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
- In adults, approximately 5-15% of ingested lead is absorbed and, in children, absorption may be as high as 40%
- Absorbed lead is distributed by blood to bone, teeth and soft tissues
- The unabsorbed lead is eliminated through the faeces. Absorbed lead is mainly excreted in the urine

**Health effects of acute exposure**
- Lead is described as a chronic toxin
- It is uncommon to see cases of acute toxicity
- Symptoms of acute lead toxicity include GI disturbances, dullness, restlessness, irritability, poor attention span, headaches, hepatic and renal damage, hypertension, hallucinations, and encephalopathy

**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
- Chronic lead exposure also causes cardiovascular and renal toxicity. In children, lead exposure may lead to cognitive deficits, such as a decrease in IQ. No threshold has been identified for these effects
- Chronic exposure to lead can cause adverse effects on both male and female reproductive functions.
- Inorganic lead compounds are classified as probably carcinogenic to humans (group 2A) by IARC

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Summary of health effects

Lead is described as a chronic toxin. It is uncommon to see acute cases of lead toxicity. Effects observed following acute exposure to high levels of lead include GI disturbances, dullness, restlessness, irritability, poor attention span, headaches, hepatic and renal damage, hypertension, hallucinations, and encephalopathy.

Chronic lead exposure may cause anaemia, basophilic stippling and decreased haemoglobin synthesis. Neurological effects have also been observed such as fatigue, sleep disturbance, headache, irritability, lethargy, slurred speech, convulsions, muscle weakness, ataxia, tremors and paralysis. Studies in children have reported neurobehavioral effects in children at a blood lead (PbB) level of <10 µg dL⁻¹. There appears to be no clear threshold for the neurodevelopmental effects in children.

Cardiovascular and/or renal toxicity may also arise following chronic lead exposure. Hepatic damage has been reported only in a few cases following occupational exposure to lead. Gastrointestinal disturbances such as nausea, vomiting, anorexia, constipation, abdominal cramps have also been observed in workers.

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

Occupational exposure to lead has been reported to cause an increase in sister chromatid exchange and chromosomal aberrations. However, the studies often involved co-exposure to lead and other compounds.

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).
**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 [1].

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 [2].

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 [1]. Approximately 35 – 50 % of inhaled lead of particle size less than 1 \( \mu m \) is deposited in the lower respiratory tract, primarily in the alveolar tract, and 50 – 70 % of an inhaled dose is absorbed [1, 3-4]. Higher deposition rates may occur with larger particles but this occurs in the upper respiratory tract and absorption occurs via the ingestion route. Smaller particles of lead, such as those generated in exhaust fumes, are almost completely (>90 %) absorbed [1].

Gastrointestinal absorption of lead is affected by physicochemical characteristics of the lead particles and by physiological factors including age, fasting, nutritional calcium and iron status and pregnancy [5]. 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. 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 % [3-4]. Low levels of calcium, iron, copper, zinc, selenium or phosphate in the diet can increase lead absorption [1, 4-5].

Dermal absorption of inorganic lead compounds is generally quite low [1]. The absorption of lead through the skin during the normal use of lead containing products has been estimated to be 0.06% [5]. 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 [4].

The route of absorption has little effect on the distribution of lead [1]. Lead is transported primarily in the red blood cells bound to plasma proteins [5]. Absorbed lead is distributed by blood to mineralising systems (bone, teeth) and soft tissues (e.g. liver). The half life of lead in blood, soft tissue and bone is approximately 36 days, 40 days and 27 years, respectively [1].

Bone accumulates lead throughout most of the human life span but, at the same time, lead is mobilised from bone by remodelling [1]. In adults, approximately 90% of the total body burden of lead found in bone. However, in children, only 70% of the body burden is found in the bones, but the concentration increases with age [5]. 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 [4].

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 blood compartment is of importance in pregnant women and nursing mothers. Lead is readily transferred via the placenta from the mother to the developing fetus during pregnancy and accumulates in fetal bone. The concentration of lead in cord blood may be 85 – 90 % that of maternal blood, hence posing a potential risk to the fetus [1].
The metabolism of inorganic lead mainly consists of reversible ligand reactions including the formation of complexes with amino acids and non-protein thiols and binding to various proteins. Organic lead compounds are metabolised to inorganic lead [6].

Any unabsorbed lead, either ingested or swallowed airborne lead, is excreted in faeces. Absorbed lead is primarily excreted in the urine (75–80%) and faeces (15%), including by biliary secretion, independent of the route of exposure [2, 7]. Sweat, saliva, hair and nails and breast milk are minor routes of excretion [2].

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 routes of systemic exposure are 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 significantly contributes to the overall exposure [1, 3-4].

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 [2, 5]. In 2009, the background lead concentration in air was <10 ng m$^{-3}$ for most of the UK. Higher levels were detected in urban areas, particularly in industrial areas [8].

Lead in water may result from industrial sources, but urban runoff and atmospheric deposition significantly contribute to the total burden [5]. Depending on the pH of drinking water, temperature, water hardness and standing time of the water, lead may be leached from water systems containing lead in pipes, solder, fittings or service connections [9].

Solid wastes such as ammunition, sewage sludge, leaded paints and industrial sources all contribute to the levels of lead found in soil [1]. Industrial sectors that heavily contribute to the release of lead include metal mining, coal mining and electrical facilities [5]. Soil and household dust are important sources of lead exposure for infants and young children, due to hand to mouth activities [5, 9]. It has been estimated that an average child may ingest up to 100 mg soil day$^{-1}$ [5].

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 [10]. Domestic sources include the contamination of food and drink from contact with utensils such as earth-glazed pottery or the use of traditional remedies [11].

Occupational exposure to lead and inorganic lead compounds may occur in a variety of occupations, including lead smelting and refining, steel welding or cutting operations, battery manufacturing or recycling, radiator repair shops, construction and other occupations involving flame soldering of lead solder. The US National Institute for Occupational Safety
and Health (NIOSH) identified over 100 occupations in which workers may be exposed to inorganic lead compounds [2].
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 [10].

Lead is described as a classic chronic toxin [6]. Few adverse health effects are observed following acute exposure to relatively low levels. Effects observed following acute exposure to high levels of lead include GI disturbances, dullness, restlessness, irritability, poor attention span, headaches, hepatic and renal damage, hypertension, hallucinations, and encephalopathy [3-4, 9].

Neurotoxicity

In children, the most frequent neurotoxicological effect observed following acute exposure is encephalopathy, which is likely to occur at PbB concentrations of 80 – 100 µg dL⁻¹ [2, 12]. In adults, encephalopathy may occur at PbB levels of 100 – 120 µg dL⁻¹ [9]. Symptoms of lead induced encephalopathy include irritability, agitation, poor attention span, headache, confusion, ataxia, drowsiness, convulsions and coma [7, 12].

Renal toxicity

Acute exposure to lead can cause proximal renal tubular dysfunction with proteinuria, aminoaciduria, glycosuria, renal tubular acidosis and cellular casts [7, 12]. Most effects are largely reversible [7]. Prominent inclusion bodies are visible in the cells of the proximal tubules at PbB concentrations of 40 – 80 µg dL⁻¹ [9]. This form of acute renal impairment is generally reversible [7].

Acute interstitial nephritis has also been reported at PbB concentrations of 40 – 80 µg dL⁻¹ [1].

Cardiovascular toxicity

Acute exposure to lead leading to PbB concentrations of 48 – 120 µg dL⁻¹ has been reported to cause hypertension [3-4].

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 µg dL⁻¹ although effects have been observed at concentrations as low as 40 – 60 µg dL⁻¹ [2, 4, 10]. In children, gastrointestinal disturbances
including abdominal pain, constipation, cramps, nausea, vomiting, anorexia and weight loss occur at PbB of 60 - 100 µg dL⁻¹ [2, 4, 10].

**Hepatotoxicity**

Hepatic damage has been reported following acute exposure to lead although PbB concentrations at which this occurs were not stated [3-4, 7]. The effects of lead on haem synthesis may alter functional 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 [1-2].
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 µg dL\(^{-1}\) and 40 µg dL\(^{-1}\), respectively [1-2, 10].

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 µg dL\(^{-1}\) with no threshold yet apparent. The activity has been reported to inversely correlate with PbB concentrations over the whole dose range [2, 10].

Other reported haematological effects include coarse basophilic stippling, anisocytosis, poikilocytosis, nucleated erythrocytes and polychromasia or achromasia [7].

**Neurotoxicity**

Chronic lead exposure may lead to dizziness, fatigue, sleep disturbance, headache, irritability, lethargy, malaise, slurred speech and convulsions at PbB concentrations of 40 – 120 µg dL\(^{-1}\)[2]. Muscle weakness, paraesthesia, ataxia, tremors and paralysis may also occur [2, 7].

Neurobehavioural effects may be observed in lead workers with PbB concentrations of 40 - 80 µg dL\(^{-1}\), including disturbances in reaction time, visual motor performances, hand dexterity, IQ and cognitive performance, anxiety and mood [2, 11].

Several studies have been carried out to investigate the correlation between behaviour and intelligence and lead exposure in children. Overall, most studies reported an inverse association between PbB and IQ in children. Exposures that correspond to a PbB as low as 2 µg dL\(^{-1}\) have been reported to cause developmental lead neurotoxicity [5].

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that it was not possible identify a threshold for the association between lead exposure and decrements in IQ [13].

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) also concluded that it was not possible to establish a threshold for the neurological effects of lead in children. The Committee carried out a dose response analysis and reported that a lead exposure level of 0.3 µg kg\(^{-1}\) bw day\(^{-1}\) was calculated to be associated with a population decrease of 0.5 IQ points. A lead exposure level of 1.9 µg kg\(^{-1}\) bw day\(^{-1}\) was calculated to be associated with a population decrease of 3 IQ points, the Committee deemed this to be of concern [14].

The European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM) also concluded that there is no evidence for a threshold for lead-induced developmental neurotoxicity in young children. The Panel reported that an estimated intake of 0.5 µg kg\(^{-1}\) bw day\(^{-1}\) was associated with decrease in IQ of 1 point on the full scale IQ
score. The panel concluded that such a change could have significant consequences for human health on a population basis [5].

**Renal toxicity**

Chronic exposure to lead may cause lead nephrotoxicity characterised by glomerular sclerosis, interstitial fibrosis and proximal tubular nephropathy [2]. Depressed glomerular filtration rate has been observed in association with exposures resulting in average PbB levels <20 µg dL\(^{-1}\) [2, 5]. Enzymuria and proteinuria are generally observed at PbB >30 µg dL\(^{-1}\) and severe deficits in renal function and pathological changes are associated with PbBs >50 µg dL\(^{-1}\) [2]. Mortality following chronic nephropathy may occur at PbB concentrations exceeding 60 µg dL\(^{-1}\) [11].

The EFSA CONTAM Panel concluded that there is no evidence for a threshold for lead-induced nephrotoxicity in adults. The Panel reported that an estimated lead intake of 0.63 µg kg\(^{-1}\) bw day\(^{-1}\) was associated with a 10% change in prevalence of chronic kidney disease and concluded that such a change could have significant consequences for human health on a population basis [5].

**Cardiovascular toxicity**

Lead exposure has been associated with changes in cardiac conduction and rhythm. The effects reported include increased QT and QRS interval and ventricular arrhythmias [7].

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 association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of PbB, without any identifiable threshold [2, 5]. The lead contribution to elevated blood pressure appears to be more pronounced in middle age than at younger ages [2].

JECFA concluded that it was not possible to establish a threshold for cardiovascular effects in adults (critical endpoint being increase in systolic blood pressure). The Committee carried out dose response analysis and reported that a lead exposure level of 3.0 µg kg\(^{-1}\) bw day\(^{-1}\) would be expected to cause a population increase of approximately 2 mmHg in systolic blood pressure. An increase on this scale has been associated with moderate increases in risk of ischaemic heart disease and cerebrovascular stroke. The Committee considered this to be of some concern, but less so than the neurodevelopmental effects observed in children [14].

The EFSA CONTAM Panel concluded that there is no evidence for a threshold for lead-induced cardiovascular effects in adults. The Panel reported that an estimated lead intake of 1.50 µg kg\(^{-1}\) bw day\(^{-1}\) was associated with a 1% change in systolic blood pressure, which corresponds to a 1.2mmHg from the baseline value of 120mmHg in a normotensive adult. The panel concluded that such a change could have significant consequences for human health on a population basis [5].

**Gastrointestinal toxicity**

Following chronic lead exposure, nausea, vomiting, anorexia, constipation and abdominal cramps have been observed in workers with PbB concentrations of 100 – 200 µg dL\(^{-1}\)
although effects have been observed at concentrations as low as 40 – 60 μg dL⁻¹ [2, 10]. Individuals may also experience a metallic taste [7].

Gastrointestinal disturbances also occur in children with a PbB of approximately 60 – 100 μg dL⁻¹ [2].

**Hepatotoxicity**

Chronic exposure to lead may cause hepatic damage and mild hepatitis, although few cases have been reported [10].

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 μg dL⁻¹. Few data are available in adults [1].

**Reproductive and developmental toxicity**

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

Occupational maternal exposure to lead resulting in PbB of ≥10 μg dL⁻¹ is associated with an increased risk of spontaneous abortion, preterm delivery and low birth weight. There is evidence to suggest that the risk of spontaneous abortion may be increased at lower PbB concentrations. In one study, the risk of spontaneous abortion doubled at maternal PbB levels of 5 – 9 μg dL⁻¹ [6, 15].

Occupational exposure to lead resulting in PbB concentrations of > 40 μg 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 [1-2].

It has been reported that fertility may be reduced in couples during periods when the male has a PbB level > 40 μg dL⁻¹ or a blood lead level > 25 μg dL⁻¹ for several years. Number of live births, likelihood of conception and time to pregnancy were considered when assessing fertility [6].

The most critical effects of lead toxicity occur in children exposed during fetal and/or postnatal development [11]. Evidence from numerous studies suggests that the higher the maternal concentration of lead, the greater the risk adverse neurodevelopmental effects in the child. Significant reductions in intellectual function have been reported in the offspring of mothers with PbB levels of < 10 μg dL⁻¹ [15].

In children, encephalopathic symptoms and death may occur at PbB concentrations ≥100 μg dL⁻¹ [12]. Overt symptoms of the subencephalopathic central nervous system may occur at PbB concentrations of 40 – 60 μg dL⁻¹. Peripheral nerve dysfunction, detected by a reduction of nerve conduction velocity, can occur at PbB concentrations of 30 – 50 μg dL⁻¹ [10-11]. Recent studies have reported neurobehavioral deficits in children with PbB concentrations of < 10 μg dL⁻¹ [2, 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 - 100µg dL⁻¹ showed squint, foot drop and delayed growth [4].

**Genotoxicity**

Evidence of genotoxicity (including chromosomal aberrations, induction of micronuclei and sister chromatid exchanges in peripheral blood cells) has been reported in individuals occupationally exposed to lead [1-2, 16]. However, the studies often involved co-exposure to lead and other compounds. Therefore it is not possible to attribute the genotoxic effects to lead alone [16].

**Carcinogenicity**

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 [16]. 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 if exposure is sustained.

The Working Group reached the evaluation that inorganic lead compounds are probably carcinogenic to humans (group 2A) [16].
Animal and In-Vitro Data

Genotoxicity

Pregnant mice exposed to lead nitrate (12.5 – 75 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 [16]. Lead chloride did not have an effect in the dominant lethal assay in mice exposed via the drinking water [5].

Lead chloride was not mutagenic in bacterial test systems. However lead chromate and lead bromide were mutagenic in *E.coli* and *Salmonella typhimurium*. The mutagenic activity of these lead compounds appeared to be due to the anions [16].

Micronucleus induction has been reported in *in vitro* test systems at low lead concentrations. Tests for sister chromatid exchange have produced variable results [16].

Carcinogenicity

IARC concluded there is sufficient evidence in experimental animals for the carcinogenicity of inorganic lead compounds [16].

Extensive evidence from carcinogenicity studies demonstrates that various water-soluble and insoluble lead compounds can induce kidney tumours in rodents. Tumours in the pituitary gland, adrenal gland, thyroid gland, prostate, lungs and brain have also been reported in rodents exposed to lead compounds [16].
References


2. Agency for Toxic Substances and Disease Registry (ATSDR), Toxicological Profile for Lead. 2007
   US Department of Health and Human Services: Atlanta, US.


