Public Health England

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Lead

Toxicological Overview

Key Points

Kinetics and metabolism

- ingestion is the main route of exposure to lead for the general public, while inhalation is a major route of exposure in an occupational setting
- between 30-50% of inhaled lead is deposited in the lungs, with smaller particles having higher deposition and absorption rates
- in adults, 5-15% of ingested lead is absorbed and up to 45% in fasting conditions; the proportion may be as high as 53% in children
- dermal absorption is generally quite low
- absorbed lead is distributed by blood to soft tissues and the bone where it accumulates

Health effects of acute exposure

- the effects of lead are typically observed following lower level chronic exposure
- very high acute doses may result in GI disturbances, encephalitis and other effects on the central nervous system, on renal function and the haematological system

Health effects of chronic exposure

- developmental neurotoxicity, elevation of blood pressure and nephrotoxicity are considered to be the most sensitive lead toxicity endpoints, having no apparent threshold
- inorganic lead compounds are classified as probably carcinogenic to humans (IARC group 2A)
- lead is detrimental to male and female fertility and exposure during pregnancy is associated with an increased risk of various adverse birth outcomes

PHE publications gateway number: 2014790
Published: October 2017

Summary of Health Effects

Lead is described as a chronic toxicant. Following acute exposure to high levels of lead effects on the gastrointestinal (GI) system, nervous system, haematopoietic system and on renal function are observed. Colic is a common early sign, with encephalopathy being characteristic of very high level exposure; children are more sensitive to these effects.

Neurological effects have also been observed such as reduced nerve conduction velocity, postural sway, tremor, amyotrophic lateral sclerosis, and intelligence and neurobehavioral effects in children and adults. The developing brain and nervous system appears to be more vulnerable as to the effects of lead, with exposures that correspond to BLL as low as 2 µg/dL having been reported to cause developmental neurotoxicity. A dose-dependent association between IQ and BLL in children has been observed with no threshold.

Chronic lead exposure may cause anaemia due to reduced haemoglobin production and a shortened life-span of erythrocytes. It may also cause nephrotoxicity, from depressed glomerular filtration rate to severe deficits in renal function. There is no evidence for a threshold for these effects. Similarly lead causes cardiovascular toxicity with no apparent threshold, the critical endpoint being increased systolic blood pressure. These endpoints are considered the most sensitive in adults.

Chronic exposure to lead may cause adverse effects on both male and female reproductive functions. Studies of men exposed occupationally to lead have shown a reduction in semen volume, sperm count, sperm motility and an increase in abnormal sperm morphology. Chronic exposure to lead during pregnancy has been associated with adverse outcomes including spontaneous abortion, premature birth, fetal growth restriction, neurodevelopmental delay and maternal hypertension.

Lead has shown variable results for genotoxicity in-vitro and following in-vivo animal studies. Some evidence for genotoxicity comes from workers exposed occupationally, however these studies often involve co-exposures. The IARC have suggested lead does not interact directly with DNA but may have an indirect effect. Based on epidemiological and experimental data, the Working Group concluded that inorganic lead compounds are probably carcinogenic to humans (IARC group 2A).

Kinetics and Metabolism

Absorption of lead depends on the physical and chemical state of the metal and is influenced by a person's age, physiological status, nutritional status and genetic factors [1].

Following inhalation, deposition of lead within the respiratory tract and its subsequent absorption are determined by ventilatory rate, particle size and solubility [2, 3]. Deposition in adults has been estimated at between 30-50% of inhaled lead. Particles smaller than 1 µm have been shown to have greater deposition and absorption rates than larger particles as they are able to reach the lower respiratory tract where absorption appears to be complete [2]. Larger particles (i.e. over 5 µm) are deposited in the trachea and bronchi. From there they may be cleared from the respiratory tract by mucociliary transport and subsequently ingested, leading to potential absorption from the gastrointestinal (GI) tract [3].

GI absorption of lead is affected by the physicochemical characteristics of the ingested lead particles and by other factors including age, fasting status, diet and pregnancy [3, 4]. Lead competes with calcium for binding proteins involved with GI absorption as they have a similar ionic size. Certain groups such as nursing mothers and children are more efficient at absorbing calcium than other populations; it has been hypothesised that this is why these groups also take up lead more efficiently (especially where there is a calcium deficiency) [4]. Low levels of iron, copper, zinc, selenium or phosphate in the diet can also increase lead absorption [1, 2, 5]. In adults, approximately 5-15 % of ingested lead is absorbed in the gut, which may rise as high as 45% under fasting conditions. In children and infants, absorption may be as high as 53% [6].

Dermal absorption of inorganic lead compounds is generally quite low [1]. Skin absorption of lead during the normal use of lead containing products has been estimated to be 0.06% [3]. One study reported increased lead levels in saliva and sweat following dermal exposure to inorganic lead, although blood and 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 [5].

The route of absorption has little effect on the distribution of lead throughout the body [1]. Following absorption lead is mainly transported in blood, bound to erythrocyte proteins. It is distributed to soft tissues (e.g. liver, kidneys) and bone, where it accumulates with time. In adults approximately 90% of the lead body burden is in the bone, while in children it is approximately 70% (blood accounts for around 5% of the body burden) [3]. The half-life of lead in the blood and soft tissue, and bone are 20-40 days and 10-30 years respectively [2, 3]. Lead is deposited in the bone in the form of insoluble lead phosphate, in areas that are rapidly growing, such as the radius, tibia and femur. Characteristic 'lead lines' may be seen on X-ray images, with their width related to the duration of exposure [5]. There is constant low-level interchange of lead between the tissues, however conditions causing bone resorption or increased calcium demand (particularly pregnancy, lactation, menopause and osteoporosis) may cause increased mobilisation of lead from the bone. This can result in a rise in Blood Lead Levels (BLLs) after the original exposure has ceased [7].

In pregnant women with elevated body burdens, BLLs gradually rise from the middle of the second trimester until delivery. Lead has been shown to cross the placenta from as early as 12 weeks (although there is no evidence that it does not do so before) and accumulates in fetal bone [8]. The concentration of lead in the cord blood may be 85-90% of the level in maternal blood, hence posing a potential risk to the fetus [1].

Lead is readily transferred into maternal milk during breast feeding; data suggest that women with higher bone lead burdens will redistribute more lead to blood and milk than those with lower lead burdens [4]. However, maternal milk has been estimated to be a minor source of exposure for infants [7].

The metabolism of inorganic lead mainly consists of binding to various proteins and reversible ligand reactions including the formation of complexes with amino acids and non-protein thiols. Organic lead compounds are metabolised to inorganic lead [2].

Lead is primarily excreted in the urine, while approximately a third is excreted in the faeces. Sweat, saliva, hair and nails, and breast milk are minor routes of excretion [7].

Sources and route of human exposure

Lead is a naturally occurring element in the earth's crust, mostly as lead (II) sulphide (galena). Much of the lead emitted into the atmosphere is in the form of inorganic salts. Hence this report focuses on inorganic lead. For 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 of lead are the same regardless of the route of exposure [9].

While lead is naturally present in the earth's crust, it has been widely distributed throughout the environment in soil, air and water by anthropogenic activities. UK Lead emissions to air have greatly declined in recent years; between 1990 and 2014 emissions dropped by 98%. Prior to 1999 the largest source of lead emissions was from its use as an anti-knock additive in petrol; following the ban of leaded petrol, emissions from transport are now a minor fraction. In 2014 the major sources of lead emissions in the UK were steel production and the industrial combustion of waste oils and solid fuels. With the declining use of coal and the reduction in emissions from metal production, total lead emissions continue to fall [10]. Following release, lead persists in the atmosphere for a relatively short time (days or weeks), however there is the potential for atmospheric transport hundreds, even thousands of kilometres from the source [11].

In the UK, typical annual mean lead concentrations in air for rural and industrial sites have been given as less than 0.005 µg/m^3 and up to 0.09 µg/m^3 respectively [12]. Lead levels in indoor air are usually 0.3-0.8 times lower than in outdoor air [9].

Inhalation may be an important route of exposure for people near point emissions sources of lead; for instance exposure to lead is greater for those living near hazardous waste sites [3,

11]. Additional sources of exposure to lead in air include smoking (mainstream, side stream and environmental tobacco smoke) and exposure in certain occupations [3]. Traces of lead may be found in coal and can be released as the fuel is burnt either domestically or by industry. The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) have stated that for infants and children, the relative contribution of inhalation exposure is negligible [4].

Atmospheric lead may be deposited onto land and into aquatic environments, enriching the natural levels. The content of lead in the top layer of soil may be defined by atmospheric deposition from anthropogenic sources [3]. Modelling data suggests that up to 5% of lead deposited on land within a year in Europe comes from external sources [11]. Previous atmospheric emissions of lead from leaded petrol and industrial emissions are considered to have had the greatest impact on levels of lead in soil. In the industrial sector, metal mining, coal mining and electrical utilities have contributed the most to releases to land. Lead in land is not very mobile and the rate of leaching into groundwater is typically very slow. Some plants may take up lead from their root systems and their consumption may represent a source of exposure [3].

A study by the British Geological Survey to define the normal background concentrations for soil contaminants in England found that lead concentrations throughout the majority of England (94%) were approximately 180 mg/kg, in urbans areas concentrations were 820 mg/kg and in areas of lead mineralisation levels were approximately 2,400 mg/kg. A similar study conducted in Wales determined 230 mg/kg as normal for the majority of the country (86%), 280 mg/kg for lead mineralised areas in Anglesey, North, Central and South Wales, 1,300 mg/kg for the urban areas of Swansea and the catchments of Loughor, Tawe and Neath and 890 mg/kg in the remaining urban areas [13, 14].

Ingestion of soil and dust may be an important source of exposure in infants and young children. Exposure from these sources may occur from direct ingestion or hand to mouth activities. It has been estimated that an average child may ingest up to 100 mg of soil per day [3].

Ingestion is the major route of exposure to lead for the general population. In a recent dietary evaluation the European Food Safety Authority (EFSA) stated that it was the foods consumed in the greatest amount that had the biggest impact on dietary lead exposure; with grains and grain products (16.1%), milk and dairy products (10.4%), non-alcoholic beverages (10.2%) and vegetables and vegetable products (8.4%) being the categories contributing the greatest amount [7]. However, previous survey has suggested that non-dietary sources were likely to be of only minor importance [3, 7]. Lead may be found in food as a result of environmental contamination (e.g. by atmospheric deposition), processing, handling and packaging [2]. Dietary surveys suggest that game shot with lead ammunition may be a significant source of exposure for those who consume it; the UK Food Standards Agency have stated that there is the potential for harmful levels of exposure amongst frequent consumers, though this is likely to be only a very small proportion of the population [15].

Lead may be found in drinking water where historic lead piping, soldering or fittings are present in the home or at service connections. It is rarely present in tap water as a result of its dissolution from natural sources. The ability of lead to leach from water systems is dependent on the pH, temperature, hardness and the standing time of the water with soft acidic water causing the most dissolution [16]. Tap water, as a separate category to non-alcoholic beverages, has been estimated to contribute 6.1% of total dietary lead exposure for the European population [7].

Flaking or chipped leaded paint can be a source of lead exposure in young children who may be exposed via direct ingestion or by hand to mouth activities. Concentrations of up to 1-5 mg/cm^2 have been reported in chips of lead-based paint. Incautious removal of the paint can result in high localised concentrations of lead in indoor air [17]. The sale of lead paint was banned from general sale in the UK from 1992.

Exposure to lead may also arise from imported spices, glazed cookware and some traditional medicines and cosmetics. EU [2].

Lead compounds are currently used as stabilisers in the production of poly vinyl chloride (PVC); exposure from lead stabilised PVC in children and adults may occur following hand-to-mouth behaviour. However only very small quantities of lead are expected to leach from lead stabilised PVC during its service life [18].

Occupational exposure may occur in individuals working with lead metal (e.g. smelting, refining, alloying and casting) or in those working with old lead paint (e.g. removal or burning), waste or scrap, lead-acid batteries, leaded glass, pigments or solders [19]. In the UK an occupational exposure limit of 0.15 mg/m^3 in air and action levels of 25 and 50 µg/dL in the blood for women capable of having children and general employees respectively are enforced to protect workers from the harmful effects of lead [20].

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. BLLs are used as a measure of exposure. Therefore, the effects associated with exposure to lead are described in terms of BLL rather than route of exposure. In this document the term “lead” is used to refer to both elemental lead and lead compounds, unless otherwise specified.

Lead is generally described as a classic chronic toxin. However, higher level acute exposure to lead can have an adverse effect on the gastrointestinal system, nervous system (particularly in children), renal function and haematopoetic system [2]. Table 1 gives a summary of the BLLs at which certain acute effects have been observed.

Table 1: Acute effects and corresponding blood lead levels

BLL (µg/ dL)	**Observed Effects**
40-60	Gastrointestinal symptoms (children)
40-80	Acute interstitial nephritis
48-120	Hypertension
80-100	Encephalopathy (children)
100-120	Encephalopathy (adults)
100-400	Gastrointestinal symptoms (adults)
References [1, 5, 6, 8, 9, 21, 22]	

Colic is a common early sign of acute lead poisoning, effects include abdominal pain, constipation, nausea, vomiting and anorexia [4, 17].

Very high level exposures can result in encephalopathy in both children and adults. Symptoms of lead induced encephalopathy include headache, confusion, drowsiness,

convulsions and coma. Encephalopathy is more common in children, and is more likely to occur at BLLs over 100 µg/ dL [22].

Changes in hepatic function have been reported following acute exposure to lead, although the BLL at which these effects were observed were not stated [5, 23]. The effects of lead on haem synthesis may alter functional capacity of hepatic cytochrome P450 enzymes. In children with a urinary lead excretion of 500 µg per 24 hours, acute exposure to lead has been reported to inhibit hepatic cytochrome P450 enzymes [1, 9].

Acute exposure to lead can cause proximal renal tubular dysfunction with phosphaturia, aminoaciduria, glycosuria, and renal tubular acidosis [22].

Health Effects of Chronic/Repeated Exposure

Human data

Heamatotoxicity

Since the ban in the use of leaded petrol, average blood lead levels have reduced [24].

Lead exposure may lead to anaemia, due to reduced haemoglobin production and a shortened life-span of erythrocytes. Reduced haemoglobin synthesis has been observed in adults and children at a BLL of 50 µg/dL and 40 µg/dL, respectively [1, 9, 17].

Lead has a significant effect on haemoglobin synthesis as it inhibits δ-aminolevulinic acid dehydrogenase (ALAD), which leads to an increase in δ-aminolevulinic acid synthase. The activity of ALAD may be inhibited at BLLs as low as 3-34 µg/dL with no threshold yet apparent. This effect has been reported to inversely correlate with BLLs over the whole dose range [9, 17]. Other reported haematological effects include basophilic stippling and reticulocytosis [9]. Inhibiton of δ-aminolevulinic acid synthase could also be responsible for liver toxicity.

Hepatotoxicity

There is limited evidence on the effects of chronic exposure to lead on the liver. 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 [1].

Neurotoxicity

Chronic exposure to lead has been associated with a number of effects on the nervous system; notable studied endpoints include reduced nerve conduction velocity, postural sway, tremor, amyotrophic lateral sclerosis, and intelligence and neurobehavioral effects in children and adults [2]. The developing brain appears to be more vulnerable to the effects of lead. Features of neurotoxicity have been observed at lower BLLs in children than adults [4].

Chronic lead exposure may lead to dizziness, fatigue, sleep disturbance, headache, irritability, lethargy, malaise, slurred speech and convulsions at a BLL of 40-120 µg/dL. Muscle weakness, paraesthesia, ataxia, tremors and paralysis may also occur [9].

Neurobehavioral effects have been observed in lead workers with BLLs of 40-80 µg/dL, including disturbances in reaction time, visual motor performances, hand dexterity, IQ and cognitive performance, anxiety and mood [9].

Several studies have been carried out to investigate the correlation between lead exposure in children and behaviour and intelligence. Overall, most studies reported an inverse association between BLL and IQ in children. Exposures that correspond to a BLL as low as 2 µg/dL have been reported to cause developmental lead neurotoxicity [3].

The COT concluded that it was not possible to identify a threshold for the association between lead exposure and decrements in IQ [25].

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 bw/day was calculated to be associated with a population decrease of 0.5 IQ points. A lead exposure level of 1.9 µg/kg bw/day was calculated to be associated with a population decrease of 3 IQ points; the committee deemed this to be of concern [2].

The 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 bw/day 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. [3].

Renal toxicity

Chronic exposure to lead may cause lead nephrotoxicity characterised by glomerular sclerosis, interstitial fibrosis and proximal tubular nephropathy. In humans, a dose-dependent increase in nephrotoxicity has been observed with increasing BLLs. Depressed glomerular filtration has been observed at BLLs below <20 µg/dL, enzymuria and proteinuria are more apparent at levels above 30 µg/ dL and severe deficits in renal function and pathological changes are associated with BLLs greater than 50 µg/dL [9].

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 bw/day was associated with a 10% change in prevalence of chronic kidney disease and concluded that that such a change could have significant consequences for human health on a population basis [3].

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 [9].

Meta-analyses of epidemiological data have found a persistent trend in the data that supports a significant, albeit weak, association between BLL and blood pressure. The association amounts to an increase in systolic blood pressure of approximately 1 mm Hg with each doubling of BLL, without any identifiable threshold [3, 9]. The lead contribution to elevated blood pressure appears to be more pronounced in middle age than at younger ages [9].

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 bw/day would be expected to cause a population increase of approximately 2 mm Hg 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 [2].

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 bw/day was associated with a 1% change in systolic blood pressure, which corresponds to a 1.2 mm Hg from the baseline value of 120 mm Hg in a normotensive adult. The panel concluded that such a change could have significant consequences for human health on a population basis [3].

Some studies have also suggested an association between BLL and maternal hypertension [8]

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, 9, 26]. 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 [26].

In-vitro and in-vivo (animal) studies for genotoxicity (including DNA strand breaks, sister chromatid exchange, micronucleus induction, chromosomal aberration) have yielded variable results [26].

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. 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 [26].

The Working Group reached the evaluation that inorganic lead compounds are probably carcinogenic to humans (group 2A) [26].

The Working Group also concluded that there is sufficient evidence in experimental animals for the carcinogenicity of inorganic lead compounds [26].

Reproductive and developmental toxicity

Studies of men exposed occupationally to lead have shown a reduction in fertility, semen volume and sperm counts, decreased sperm motility and an increase in abnormal sperm morphology (UKTIS). It has been reported that fertility may be reduced in couples during periods when the male has a BLL level over 40 µg/dL or a BLL of over 25 µg/dL for several years. Number of live births, likelihood of conception and time to pregnancy were considered when assessing fertility [2].

Current evidence suggests that chronic exposure to lead during pregnancy is associated with adverse outcomes including spontaneous abortion, premature birth, fetal growth restriction, neurodevelopmental delay and maternal hypertension [2, 8].

A prospective case-control study of 668 women found a dose dependent increase in the risk of spontaneous abortion, with a 5 µg/dL BLL increase resulting in an increased odds ratio (OR) of 1.8. Compared to women with BLLs of 5 µg/dL, ORs were more than double in groups of women with a BLL of 5-9 µg/dL (OR 2.3) and more than 5 times in those with BLLs of 10-14 µg/dL (OR 5.4) [2, 8].

A number of studies have suggested that higher maternal BLLs are associated with increased pre-term births, reduced birthweight and reduced head circumference. One study demonstrated a twofold increased risk for pre-term births in women with a BLL of above 5 µg/dL. Studies have shown elevated lead in placental tissues following pre-term births, leading to the suggestion that lead contributes by causing structural damage to the membranes [8].

Data on the ability of lead to cause congenital abnormalities is inconclusive. There are a small number of reports suggesting maternal lead exposure was associated with major abnormalities including neural tube defects and congenital heart defects. However these studies have methodological limitations [8].

The most critical effects of lead toxicity occur in children exposed during fetal and/or postnatal development. Evidence from numerous studies suggests that the higher the maternal concentration of lead, the greater the risk of adverse neurodevelopmental effects in the child. Significant reductions in intellectual function have been reported in the offspring of mothers with BLL levels of < 10 µg/dL [8]. For further detail on this topic please refer to the Neurotoxicity section above.

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 BLLs of 60–100 µg/dL showed squint, foot drop and delayed growth [5].

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This information contained in this document from the PHE Centre for Radiation, Chemical and Environmental Hazards is correct at the time of its publication.

First published: October 2017

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