, stomach, kidney, brain and nervous system were evaluated. Based on the available data, the Working Group concluded that there is limited evidence for the carcinogenicity to humans following exposure to inorganic lead compounds [12]. In considering the genetic and related effects of exposure to lead, the Working Group discussed the mechanistic aspects of lead as a potential carcinogen. They concluded that there is little evidence that lead interacts directly with DNA. The genetic effects of lead appear to be mediated in part by the modulation of reactive oxygen species and the interaction with proteins, including those involved in DNA repair. This may result in mutation, cell proliferation and changes in gene expression, all of which may contribute to a carcinogenic response following chronic exposure. The Working Group reached the evaluation that inorganic lead compounds are probably carcinogenic to humans (group 2A) [12].

Animal and In-Vitro Data

Genotoxicity

Pregnant mice exposed to lead nitrate ($12.5 - 75 \text{ mg kg}^{-1}$) on the 9th day of gestation showed chromosomal aberrations in the form of deletions at all doses administered in both maternal and fetal cells, indicating that prenatal exposure to lead may induce genotoxic changes in the fetus [6]. There was no treatment effect on sister chromatid exchange in lymphocytes or number of micronuclei in bone marrow erythrocytes obtained from rabbits treated with up to 0.5 mg lead acetate. Monkeys orally exposed to 1 or 5 mg lead showed an increase in chromosomal aberrations, although statistical significance was not reached. Other studies showed that only animals receiving a calcium deficient diet showed several chromosome aberrations [6].

Lead chloride was shown to be mutagenic in *Salmonella typhimurium* TA102 without S9 activation, but was non-mutagenic in three other strains with and without metabolic activation.

Carcinogenicity

The kidney is the primary site for tumour formation in rats and mice. However, at high concentrations tumours in the pituitary gland, adrenal gland, thyroid gland, prostate, lungs and nervous system have also been reported in rodents exposed to lead compounds [5]. The kidney tumours are generally assumed to be produced by a non-genotoxic mechanism and therefore to exhibit a threshold [7].

Carcinogenicity studies have been carried out in rodents with lead acetate, lead subacetate and lead phosphate. Renal tumours were observed in both female and male rats, a greater incidence occurring in male rats, at concentrations of lead exceeding 10 mg kg^{-1} per day [1]. Animal data led the Working Group of IARC to conclude that there is sufficient evidence for the carcinogenicity in experimental animals following exposure to inorganic lead compounds [12, 13].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.