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Lead and inorganic lead compounds

Evaluation of health hazards and estimation of a quality criterion in soil

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Content

Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to lead and inorganic lead compounds and an estimation of a quality criterion in soil. This resulted in 2004 in the present report, which was prepared by Elsa Nielsen, Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of representatives from the following Danish authorities:

The Danish Nature Agency,
The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences),
The Danish Veterinary and Food Administration,
The National Board of Health, Denmark,
Danish Regions (former Amternes Videncenter for Jordforurening)
The Danish Environmental Protection Agency

The Danish Environmental Protection Agency
Copenhagen, December 2013.

1 General description

The effects of inorganic lead and lead compounds have been studied extensively. The purpose of this evaluation is to give a review of the adverse health effects observed following oral exposure to lead and inorganic lead compounds in order to propose a health based quality criterion for lead in soil. Numerous data are available regarding effects in humans as well as in experimental animals. This evaluation will primarily focus on the human data, and primarily based on the reviews and evaluations prepared by ATSDR (1999), US-EPA (IRIS 2004), JECFA (2000), CSTEE (2000), WHO (1995), and WHO (1996).

WHO is currently reviewing their 'Guidelines for drinking-water quality'. According to the revised volume 1 (WHO 2004), the Final Task Force Meeting in 2003 agreed that the risk assessment originally conducted in 1993 should be brought forward to the revised edition of the 'Guidelines for drinking-water quality'. Furthermore, only a very short toxicological review is available in the revised volume 1 (WHO 2004). Consequently, this evaluation will be based on the risk assessment conducted in 1993 (WHO 1996).

1.1 Identity and physical / chemical properties

Lead is a metallic element and is the most common of the heavy elements. It is a soft, silvery grey metal with a melting point of 327.5 °C. Lead displays three oxidation states: 0, +2 and +4. The usual oxidation state of lead in inorganic compounds is +2. Lead can form a number of salts. (WHO 1995, WHO 1996).

In this evaluation, the term 'lead' refers to ionic lead, except when specific lead compounds are mentioned.

1.2 Use

Major uses of lead and lead compounds are in batteries, cables, pigments, gasoline additives, solder and steel products. Other uses are in solder applied to water distribution pipes and to seams of food cans, in some traditional remedies, in bottle closures for alcoholic beverages, in ceramic glazes and crystal tableware, and in ammunition. (WHO 1995).

The use patterns vary from country to country. The largest use of lead within OECD countries is for battery production, whereas there has been a large drop in the demand for lead-containing gasoline additives. However, this pattern is not valid world-wide as leaded petrol is still used in eastern Europe and many developing countries. (WHO 1995, WHO 1996, IARC 2004).

1.3 Environmental occurrence and fate

Lead is relatively abundant in the earth's crust and is therefore found naturally throughout the world. The major natural sources are volcanic emissions, geochemical weathering, and emissions from sea spray. The average concentration of lead in the earth's crust is between 10 and 20 mg/kg. However, lead and its compounds are

dispersed in the environment primarily as the result of anthropogenic activities such as mining, smelting, processing, use, recycling or disposal. Lead in the environment exists almost entirely in the inorganic form. Environmental fate processes may transform one lead compound to another; however, lead is not degraded and is still available for human exposure, even though the compounds containing it vary enormously. (WHO 1995, WHO 1996, ATSDR 1999).

1.3.1 Air

The transport and distribution of lead are primarily via air with non-organic compounds existing primarily in the particulate form. Most lead emissions are deposited near the source, although some particulate matter (< 2 µm in diameter) is transported over long distances and results in the contamination of remote sites. Lead particles are removed from the atmosphere primarily by wet or dry deposition. Reported concentrations of lead range from 76 pg/m^3 in remote areas to above 10 µg/m^3 near stationary point sources such as smelters, with an average annual concentration below 1.0 µg/m^3 for urban areas. (WHO 1995, WHO 1996, ATSDR 1999).

1.3.2 Water

Lead is present in tapwater as a result of its dissolution from natural sources but primarily from household plumbing systems in which the pipes, solder, fittings, or service connections to homes contain lead. Background or natural levels in surface and ground water are generally low (around 0.02 µg/l) and rarely exceed a few µg/l in drinking water except in cases of plumbosolvent water in which concentrations above 100 µg/l have been reported. (WHO 1995, WHO 1996).

1.3.3 Soil

In rural and remote areas, lead in soil is derived mainly from natural geological sources, which account for 1 to 30 mg lead/kg. Regarding anthropogenic sources, atmospheric deposition is generally the largest source of lead in soils; however, in countries in which leaded gasoline is banned, industrial processes are the major sources. Lead in soil is immobile due to a very strong adsorption and only small amounts are removed by leaching to the groundwater or by uptake into crops. Thus, levels in contaminated soils will remain essentially unchanged unless action is taken to decontaminate them. The highest lead concentrations usually occur in surface soil at depths of 1 to 5 cm and e.g., continuous application of sewage sludge will result in an accumulation of lead in the upper soil. (WHO 1995, WHO 1996, ATSDR 1999).

Concentrations of lead in urban soil vary greatly.
In Copenhagen and Frederiksberg, 51% of soil samples (7505 samples) taken from 1996 to 2001 showed lead concentrations below 40 mg/kg, 44% between 40 and 400 mg/kg, and 5% above 400 mg/kg. The average concentration was 123 mg/kg with the 95 percentile being 360 mg/kg. (Embedslægerapporten 2002).
In Sweden, the median soil lead concentration in urban Stockholm was 100 mg/kg (range: < 10-330 mg/kg) compared with a median value of 16 mg/kg (range: < 10-50 mg/kg) in a reference area (Sundbyberg, suburb to Stockholm); soil samples were collected in 1992 and 1993. In a mining town (Sala), the median soil lead concentration was 295 mg/kg (range: 20-5000 mg/kg) compared with a median value

of 31 mg/kg (range: 10-39 mg/kg) in a reference area (Heby); soil samples were collected in 1991 and 1992. (Berglund et al. 2000).

In Danish soils (agricultural, forests), an average concentration of 11 mg/kg (median) has been reported with the 95 percentile being 19 mg/kg (DMU 1996).

1.3.4 Foodstuffs

In foodstuffs, lead is predominantly present from atmospheric dust deposition on fruits, vegetables and grains, whereas uptake in crops from contaminated agricultural soils is of less significance. Meat, seafood, and fish also contain lead due to contamination via the environment. Other important sources of lead in food include the use of lead-soldered cans, lead containing kitchen devices used for storage and cooking, and the presence of lead chromates in pigments used to print plastic food wrappers. Lead may also leach from lead crystal vessels. (CSTEE 2000, FDIR 2000).

In Denmark, lead has been measured in 82 foodstuffs (1988-1992). Median concentrations ranged from < 3 to 71 µg/kg wet weight; the highest concentrations were measured in the kidney and liver from cattle. Generally, the concentrations in foodstuffs have either decreased or remained unchanged compared with the previous surveying period (1988- 1992). (FDIR 2000).

1.4 Human exposure

In the general non-smoking adult population and older children, the major source of lead is food with an estimated intake of around 10 µg/day (WHO 1995).

In Denmark, the estimated average dietary intake for adults (1988-1992) was 27 µg/day with the 95 percentile being 46 µg/day. The dietary intake has decreased during the recent 5-year period (1993-1997) with an average daily intake for an adult person of 18 µg/day and a 95 percentile of 28 µg/day (FDIR 2000).
For 2-year old children, an average dietary intake of 11 µg/day has been estimated based on an assumption that the average intake of lead of a 2-year old child is 59% of the intake of adults; this assumption is based on Danish dietary studies (Samsøe-Petersen et al. 2000).

In the EU Member States, the mean intake of lead is 14% of the PTWI (1.75 mg for a person weighing 70 kg). Specific foodstuffs from some Member States were reported to contain very high lead levels (wine, game, fish and meat). Data indicate that children have a lower intake of lead than adults. However, children have a larger burden/kg b.w., due to their lower body weight, and may reach 35% of the PTWI. (EC 2003).

In addition to exposure from the diet, some infants and young children receive high doses of lead through mouthing or swallowing non-food items such as soil, dust, or flakes of lead-based paint; these sources often constitute the major exposure with the intake of lead being influenced by the age and behavioural characteristics of the child and bioavailability of lead in the source material (WHO 1995).

Recently published studies (Lanphear et al. 1998, Murgueytio et al. 1998, Mielke & Reagan 1998, Lanphear & Roghmann 1997, Lanphear et al. 1996 – all quoted in Toxline 1995-1999/04) confirm that, in the United States, lead-contaminated house dust or soil plays a significant role in contributing to blood lead levels in children. One

of the studies (Lanphear & Roghmann 1997) indicates that lead-based paint is a more important contributor of lead to house dust than is lead-contaminated soil.

A Swedish study (Berglund et al. 2000) has shown that food is now the main source of lead exposure, even in young children living in areas with high soil lead concentrations, i.e., downtown Stockholm (<10-330 mg/kg in soil) and mining areas (20-5000 mg/kg). It was concluded that lead in soil and dust contributed little to the total intake. There were no significant differences in blood lead levels between the differently contaminated areas (median 2.8 µg Pb/dl in an urban area and 1.9 µg Pb/dl in the mining area) and control areas with much lower concentrations of lead in soil (average 2.7 µg Pb/dl in an urban area and 2.1 µg Pb/dl in a rural non-mining area). In the urban area, there was a peak in blood lead levels at around two years of age, probably due to the mouthing behaviour of the children. There was also an association between blood lead levels and indoor dust lead concentrations, which was not seen in the mining area.

During the last few years, several case reports of high lead exposure from previously unidentified sources have been published, including candles having lead metal wick cores, a toy necklace with lead containing cubes which the child frequently put in its mouths, ceramics containing lead beyond the regulatory limits, a nipple shield made of a lead-containing metal which was being used by a breast-feeding woman, and ingestion of several traditional medicines from India. (CSTEE 2000).

2 Toxicokinetics

2.1 Absorption

Lead is absorbed in humans following inhalation or ingestion whereas percutaneous absorption is minimal.

2.1.1 Inhalation

Depending upon chemical speciation, particle size, and solubility in body fluids, up to 50% of inhaled lead in lead compounds may be absorbed (WHO 1995, WHO 1996).

2.1.2 Oral intake

Absorption of lead from the gastrointestinal tract after ingestion can range from 3 to 80% and is influenced by the physico-chemical nature of the ingested material, nutritional status, and type of diet consumed. Absorption is predominantly influenced by food intake with much higher absorption occurring after fasting than when lead is ingested with a meal. Children absorb lead with a greater efficiency than do adults with about 40 to 50% of dietary lead being absorbed in infants and young children compared to around 5 to 10% in adults. Absorption of lead from ingested dust and soil is somewhat lower than from food, approximately 30% in infants and young children. (JECFA 2000, WHO 1995, WHO 1996).

2.2 Distribution

Following absorption, there is a rapid uptake of lead into blood and soft tissues, followed by a slower redistribution to bone.
Blood lead (PbB) is distributed between the plasma and the erythrocyte with less than 1% in plasma for PbB levels of up to 100 µg/dl. In the erythrocytes lead is bound primarily to haemoglobin; foetal haemoglobin appears to have a higher affinity for lead than adult haemoglobin. Lead in plasma and in soft tissues binds predominantly to proteins.
Bone accumulates lead over much of the human life span and may serve as an endogenous source of lead long after exposure has ended. About 95% of the body burden in adults is located in the bones, compared with about 70% in children. For adults, the half-life of lead has been reported to be 36 days in blood, 40 days in soft tissues, and 27 years in the bone compartment; the biological half-life may be considerably longer in children than in adults.
(WHO 1995, WHO 1996, ATSDR 1999, JECFA 2000, IARC 2004).

Placental transfer of lead occurs in humans as early as week 12 of gestation, and uptake of lead by the foetus continues throughout development. The PbB level in umbilical cord blood is 80 to 100% of the maternal PbB level; the same applies to the PbB level in the foetus. (WHO 1995, WHO 1996).

2.3 Elimination

Inorganic lead is not metabolised in the body. Unabsorbed dietary lead is eliminated in the faeces. Lead that is absorbed but not retained in the body is excreted unchanged via the kidneys and to a lesser extent by biliary clearance. (WHO 1995, WHO 1996, ATSDR 1999, JECFA 2000).

2.4 Mode of action

Lead is known to affect a number of enzymes and physiological systems and the toxicity of lead may to some extent be explained by its inactivation of certain enzyme systems by binding to protein sulfhydryl groups or by displacing other essential metal ions. For this reason, almost all organs and organ systems may be considered as potential targets resulting in a wide variety of biological effects in humans including effects on the nervous, haematopoietic, and reproductive systems, and cardiovascular, hepatic, renal, and gastrointestinal effects. (WHO 1995, JECFA 2000).

3 Human toxicity

A wide range of biological effects of lead has been documented including effects on the nervous, haematopoietic and reproductive systems, and cardiovascular, hepatic, renal, gastrointestinal and carcinogenic effects.

Lead is a cumulative general poison with pregnant women, the foetus, infants, and children up to 6 years of age being the most susceptible subgroups to adverse health effects (WHO 1995, WHO 1996).

Most of the human studies on adverse health effects of lead have focused on children because they, in comparison with adults, are more susceptible to lead in several respects. Children generally have a greater exposure to lead than adults because of their hand-to-mouth activities e.g., sucking fingers and putting non-food items into the mouth. Children also have a greater absorption and retention of lead than adults resulting in a higher body burden from a given external exposure. Furthermore, the relatively greater exposures and body burdens of children occur during sensitive periods of development. Finally, it appears that children are generally more sensitive to the toxicological effects of lead at a given internal exposure (PbB) level as the lowest observed effect levels (LOAELs) for various end-points (e.g. slowed nerve conduction velocity, impaired neurobehavioural function, encephalopathy, anaemia, reduced haemoglobin levels) are lower in children than in adults.

3.1 Relationship between lead exposure and blood lead levels

Humans are exposed to lead from various environmental media such as food, water, air, soil and dust, and the external exposure is the sum of lead from all sources. Most of the data on adverse health effects of lead in humans are expressed in terms of internal exposure (blood lead (PbB) levels) rather than external exposure (i.e., mg/kg b.w./day). The relationship between external exposure and PbB is very difficult to ascertain for several reasons. One is that the majority of studies have attempted to correlate PbB levels and lead concentrations in specific media rather than correlating PbB levels with the total external exposure. Furthermore, PbB levels reflect the absorbed dose of lead; however, in view of the relatively short half-life in blood (about 36 days) PbB levels generally reflect relatively recent exposures. In addition, lead in blood is derived from uptake of lead from environmental media as well as from lead stored in tissues, particularly bone) that re-enters the blood during tissue mobilisation. Based on the available studies, the relationship between exposure and PbB appears to be curvilinear, i.e., as exposure increases the corresponding PbB increments become smaller, and interpretation of PbB levels over a wide range of values must therefore take this curvilinear relationship into account. (WHO 1995, WHO 1996, ATSDR 1999, JECFA 2000).

The relationship of PbB to dietary intake has been estimated from experimental as well as population studies. Data are available for adults and children from studies with control of important variables such as intake of dietary lead and of other dietary constituents, and minimal exposure to sources other than the diet in the studies of infants. In studies of infants with exposure levels associated with PbB levels below 20 µg/dl (Ryu et al. 1983, Lacey et al. 1985 – both quoted in WHO 1995), the ratio of PbB to ingested lead was determined to be 0.16 µg/dl per µg lead ingested per day. (WHO 1995).

According to JECFA (2000), the best study for evaluating the relationship between dietary intake of lead and PbB levels in infants is the study by Lacey et al. (1985 – quoted in JECFA 2000), in which the concentrations of lead in water and blood were measured. Although the infants were exposed to low concentrations of lead in drinking water, they had PbB levels above 10 µg/dl probably reflecting exposure from other sources. The data were fit into several models, which were all based on the assumption of a linear relationship between dietary intake and PbB but with different population models. The models all yielded an intercept of roughly 15 µg/dl, which may reflect exposure from dust or air, or *in utero* exposure. The models also yielded a slope of roughly 0.05 µg/dl per µg/l in drinking water. The slope attributable to dietary intake corresponds roughly to a PbB level of 0.05-0.1 µg/dl per µg of lead intake per day, where the range reflects the uncertainty in the relationship. (JECFA 2000).

According to WHO (1995), it is extremely difficult to choose the most appropriate model to describe the soil/dust to PbB relationship. A review of the available studies has shown an extreme variability in slopes (relationships) obtained. The relationship between PbB and lead in soil/dust depends on the lead concentrations and bioavailability as well as on the proximity and linkage between humans and their environment, and the relations varies among locales. A median PbB level of 1.8 µg/dl per 1000 µg lead/g house dust and of 2.2 µg/dl per 1000 µg lead/g soil has been estimated for a specific community in the USA. (WHO 1995).

According to Embedslægerapporten (2002), several studies have shown an association between the concentration of lead in soil and the PbB level in children. Various associations were found; for an increase of 1000 mg/kg lead in soil, increases in PbB levels ranging from 0.9 to 9 µg/dl have been reported, and US-EPA has considered that the most probable increase was 2 µg/dl. In another study, also quoted in Embedslægerapporten (2002), regarding an association between lead in dust/soil and the PbB level in children (½-3 years old) at low (1 $\mu g/ft^2$) or medium exposure (15 $\mu g/ft^2$), the results from 12 epidemiological studies (1982-1997) were pooled. At a lead soil concentration of 10 mg/kg, the PbB level was estimated to 2.3 and 4.0 µg/dl for low and medium exposure, respectively; at 100 mg/kg soil, 2.9 and 5.1 µg/dl, respectively; and at 1000 mg/kg soil, 3.8 and 6.6 µg/dl, respectively. Based on these data, Embedslægerapporten assumed that children exposed to lead in soil at 1000 mg/kg have an average PbB level of 1.5-2.6 µg/dl higher than if they were exposed to lead in soil at 10 mg/kg, and a conversion factor of 2 µg/dl was chosen for the effect assessment.

3.2 Single dose toxicity

Overt signs of acute intoxication include dullness, restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, loss of memory, and encephalopathy occurring at PbB levels of 100 to 120 µg/dl in adults and 80 to 100 µg/dl in children (WHO 1996).

Colic is an early symptom of lead poisoning in individuals acutely exposed to high levels of lead. A PbB threshold of 60 to 100 µg/dl has been identified for children and of 100 to 200 µg/dl for adults. (WHO 1995, ATSDR 1999).

3.3 Repeated dose toxicity

3.3.1 Effects on the nervous system

Lead causes a continuum of nervous system effects in children and adults ranging from slowed nerve conduction, behavioural changes, and small decrements in cognitive ability, to mental retardation and encephalopathy. The effects on the nervous system generally develop at lower PbB levels in children than in adults.

3.3.1.1 Peripheral nerve function

Peripheral neuropathy is a common sign of chronic, high level lead exposure, often manifesting as weakness in the upper or lower limbs. Measurements of nerve conduction velocity (NCV) are generally used as a sensitive indicator of peripheral nerve dysfunction. (WHO 1995).

Numerous studies of adults have measured the conduction velocity of electrically stimulated sensory and motor nerves in workers exposed to lead. Most of the studies have shown a decrease in NCV in relation to lead exposure; decreased NCV has been observed at a PbB level of 30 µg/dl. (WHO 1995, ATSDR 1999, JECFA 2000). Autonomic nervous system function may be affected at a PbB level of approximately 35 µg/dl (WHO 1995).

Frank peripheral neuropathy has been observed in children at PbB levels of 60 to 136 µg/dl (ATSDR 1999). Studies on NCV have indicated an inverse correlation between peroneal NCV and PbB levels ranging from 13 to 97 µg/dl in children living near a smelter (Landrigan et al. 1976 - quoted from ATSDR 1999). These data were reanalysed (three different methods of analysis) to determine whether a threshold exists for this effect; a threshold for NCV at PbB levels of 20 to 30 µg/dl was estimated (Schwartz et al. 1988 - quoted from ATSDR 1999).
A recent study has reported significant effects on peripheral nerve function in a group of young adults 20 years after childhood environmental exposure to lead (Stokes et al. 1998 - quoted from Toxline 1995-1999/04).

3.3.1.2 Behavioural function

In adults, neurobehavioral testing of lead workers has revealed effects at PbB levels from 40 to 60 µg/dl. A number of neurobehavioral parameters are affected including disturbances in reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, impaired memory and learning ability, nervousness, mood, or coping ability. (ATSDR 1999, WHO 1995).

In children, the most critical effect of lead at low exposure levels is the association with reduced cognitive development and intellectual performance. A number of cross-sectional and longitudinal epidemiological studies (reviewed in WHO 1995, ATSDR (1999, and/or Banks et al. 1997 as well as recent studies quoted in Toxline 1995-1999/04) have been carried out to investigate these effects. Most studies have primarily been concerned with documenting effects arising from exposure to low levels of lead (i.e., PbB levels below 40 µg/dl).

Most cross-sectional studies (as reviewed in WHO 1995, WHO 1996, ATSDR 1999, and/or Banks et al. 1997) indicate a negative association between lead exposure (assessed as either lead level in blood, teeth or hair) and IQ measures in uncontrolled data; this difference is usually in the range of 4 to 6 IQ points and most marked in

verbal IQ. The cross-sectional studies are consistent in demonstrating statistically significant associations between PbB levels from 25-30 µg/dl and IQ deficits of about 4 points. Associations between lower PbB levels and IQ deficits of about 2 points were marginally statistically significant, except in one study (Fulton et. al. 1987 – quoted in WHO 1995, WHO 1996) in which there was a dose-response relationship in the PbB range of 5.6 to 22.1 µg/dl.

Several prospective studies have reported an inverse relationship between lead exposure during the foetal period and in early childhood and neurobehavioral deficits in children. The average maternal and cord PbB levels were generally less than 10 µg/dl (range 6.0-9.5 µg/dl). The results of the prospective studies are inconsistent as some studies have reported no association between neurobehavioral impairment and lead exposure. Some studies indicate that prenatal exposure may have early effects on mental development, but that these do not persist up to age 4; other studies indicate that the generally higher exposures of children in the 18 to 36 month age range may be negatively associated with mental development. (WHO 1995, WHO 1996, ATSDR 1999, Banks et al. 1997).

Several recently published studies (Mendelsohn et al. 1998, Shen et al. 1998, Stokes et al. 1998, Tong et al. 1998, 1996, Wasserman et al. 1998, 1997, Dudek & Merecz 1997, Fergusson et al. 1997, Ruff et al. 1996, Baghurst et al. 1995 - quoted in Toxline 1995-1999/04) support the findings of negative effects of pre- and/or postnatal low-level lead exposure on cognitive function in children. Some of these studies (Stokes et al. 1998, Fergusson et al. 1997, Tong et al. 1996) indicate that the cognitive deficits seem to persist into later childhood. One of the studies (Tong et al. 1998) indicates that the cognitive deficits associated with exposure to environmental lead in early childhood appear to be only partially reversed by a subsequent decline in PbB level.

The inconsistency in the results of the studies on lead-induced neurobehavioral effects in children has been the subject of many reviews (e.g., Bellinger 1995, Mushak 1993, Winneke et al. 1996 - quoted in ATSDR 1999). Several factors affect the validity of the conclusions drawn from the available studies. The overall conclusion is that there appears to be an association between indices of lead burden (usually blood lead) and global indices of development or neurophychological functioning (usually IQ) (ATSDR 1999, WHO 1995, Banks et al. 1997).
Support for this conclusion is provided by the results of several meta-analysis of cross-sectional and/or prospective studies (e.g., Needleman & Gatsonis 1990, Pocock et al. 1994, Schwartz 1993 - quoted in ATSDR 1999 and Banks et al. 1997; WHO 1995); these studies concluded that a doubling of PbB from 10 to 20 µg/dl is associated with an average IQ decrement of 2.5 points (ATSDR 1999, WHO 1995, Winneke & Kramer 1997 - quoted from Toxline 1995-1999/04). However, one study (de Silva & Christophers 1997 - quoted from Toxline 1995-1999/04), which has interpreted the literature since the 1930s, argues that a reverse causation hypothesis (i.e., that mental deficit causes pica which causes lead exposure) is a more plausible explanation of the facts. (ATSDR 1999, WHO 1995, Banks et al. 1997, Toxline 1995-1999/04, CSTEE 2000).

The epidemiological studies do not provide definitive evidence of a threshold. Below the PbB range of 10 to 15 µg/dl, the effects of confounding variables and limits in the precision in analytical and psychometric measurements increase the uncertainty of any estimate of effect. However, there is some evidence of an association between lead exposure and cognitive deficits even below this range (WHO 1995; Winneke & Kramer 1997, Rosen 1995 - quoted from Toxline 1995-1999/04). One study (Minder et al. 1998) has reported that the PbB level (mean: 4.4 µg/dl) did not influence any of the cognitive factors assessed in schoolboys (aged 9-12 years) in the Netherlands. However, a study, which focused on the mechanisms of

lead neurotoxicity concluded that there is no threshold below which lead remains without effect on the central nervous system (Finkelstein et al. 1998 - quoted from Toxline 1995-1999/04). (ATSDR 1999, CSTEE 2000, JECFA 2000, IARC 2004).

In a very recent study (Canfield et al. 2003), associations between low-level exposure to lead and children's performance on intelligence tests were examined in a population that included many children whose PbB levels remained below 10 µg/dl. PbB levels were measured in 172 children at 6, 12, 18, 24, 36, 48 and 60 months of age and intelligence tests were performed at the ages of three and five years. The mean level was lowest at the age of 6 months (3.4 µg/dl), maximal at 2 years (9.7 µg/dl), and then decreased to 6.0 µg/dl at 5 years. The lifetime average PbB was 7.7 µg/dl at the age of 3 years and 7.4 µg/dl at the age of 5 years. At 3 years of age, 86 children (57%) had a peak PbB below 10 µg/dl, as did 86 (55.8%) at the age of 5 years; 71 of these children had such a concentration at both ages, and the remaining 30 had data at either 3 or 5 years. The mean IQ was approximately 90 at both 3 and 5 years of age. The PbB was inversely and significantly associated with IQ. Using a linear model with the full sample, an increase in the lifetime average PbB of 1 µg/dl was associated with a change of –0.46 IQ point; for the sub-sample of 101 children whose maximal PbB remained below 10 µg/dl, the difference in IQ for each increase in the lifetime average PbB of 1 µg/dl was –1.37 points. When estimated in a non-linear model with the full sample, IQ declined by 7.4 points as lifetime average PbB levels increased from 1 to 10 µg/dl. The authors concluded that PbB levels, even those below 10 µg/dl, are inversely associated with children's IQ scores at 3 and 5 years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations.

3.3.1.3 Neurological signs and symptoms

High-level exposure to lead produces encephalopathy in children and adults. Early symptoms that may develop within weeks of initial exposure include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. The condition may then worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death. Severe lead encephalopathy is generally observed at high PbB levels (> 300 µg/dl), but may occur at PbB levels of 100 to 120 µg/dl in some adults and of 80 to 100 µg/dl in some children. (WHO 1995, ATSDR 1999, JECFA 2000, CSTEE 2000).

Occupational exposure to lead has often been associated with subjective signs of neurotoxicity. The literature contains numerous case reports and small cohort studies that describe a higher incidence of these subjective symptoms, including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia at PbB levels that range from approximately 40 to 120 µg/dl. (WHO 1995, ATSDR 1997).

3.3.1.4 Hearing impairment in children

Suggestive evidence of a lead-related decrease in hearing acuity in children has been reported. In one study (75 black children, 3-7 years old), hearing thresholds at 2000 Hz increased linearly with PbB levels ranging from 6 to 59 µg/dl (mean, 26 µg/dl) (Robinson et al. 1985 - quoted from ATSDR 1999). In another study (3262 children aged 6 to 19 years), an increase in the PbB level from 6 to 18 µg/dl was associated with a 2-dB loss in hearing at frequencies of 500, 1000, 2000, and 4000 Hz, and an additional 15% of the children had hearing thresholds that were below the standard at 2000 Hz (Schwartz & Otto 1991 - quoted from WHO 1995 and ATSDR 1999).

In a third study (4519 children aged 4 to 19 years), the probability of elevated hearing thresholds at 500, 1000, 2000, and 4000 Hz increased significantly with increasing PbB levels from <4 to >50 µg/dl (Schwartz & Otto 1987 - quoted from WHO 1995 and ATSDR 1999).
One recent study has reported that auditory function in children (4-14 years old) was impaired at a PbB level even below 10 µg/dl (Osman et al. 1999 – quoted from CSTEE 2000).

3.3.2 Effects on the haematological system

Lead is shown to affect several enzymatic reactions critical in haem synthesis, causing abnormal concentrations of haem precursors in blood and urine. Lead inhibits the activity of three enzymes (δ-aminolaevulinic acid dehydratase (ALAD), coproporphyrinogen oxidase, and ferrochelatase) involved in the haem synthesis resulting in decreased haem synthesis and subsequently increased activity of the rate limiting enzyme (δ-aminolaevulinate synthase) leading to an accumulation of δ-aminolaevulinate, a neurotoxin. (WHO 1995, WHO 1996, ATSDR 1999, JECFA 2000).

General population studies indicate that the activity of ALAD is inhibited at very low PbB levels, with no threshold apparent. ALAD activity was inversely correlated with PbB levels (3 to 34 µg/dl) in urban subjects never exposed occupationally (Hernberg & Nikkanen 1970 - quoted from ATSDR 1999). A similar relationship was reported in a population of children (aged 10-13 years) having PbB levels of 4.7 to 41 µg/dl (Roels & Lauwerys 1987 - quoted from WHO 1995). Other reports have confirmed this correlation and apparent lack of a threshold in different age groups and exposure categories (e.g., children: Chisolm et al. 1985; adults: Roels et al. 1976 - quoted in WHO 1995 and ATSDR 1999).
A negative linear relationship between PbB levels and ALAD activity was found between mothers (at delivery) and their new-born babies (cord blood); PbB levels ranged from approximately 3 to 30 µg/dl (Lauwerys et al. 1978 - quoted from WHO 1995 and ATSDR 1999).

Lead-induced anaemia may result from either a decrease in haemoglobin production or an increase in the rate of destruction of erythrocytes. Haemoglobin concentrations are generally not inhibited sufficiently to result in clinically observable anaemia until a PbB level of at least 80-100 µg/dl is reached (JECFA 2000).
In adults, the estimated PbB associated with a decrease in haemoglobin level in adults is 50 µg/dl (WHO 1995, WHO 1996, ATSDR 1999).
Decreased haemoglobin levels in children have been reported to occur at a PbB level of 40 µg/dl (WHO 1995, WHO 1996, ATSDR 1999). However, a cross-sectional epidemiological study of 579 children (aged 1 to 5 years in 1974) living in close proximity to a primary lead smelter revealed that adverse effects on haematocrit may occur at lower PbB levels (Schwartz et al. 1990 - quoted from WHO 1995 and ATSDR 1999). Anaemia was defined as a haematocrit value below 35% and was not observed at PbB levels below 20 µg/dl. There was a strong non-linear dose-response relationship between PbB levels and haematocrit at higher PbB levels, which was influenced by age, and the effect was strongest in the youngest children.

3.3.3 Cardiovascular effects

There is currently considerable debate whether there is a causal relationship between lead exposure and hypertension. The possible relationship between PbB levels and blood pressure has been examined in several large-scale population studies including the National Health and Nutrition Examination Survey (NHANESII), the British Regional Heart Study (BRSH), and studies in Denmark, Wales, Canada and Belgium, as well as studies on occupationally exposed cohorts. Data from these studies suggest that lead exposure is associated with a small increase in systolic rather than diastolic blood pressure for adult middle-aged men; this association is most apparent for PbB levels as low as 7 µg/dl, and a mean increase in systolic blood pressure of 1 to 2 mmHg appears to occur for every doubling in PbB levels. However, when adjusting for important confounding factors, the results do not allow an establishment of a relationship between PbB levels and hypertension. Thus the studies do not provide conclusive evidence that lead exposure, as assessed by PbB levels, is positively associated with hypertension. (WHO 1995, WHO 1996, ATSDR 1999).

A recent study examining the associations between PbB and blood pressure in 282 children (age 5.5 years) found that a 10 µg/dl increase in PbB was associated with 0.5 mmHg increase in systolic and a 0.4 mmHg increase in diastolic blood pressure (Factor-Litvak et al. 1996 - quoted from Toxline 1995-1999/04).

Qualitative evidence linking lead exposure to cardiac effects includes the finding of degenerative changes in cardiac muscle, reported as the proximate cause of death in five fatal cases of lead poisoning in young children with histories of pica. Additional evidence indicates that ECG abnormalities are fairly common in cases of overtly lead-intoxicated children but disappear following chelation therapy. (WHO 1995, ATSDR 1999).
According to WHO (1995), lead has no direct effect on the myocardium and the observed cardiac effects occur via the autonomic nervous system.

3.3.4 Hepatic effects

In children, exposure to lead has been shown to inhibit formation of the haem-containing protein cytochrome P450, as reflected in decreased activity of hepatic mixed-function oxygenases, which consequently may result in impaired metabolism of a number of chemicals in the liver (WHO 1995, ATSDR 1999).

3.3.5 Renal effects

Lead is known to cause proximal renal tubular damage. Acute exposure is characterised by generalised aminoaciduria, hypophosphataemia with relative hyperphosphaturia, and glycosuria. Cellular structural changes include nuclear inclusion bodies, mitochondrial changes and cytomegaly of the proximal tubular epithelial cells. These effects appear to be reversible. The acute form is reported in lead-intoxicated children and sometimes in lead workers. (WHO 1995, WHO 1996).
In children, the available studies suggest that renal effects occur at PbB levels above 80 µg/dl, and usually exceeding 120 µg/dl (ATSDR 1999).

Characteristics of chronic lead nephropathy include progressive interstitial fibrosis, dilation of tubules and atrophy or hyperplasia of the tubular epithelial cells,

reduction in glomerular filtration rate, and azotemia. These effects are irreversible. The chronic form is reported mainly in lead workers. (WHO 1995, WHO 1996). Increased risk from nephropathy was noted in workers with PbB levels ranging from 40 to >100 µg/dl (ATSDR 1999).

Renal effects have recently been seen among the general population when more sensitive indicators of function were measured. Results from a longitudinal study of 459 men (mean age 56.9 years; range, 37.7-87.5) showed that PbB levels from 10 µg/dl may impair renal function in middle-aged and older men (Kim et al. 1996 - quoted from ATSDR 1999).

In a cross-sectional study, adverse effects of chronic low-level lead exposure on kidney function could be detected by measuring urinary markers in children with PbB levels of approximately 13 µg/dl; the pattern of effects was similar to that previously observed in adults (Fels et al. 1998 - quoted from Toxline 1995-1999/04).

3.4 Toxicity to reproduction

Reproductive effects of lead have been studied extensively and the studies clearly indicate that high levels of lead cause adverse effects on human reproduction, including increased incidences of spontaneous abortion, miscarriages, and stillbirths. The mechanisms responsible for these effects are unknown, but many factors may contribute to these results. These factors include indirect effects of lead on maternal nutrition or hormonal status before and during pregnancy to more direct gametogenic effects that could affect parental fertility in either sex. (ATSDR 1999, CSTEE 2000).

The available data do not permit any estimate of effect levels in women. One study has reported that women with a PbB close to 50 µg/dl have a greater risk of miscarriage. Two studies found no effect on the rate of spontaneous abortions at PbB levels of 10 µg/dl. Regarding male reproductive function, adverse effects such as lowered sperm counts and increases in the numbers of abnormal sperm may occur at PbB levels of 40 to 50 µg/dl. (WHO 1995, WHO 1996, ATSDR 1999, CSTEE 2000).

Developmental effects observed in humans following exposure to low levels of lead include reduced birth weight, reduced gestational age and neurobehavioral deficits or delays. The evidence for an association between PbB levels and reduced birth weight and gestational age is inconsistent and the weight of evidence indicates that there may not be a direct association. There is a predominance of negative results, with the most recent studies showing no such association. The evidence in support of neurobehavioral deficits or delays is more consistent, with most of the studies indicating that there is an association between lead exposure at low levels and developmental neurobehavioral effects, see section 3.2.1.2.
No evidence of an association with major congenital malformations has been found. One study has reported an association between cord blood lead levels and minor anomalies; the relative risk doubled at blood lead levels of about 7 to 10 µg/dl (Needleman et al. 1984 - quoted from WHO 1996 and ATSDR 1999). (WHO 1995, WHO 1996, ATSDR 1999).

3.5 Mutagenic and genotoxic effects

Studies of chromosomal aberrations in humans exposed to lead (PbB > 40 µg/dl) have given conflicting results. Positive reports have been published concerning workers in lead-battery industries and lead smelters, but other studies of workers under comparable conditions have given negative results. Increased incidences of sister chromatid exchanges have been reported in the peripheral blood lymphocytes of workers exposed to lead, but not in those of children exposed to high levels of lead in the environment. (IARC 1987, WHO 1995, WHO 1996, IRIS 2004).

3.6 Carcinogenic effects

The carcinogenicity of lead in humans has been examined in several epidemiological studies, which either have been negative or have shown only very small excess mortalities from cancers. One major difficulty in many of the studies is the concurrent exposure to potential carcinogens such as arsenic and chromium. (IARC 1987, WHO 1995, WHO 1996, ATSDR 1999, IRIS 2004).

According to US-EPA (IRIS 2004 – last revised 11/01/1993) *"All of the available studies lacked quantitative exposure information, as well as information on the possible contribution from smoking. All studies also included exposures to other metals such as arsenic, cadmium, and zinc for which no adjustment was done. The cancer excesses observed in the lung and stomach were relatively small (<200). There was no consistency of site among the various studies, and no study showed any dose-response relationship. Thus, the available human evidence is considered to be inadequate to refute or demonstrate any potential carcinogenicity for humans from lead exposure."*

An IARC Working Group has recently evaluated the epidemiological evidence of possible cancer hazards from exposure to lead and lead compounds (IARC 2004). Six occupational cohort studies of high-exposed workers were considered to be particularly informative; these concerned battery workers in the USA and the United Kingdom, and primary smelter workers in Italy, Sweden and the USA (2 studies). One of the six cohort studies showed a statistically significant two-fold excess of lung cancer among smelter workers, but this excess may well have been caused by exposure to arsenic. Five of the six cohort studies were judged to be informative for stomach cancer; in four of these studies, there was a fairly consistent 30-50% excess of stomach cancer, but it was considered possible that other factors than lead played a role in the stomach cancer excesses. Five of the six cohort studies reported findings for kidney cancer; in one study, there was a statistically significant two-fold excess of kidney cancer. Four of the six cohort studies reported tumours of the brain and nervous system, but there was no consistent pattern in these studies. Based on these data, it was concluded that there is limited evidence for the carcinogenicity to humans of exposure to inorganic lead compounds.

4 Animal toxicity

4.1 Single dose toxicity

Health effects are generally not observed in laboratory animals after a single exposure, and no LD_{50}-values have been reported in the literature. The lowest observed lethal doses in animals after short-term oral exposure range from 300 to 4000 mg/kg b.w. (JECFA 2000).

4.2 Repeated dose toxicity

In experimental animals, including non-human primates, repeated exposure to lead causes a number of adverse effects in several organs and organ systems, including the haematopoietic, nervous, renal, cardiovascular, reproductive and immune systems. Lead also affects the bone tissue. Impaired learning ability has been reported in rats at PbB levels of 15-20 µg/dl and in non-human primates at PbB levels lower than 15 µg/dl. Visual and auditory impairments have also been reported in experimental animals. Renal toxicity in rats appeared to occur at PbB levels above 60 µg/dl and cardiovascular effects have been noted at 40 µg/dl. Despite kinetic differences between experimental animal species and humans, these studies provide strong biological support and plausibility for the findings in humans. (IARC 1987, WHO 1995, IRIS 2004, JECFA 2000).

4.3 Toxicity to reproduction

Effects on the testes (testicular atrophy) in male rats have been observed at PbB levels above 70 µg/dl but not at 54 µg/dl, and on oestrous cycles in female rats at PbB levels above 30 µg/dl (WHO 1995, WHO 1996).

4.4 Mutagenic and genotoxic effects

A few studies in rodents treated with lead salts *in vivo* have shown small, but significant, increases in the frequency of chromosomal aberrations and micronuclei in bone-marrow cells, but most studies have shown no increase. Lead salts caused morphological sperm abnormalities in mice, but not in rabbits. Sister chromatid exchanges and unscheduled DNA synthesis were not induced in cells of animals treated with lead salts *in vivo*, and chromosomal aberrations were not induced in human lymphocytes *in vitro*. Conflicting results have been obtained in assays for transformation in cultured rodent cells. Lead salts did not cause aneuploidy in *Drosophila melanogaster*, mutation or gene conversion in yeast, or mutation or DNA damage in bacteria. (IARC 1987, WHO 1995, WHO 1996, IRIS 2004).

4.5 Carcinogenic effects

There have been several experimental studies in rats and mice in which long-term administration of soluble lead compounds (primarily acetates and phosphates) in food or drinking water has produced increased frequencies of renal tumours. The

doses used in these studies were high, and production of detectable increases in renal tumour frequency apparently required doses in excess of 10 mg/kg b.w./day. (IARC 1997, WHO 1995, IRIS 2004, JECFA 2000, IARC 2004).

IARC (2004) and US-EPA (IRIS 2004) have concluded that there is sufficient evidence for the carcinogenicity to experimental animals of exposure to inorganic lead compounds.

5 Regulations

5.1 Ambient air

Denmark (C-value): 0.0004 mg Pb/m^3 (MST 2002).

WHO: 0.0005 mg Pb/ m^3 (WHO 2000).

5.2 Drinking water

Denmark: 10 µg Pb/l (MEM 2001).

WHO: 0.01 mg Pb/l (WHO 1996), retained in according to the revised volume 1 (WHO 2004).

5.3 Soil

Denmark: 40 mg/kg (MST 1995).

The Netherlands: 85 mg/kg (target value), 530 mg/kg (intervention value) (NL 1994).

5.4 Occupational Exposure Limits

Denmark: 0.05 mg Pb/m^3 (At 2002).

Germany: BAT-Werte: 400 µg Pb/l (100 µg Pb/l for women below 45 years of age) (MAK 2004).

5.5 Classification

Lead is classified Xn;R20/22 (harmful by inhalation and if swallowed), R33 (danger of cumulative effects), Rep1;R61 (may cause harm to the unborn child), Rep3;R62 (possible risk of impaired fertility), and N;R50/53 (very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment) (MM 2002, EEC 2004).

5.6 IARC

Inorganic lead compounds are probably carcinogenic to humans, Group 2A (IARC 2004).

5.7 US-EPA

Lead and compounds, inorganic, are probable human carcinogens, Group B2 (IRIS 2004).

US-EPA has not set an oral Reference Dose (RfD) and has concluded *"…it is still inappropriate to develop reference values for lead."* because of *"…the continued apparent lack of a threshold"* and because *"Lead body burdens vary significantly with age, health status, nutritional state, and maternal body burden during gestation and lactation."* (IRIS 2004).

5.8 JECFA

A provisional tolerable weekly intake (PTWI) of 25 µg/kg b.w. has been established for lead. At the Fifty-third meeting in 1999, the current PTWI was not reconsidered. (JECFA 2000).

6 Summary and evaluation

6.1 Description

Lead, a metallic element and the most common of the heavy elements, displays three oxidation states (0, +2 and +4) of which +2 is the usual oxidation state in inorganic compounds. Lead can form a number of salts.

6.2 Environment

Lead is relatively abundant in the earth's crust and is therefore found naturally throughout the world. Lead in the environment exists almost entirely in the inorganic form. In rural and remote areas, lead in soil is derived mainly from natural geological sources. Regarding anthropogenic sources, atmospheric deposition is generally the largest source of lead in soils; however, in countries in which leaded gasoline is banned, industrial processes are the major sources. Environmental fate processes may transform one lead compound to another; however, lead is not degraded and is still available for human exposure, even though the compounds containing it vary enormously. Lead in soil is immobile due to a very strong adsorption and only small amounts are removed by leaching to the groundwater or by uptake into crops.

Concentrations of lead in urban soil vary greatly; in Copenhagen, concentrations range from below 40 to above 1200 mg/kg with an average concentration of 123 mg/kg and a 95 percentile of 360 mg/kg. In Danish non-urban soils (agricultural, forests), an average concentration of 11 mg/kg (median) has been reported with the 95 percentile being 19 mg/kg.

In foodstuffs, lead is predominantly present from atmospheric dust deposition on fruits, vegetables and grains, and from contamination via environmental origin of meat, seafood, and fish. Other important sources of lead in food include the use of lead-soldered cans, lead containing kitchen devices, and lead chromates in pigments used to print plastic food wrappers. In Denmark, median concentrations in 82 foodstuffs (1988-1992) ranged from < 3 to 71 µg/kg wet weight; the highest concentrations were measured in the kidney and liver from cattle.

6.3 Human exposure

In the general non-smoking adult population and older children, the major source of lead is food. In Denmark, the estimated average dietary intake for adults (1993-1997) was 18 µg/day with the 95 percentile being 28 µg/day. For Danish 2-year old children, an average dietary intake of 11 µg/day has been estimated.

In the EU Member States, the mean intake of lead was reported to be 14% of the PTWI (1.75 mg for a person weighing 70 kg). Children have a lower intake of lead than adults but a larger burden/kg b.w., and may reach 35% of the PTWI.

In addition to exposure from the diet, some infants and young children receive high doses of lead through mouthing or swallowing non-food items such as soil, dust, or

flakes of lead-based paint; these sources often constitute the major exposure with the intake of lead being influenced by the age and behavioural characteristics of the child and bioavailability of lead in the source material. However, a recent Swedish study has shown that food is now the main source of lead exposure, even in young children living in areas with high soil lead concentrations, and it was concluded that lead in soil and dust contributed little to the total intake.

6.4 Toxicokinetics

Absorption of lead from the gastrointestinal tract after ingestion can range from 3 to 80% and is influenced predominantly by food intake with much higher absorption occurring after fasting than when lead is ingested with a meal. Absorption is also affected by age with about 40 to 50% of dietary lead being absorbed in infants and young children compared to around 5 to 10% in adults.

Following absorption, there is a rapid uptake of lead into blood and soft tissues, followed by a slower redistribution to bone. Bone accumulates lead over much of the human life span and may serve as an endogenous source of lead long after exposure has ended; about 95% of the body burden in adults is located in the bones, compared with about 70% in children. For adults, the half-life of lead has been reported to be 36 days in blood, 40 days in soft tissues, and 27 years in the bone compartment; the biological half-life may be considerably longer in children than in adults.

Placental transfer of lead occurs in humans as early as week 12 of gestation, and uptake of lead by the foetus continues throughout development.

Inorganic lead is not metabolised in the body. Unabsorbed dietary lead is eliminated in the faeces. Lead that is absorbed but not retained in the body is excreted unchanged via the kidneys and to a lesser extent by biliary clearance.

6.5 Mode of action

The toxicity of lead may to some extent be explained by its inactivation of certain enzyme systems by binding to protein sulfhydryl groups or by displacing other essential metal ions. For this reason, almost all organs and organ systems may be considered as potential targets.

6.6 Human toxicity

Most of the data on adverse health effects of lead in humans are expressed in terms of internal exposure (blood lead (PbB) levels) rather than external exposure (i.e., mg/kg b.w./day). The relationship between external exposure and PbB is very difficult to ascertain for several reasons. Most studies have attempted to correlate PbB levels and lead concentrations in specific media rather than correlating PbB levels with the total external exposure. Based on the available studies, the relationship between exposure and PbB appears to be curvilinear, i.e., as exposure increases the corresponding PbB increments become smaller, and interpretation of PbB levels over a wide range of values must therefore take this curvilinear relationship into account.
In studies of infants with exposure levels associated with PbB levels below 20 µg/dl, the ratio of PbB to ingested lead has, according to WHO (1995) been determined to be 0.16 µg/dl per µg lead ingested per day, and according to JECFA

(2000), to be 0.05-0.1 µg/dl per µg of lead intake per day, where the range reflects the uncertainty in the relationship.
The relationship between PbB and lead in soil/dust depends on the concentrations and bioavailability of lead as well as on the exposure patterns, and the relationship varies among locales. A median PbB level of 1.8 µg/dl per 1000 µg lead/g house dust, and of 2.2 µg/dl per 1000 µg lead/g soil has been estimated for a specific community in the USA. Based on data from the USA, Embedslægerapporten (2002) has assumed that children exposed to lead in soil at 1000 mg/kg have an average PbB level of 1.5-2.6 µg/dl higher than if they were exposed to lead in soil at 10 mg/kg, and a conversion factor of 2 µg/dl was chosen for the effect assessment.

6.6.1 Single dose toxicity

Overt signs of acute intoxication include dullness, restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, loss of memory, and encephalopathy occurring at PbB levels of 100 to 120 µg/dl in adults and 80 to 100 µg/dl in children. For colic, an early symptom of lead poisoning, a PbB threshold of 60 to 100 µg/dl has been identified for children and of 100 to 200 µg/dl for adults.

6.6.2 Repeated dose toxicity

Lead causes a continuum of nervous system effects in children and adults ranging from slowed nerve conduction, behavioural changes, and small decrements in cognitive ability, to mental retardation and encephalopathy.
The most critical effect of lead at low exposure levels is the association with reduced cognitive development and intellectual performance in children. A number of epidemiological studies have been carried out, primarily regarding documentation of effects arising from exposure to low levels of lead (i.e., PbB levels below 40 µg/dl). Most cross-sectional studies indicate a negative association between lead exposure and IQ with associations being observed between PbB levels from 25-30 µg/dl and IQ deficits of about 4 points; associations between lower PbB levels and IQ deficits of about 2 points were marginally statistically significant, except in one study. Several prospective studies have reported an inverse relationship between lead exposure during the foetal period and in early childhood and neurobehavioral deficits in children; average maternal and cord PbB levels were generally less than 10 µg/dl. The inconsistency in the results of the studies has been the subject of many reviews. The overall conclusion is that there appears to be an association between indices of lead burden (usually PbB) and impairment of cognitive and behavioural development of the central nervous system in children. Support for this conclusion is provided by the results of several meta-analyses of cross-sectional and/or prospective studies; these studies concluded that a doubling of PbB from 10 to 20 µg/dl is associated with an average IQ decrement of 2.5 points. The epidemiological studies do not provide definitive evidence of a threshold; below the PbB range of 10 to 15 µg/dl, the effects of confounding variables and limits in the precision in analytical and psychometric measurements increase the uncertainty of any estimate of effect. However, there is some evidence of an association between lead exposure and cognitive deficits even below this range and one study, which focused on the mechanisms of lead neurotoxicity concluded that there is no threshold below which lead remains without effect on the central nervous system. This is supported by a very recent study, which indicates that PbB levels below 10 µg/dl are inversely associated with children's IQ scores at 3 and 5 years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations.

Neurobehavioral testing of lead workers has revealed a number of effects in adults at PbB levels from 40 to 60 µg/dl.
Peripheral neuropathy is a common sign of chronic, high level lead exposure; in adults, a decrease in NCV (nerve conduction velocity, a sensitive indicator of peripheral nerve dysfunction) has been observed at PbB levels from about 30 µg/dl, and in children, a threshold for NCV at PbB levels of 20 to 30 µg/dl has been estimated.
High-level exposure to lead produces encephalopathy in children and adults. Severe lead encephalopathy is generally observed at extremely high PbB levels (>300 µg/dl), but may occur at PbB levels of 100 to 120 µg/dl in some adults and of 80 to 100 µg/dl in some children.
Suggestive evidence of a lead-related decrease in hearing acuity in children has been reported in association with PbB levels from about 4 µg/dl.

Lead is shown to affect several enzymatic reactions critical in haem synthesis, causing abnormal concentrations of haem precursors in blood and urine. The activity of ALAD (δ-aminolaevulinic acid dehydratase), which is the most sensitive marker of effects on haem synthesis, is inhibited at very low PbB levels with no threshold apparent; in adults at PbB levels from 3 to 34 µg/dl and in children having PbB levels of 4.7 to 41 µg/dl.
Lead-induced anaemia may result from either a decrease in haemoglobin production or an increase in the rate of destruction of erythrocytes. In adults, the estimated PbB level associated with a decrease in haemoglobin concentration is 50 µg/dl and in children a PbB level of 40 µg/dl. However, one study of children have revealed that adverse effects on haematocrit may occur at lower PbB levels.

There is currently considerable debate whether there is a causal relationship between lead exposure and hypertension. Data from several large-scale population studies, as well as from studies on occupationally exposed cohorts studies suggest that lead exposure is associated with a small increase in systolic rather than diastolic blood pressure for adult middle-aged men; however, when adjusting for important confounding factors, the results do not allow an establishment of a relationship between PbB levels and hypertension. A recent study examining the associations between PbB and blood pressure in children found that a 10 µg/dl increase in PbB was associated with 0.5 mmHg increase in systolic and a 0.4 mmHg increase in diastolic blood pressure.
Qualitative evidence linking lead exposure to cardiac effects includes the finding of degenerative changes in cardiac muscle, reported as the proximate cause of death in five fatal cases of lead poisoning in young children with histories of pica.

In children, exposure to lead has been shown to inhibit formation of the haem-containing protein cytochrome P450 in the liver, which consequently may result in impaired metabolism of a number of chemicals in the liver.

Lead is known to cause proximal tubular damage in the kidney. The chronic form of nephropathy is reported mainly in lead workers and an increased risk was noted in workers with PbB levels ranging from 40 to >100 µg/dl. Renal effects have recently been seen among the general population when more sensitive indicators of function were measured; PbB levels from 10 µg/dl may impair renal function in middle-aged and older men. Adverse effects of chronic low-level lead exposure on kidney function have been detected by measuring urinary markers in children with PbB levels of approximately 13 µg/dl; the pattern of effects was similar to that previously observed in adults.

6.6.3 Toxicity to reproduction

Epidemiological studies clearly indicate that lead causes adverse effects on human reproduction, including effects on sperm parameters, increased incidences of spontaneous abortion, miscarriages, and stillbirths. Developmental effects observed in humans following exposure to low levels of lead include reduced birth weight, reduced gestational age, and neurobehavioral deficits or delays. Regarding male reproductive function, decreased sperm counts and increased number of abnormal sperm may occur at PbB levels of 40 to 50 µg/dl. The available data do not permit any estimate of effect levels in women, but is probably above PbB levels of 10 µg/dl. One study has reported an association between cord PbB levels and minor anomalies; the relative risk doubled at PbB levels of about 7 to 10 µg/dl.

6.7 Animal toxicity

Health effects are generally not observed in laboratory animals after a single exposure, and no LD_{50}-values have been reported in the literature. The lowest observed lethal doses in animals after short-term oral exposure range from 300 to 4000 mg/kg b.w.

Following repeated oral exposure, lead causes a number of adverse effects in several organs and organ systems in experimental animals, including non-human primates. These include effects on the haematopoietic, nervous, renal, cardiovascular, reproductive and immune systems. Lead also affects bone and has been shown to be carcinogenic in rats and mice producing tumours of the kidney; detectable increases in renal tumour frequency apparently required doses in excess of 10 mg/kg b.w./day, doses which also caused renal toxicity in rodents. Despite kinetic differences between experimental animal species and humans, these studies provide strong biological support and plausibility for the findings in humans.

Effects on the testes (testicular atrophy) in male rats have been observed at PbB levels above 70 µg/dl but not at 54 µg/dl, and on oestrous cycles in female rats at PbB levels above 30 µg/dl.

6.8 Mutagenic and genotoxic effects

Data regarding genotoxicity are conflicting. Chromosomal aberrations have been reported in workers in lead-battery industries and lead smelters at PbB levels above 40 µg/dl, but other studies of workers under comparable conditions have given negative results. Increased incidences of sister chromatid exchanges have been reported in blood lymphocytes of workers exposed to lead, but not in those of children exposed to high levels of lead in the environment.

A few studies in rodents treated with lead salts *in vivo* have shown small, but significant increases in the frequency of chromosomal aberrations and micronuclei in bone-marrow cells, but most studies have shown no increase. Lead salts caused morphological sperm abnormalities in mice, but not in rabbits. Sister chromatid exchanges and unscheduled DNA synthesis were not induced in cells of animals treated with lead salts *in vivo*, and chromosomal aberrations were not induced in human lymphocytes *in vitro*. Conflicting results have been obtained in assays for transformation in cultured rodent cells. Lead salts did not cause aneuploidy in *Drosophila melanogaster*, mutation or gene conversion in yeast, or mutation or DNA damage in bacteria.

Regarding genetic effects of lead compounds, the IARC Working Group has recently concluded *"Lead is a toxic metal and one expression of this property is genetic toxicity. There is, however, little evidence that lead interacts directly with DNA. The genetic effects of lead appear to be mediated in part by increases in and modulation of reactive oxygen species. In addition, lead itself can interact with proteins, including those involved in DNA repair. These properties could result in mutation, cell proliferation and changes in gene expression, all of which would contribute to a carcinogenic response under conditions of sustained exposure."* (IARC 2004)

6.9 Carcinogenic effects

The carcinogenicity of lead compounds in humans has been examined in several epidemiological studies, predominantly in high-exposed workers. The studies have either been negative or have shown only small excess mortalities from cancers of the lung, stomach, kidney, and brain and nervous system. US-EPA (IRIS 2004 – last revised 11/01/1993) has concluded that the available human evidence is inadequate to refute or demonstrate any potential carcinogenicity for humans from lead exposure. IARC (2004) has recently evaluated the epidemiological evidence of possible cancer hazards from exposure to lead and lead compounds and concluded that there is limited evidence for the carcinogenicity to humans of exposure to inorganic lead compounds.

Studies in experimental animals have shown that soluble lead compounds (primarily acetates and phosphates) administered in food or drinking water has produced renal tumours at quite high doses (>10 mg/kg b.w./day). IARC (2004) and US-EPA (IRIS 2004) have concluded that there is sufficient evidence for the carcinogenicity to experimental animals of exposure to inorganic lead compounds.

6.10 Evaluation

Lead adversely affects several organs and organ systems, including effects on the nervous, haematopoietic, and reproductive systems, and cardiovascular, hepatic, renal, and gastrointestinal effects. Neurodevelopmental effects and subcellular changes, particularly the effects on haem synthesis, appear to be the most sensitive endpoints for which no threshold apparently exists.

Lead causes a continuum of nervous system effects in children and adults ranging from slowed nerve conduction, behavioural changes, and small decrements in cognitive ability, to mental retardation and encephalopathy. The effects on the nervous system generally develop at lower PbB levels in children than in adults and the most critical effect of lead at low exposure levels is the association with impaired cognitive development and intellectual performance in children. The available epidemiological studies have shown inconsistency in the results, but the overall conclusion is that there is an association between indices of lead burden (usually PbB) and impairment of cognitive and behavioural development of the central nervous system. The studies do not provide definitive evidence of a threshold but there is some evidence of an association between lead exposure and cognitive deficits below a PbB level of 10 µg/dl. This is supported by a very recent study, which indicates that PbB levels below 10 µg/dl are inversely associated with children's IQ scores at 3 and 5 years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations.

Lead is shown to affect several enzymatic reactions critical in haem synthesis. The available epidemiological studies indicate that the activity of one of the enzymes, ALAD, is inhibited at very low PbB levels (about 5 µg/dl), with no threshold apparent. The effects of lead on the haematopoietic system result in decreased haemoglobin synthesis. The estimated PbB associated with a decrease in haemoglobin level in children is 40 µg/dl and in adults 50 µg/dl. Anaemia, defined as a haematocrit below 35%, was not observed in one study of children at a PbB level below 20 µg/dl.

Other effects observed following long-term oral exposure to lead compounds include cardiovascular, hepatic, and renal effects. These effects have been reported to occur at higher exposure levels than those at which the effects on the nervous and haematopoietic systems have been observed.

Overt signs of acute intoxication have occurred in children at PbB levels of 80 to 100 µg/dl, thus implying that acute toxicity is not a critical endpoint for lead exposure via ingestion of soil.

Studies in experimental animals have shown that soluble lead compounds administered in food or drinking water has produced renal tumours at quite high doses (>10 mg/kg b.w./day), dose levels which also caused renal toxicity in rodents. The epidemiological studies have either been negative or have shown only small excess mortalities from cancers of the lung, stomach, kidney, and brain and nervous system. Many of the studies suffer from severe limitations such as lack of information of exposure levels, no adjustment for confounding factors, and concurrent exposure to potential carcinogens such as arsenic, cadmium and chromium. IARC (2004) has concluded that inorganic lead compounds are probable carcinogenic to humans, Group 2A (limited evidence for the carcinogenicity to humans, sufficient evidence to experimental animals).
Data regarding genotoxicity are conflicting. IARC (2004) has concluded that the properties of lead (increases in and modulation of reactive oxygen species, interaction with proteins including those involved in DNA repair) could result in mutation, cell proliferation and changes in gene expression, all of which would contribute to a carcinogenic response under conditions of sustained exposure. Overall, a carcinogenic potential cannot be excluded in relation to ingestion of lead with soil.

Epidemiological studies clearly indicate that lead causes adverse effects on human reproduction as well as developmental effects. Regarding male reproductive function, decreased sperm counts and increased number of abnormal sperm may occur at PbB levels of 40 to 50 µg/dl. The available data do not permit any estimate of effect levels in women, but these are probably above PbB levels of 10 µg/dl. The most critical effect of lead at low concentrations is reduced cognitive development and intellectual performance in children exposed pre- and postnatally. Overall, data indicate that the neurodevelopmental effects might occur even below a PbB level of 10 µg/dl and no clear threshold for these effects has been identified. Other developmental effects as well as reproductive effects in males and females are not considered to occur at the PbB levels associated with effects on the nervous and haematopoietic systems, i.e., above 10 µg/dl.

Most of the human data on health effects of lead are expressed in terms of internal exposure (blood lead (PbB) levels), rather than external exposure (mg/kg b.w./day). The relationship between external exposure and PbB is very difficult to ascertain for several reasons and most studies have attempted to correlate PbB levels and lead concentrations in specific media rather than correlating PbB levels with the total external exposure. For the purpose of this evaluation, it would be appropriate

to correlate PbB levels with concentrations of lead in soil. Based on data from the USA, Embedslægerapporten (2002) has assumed an increase in the PbB level of 2 µg/dl for an increase in the soil lead concentration of 100 mg/kg. However, according to WHO (1995), the available studies on the relationship between the PbB level and lead in soil/dust have shown an extreme variability in the estimates, and the relationship varies among locales. Furthermore, the US data used in Embedslægerapporten to estimate the relationship between PbB and lead exposure from soil apparently do not distinguish between lead in soil and lead in house dust and thus, the relationship is probably for a combined exposure to soil and house dust and not solely to soil. In that respect it should be noted that, in the USA, lead-based paint is probably a more important contributor of lead to house dust than is lead-contaminated soil. Consequently, the exposure patterns in the USA are probably not comparable with those in Denmark. In addition, the relationship between external exposure and the PbB level appears to be curvilinear, i.e., as exposure increases the corresponding PbB increments become smaller, and any estimated relationship between PbB and exposure is only valid for a narrow range of exposure levels. Therefore, the increase in the PbB level due to lead exposure from soil as estimated in Embedslægerapporten probably is an underestimate for low lead concentrations in soil. Because of the uncertainties in the estimated relationship between the PbB level and lead in soil, it is not considered scientifically sound to use this relationship for the purpose of setting a health based quality criterion for lead in soil.

Food is the major source of lead even in young children living in areas with high soil lead concentrations. The relationship of PbB to dietary intake has been estimated for children from studies with control of important variables such as intake of dietary lead and of other dietary constituents, and minimal exposure to sources other than the diet. For children, a relationship between the PbB level and lead intake from food has, according to (WHO 1995), been determined to be 0.16 µg/dl per µg Pb/day for PbB levels below 20 µg/dl. According to JECFA (2000), a dietary intake of lead by infants corresponded roughly to a change in the PbB level of 0.05-0.1 µg/dl per µg Pb/day, for a PbB level of about 15 µg/dl. Based upon these estimates, an increase in the PbB level of 0.1 µg/dl per µg Pb/day is considered for dietary lead intake of infants, and this estimate for the relationship between the PbB level and external exposure in form of dietary intake, the main source of lead even in young children, will be used for the purpose of setting a health based quality criterion for lead in soil.

6.10.1 Critical effects and NOAEL / LOAEL

The critical effects following intake of lead are the effects observed in the nervous, haematopoietic and reproductive systems, and carcinogenicity.

The most critical effect of lead at low concentrations is considered to be reduced cognitive development and intellectual performance in children exposed pre- and/or postnatally, with no threshold apparent. There is some evidence of an association between lead exposure and cognitive deficits below a PbB level of 10 µg/dl. This is supported by a very recent study, which indicates that PbB levels below 10 µg/dl are inversely associated with children's IQ scores at 3 and 5 years of age, and associated declines in IQ are greater at PbB levels below 10 µg/l than at higher PbB levels. Other developmental effects as well as reproductive effects in males and females are not considered to occur at PbB levels below 10 µg/dl.
Another sensitive endpoint is the effect of lead on haem synthesis. ALAD, one of the enzymes in the haem synthesis pathway, is inhibited at very low PbB levels (about

5 µg/dl), with no threshold apparent, although adverse effects are not associated with its inhibition at this level.
A carcinogenic potential of lead cannot be excluded in relation to ingestion of lead with soil, however, the mode of action has not yet been completely revealed.

The effect levels are expressed in terms of internal exposure (PbB level) and not in terms of external exposure or intake (e.g., mg/kg b.w./day). The relationship between the total external exposure to lead and the PbB level in young children (1-3 years old) cannot be ascertained for several reasons. One reason is that the majority of studies have attempted to correlate PbB levels and lead concentrations in specific media rather than correlating PbB levels with the total external exposure, and none of the estimated relationships are considered to be a valid surrogate for the relationship between the total external exposure to lead and the PbB level in young children. Furthermore, PbB levels reflect the absorbed dose of lead; however, in view of the relatively short half-life in blood (about 36 days) PbB levels generally reflect relatively recent exposures. In addition, lead in blood is derived from uptake of lead from environmental media as well as from internal lead, i.e., lead stored in tissues (particularly bone) that re-enters the blood during tissue mobilisation, and lead transferred from the mother to the child during pregnancy and lactation.

Overall, data indicate that the neurodevelopmental effects can be associated with very low PbB levels and no clear threshold for these effects has been identified. Furthermore, the relationship between the total external exposure to lead and the PbB level in young children (1-3 years old) cannot be ascertained based on the available data for several reasons. Therefore, a TDI (or preferable, a tolerable weekly intake for a cumulative substance as lead) and consequently, a health based quality criterion in soil cannot be established for lead. This conclusion is in accordance with the most recent evaluation (August 2004) of the US-EPA *"…it is still inappropriate to develop reference values for lead."* because of *"…the continued apparent lack of a threshold"* and because *"Lead body burdens vary significantly with age, health status, nutritional state, and maternal body burden during gestation and lactation."* (IRIS 2004).

7 Quality criterion in soil

The current quality criterion, 40 mg Pb/kg soil, is based on the JECFA PTWI of 25 µg/kg b.w. where 50% (i.e., 13 µg/kg b.w./week) of the PTWI value was allocated to known lead sources and where the contribution from food, air and drinking water was estimated to 8 µg/kg b.w./ week and the remaining 5 µg/kg b.w./week was allocated to intake from soil. (MST 2004).

A health based quality criterion in soil cannot be established based on the available data as discussed in section 6.10.1. However, the available data indicate that the neurodevelopmental effects can be associated with very low PbB levels, with no threshold apparent. Therefore, the exposure to lead from all sources, including soil, should be as low as reasonable achievable (ALARA) and consequently, a health based quality criterion would be lower than the current quality criterion.

Concentrations of lead in soil vary greatly:
In Danish non-urban soils (agricultural, forests), an average concentration of 11 mg/kg (median) has been reported with the 95 percentile being 19 mg/kg (DMU 1996); the median concentration can be taken as a background concentration.
In urban soils, data from Copenhagen and Frederiksberg have shown that 51% of soil samples (7505 samples) taken from 1996 to 2001 showed lead concentrations below 40 mg/kg, 44% between 40 and 400 mg/kg, and 5% above 400 mg/kg. The average concentration was 123 mg/kg with the 95 percentile being 360 mg/kg. (Embedslægerapporten 2002).
In Sweden, the median soil lead concentration in urban Stockholm was 100 mg/kg (range: < 10-330 mg/kg) compared with a median value of 16 mg/kg (range: < 10-50 mg/kg) in a reference area (Sundbyberg, suburb to Stockholm); soil samples were collected in 1992 and 1993. In a mining town (Sala), the median soil lead concentration was 295 mg/kg (range: 20-5000 mg/kg) compared with a median value of 31 mg/kg (range: 10-39 mg/kg) in a reference area (Heby); soil samples were collected in 1991 and 1992. (Berglund et al. 2000).
These data show that a reduction of the current quality criterion in soil implies that the criterion will approach the background concentration in Danish non-urban soils.

As no specific health based soil quality criterion can be established for lead, it is recommended that the current quality criterion in soil should be used also in the future as an *administrative* based soil quality criterion.
The Swedish study (Berglund et al. 2000) has shown that food is now the main source of lead exposure, even in young children living in areas with high soil lead concentrations, and it was concluded that lead in soil and dust contributed to a minor degree to the total intake. Furthermore, there were no significant differences in PbB levels between the differently contaminated areas (median 2.8 µg Pb/dl in Stockholm and 1.9 µg Pb/dl in the mining town Sala) and control areas with much lower concentrations of lead in soil (average 2.7 µg Pb/dl in Sundbyberg, the suburb to Stockholm, and 2.1 µg Pb/dl in the rural non-mining area, Heby). These findings imply that a soil quality criterion for lead of 40 mg/kg still may be considered as a preventive level although there may be some contribution to the total lead body burden at this exposure level from soil. Under these circumstances a theoretical intake from soil following ingestion of 0.1 g soil per day is estimated to 4 µg Pb/day (0.3 µg Pb/kg b.w./day) for a child weighing 13 kg. This estimated intake from soil is about 1/3 of the daily intake of lead from food and drinking water. Thus, the current quality

criterion in soil is not considered to have a significant impact on impaired cognitive development and intellectual performance in children, the most critical effect of lead.

In conclusion, the current quality criterion of 40 mg Pb/kg soil should be retained as an administrative based quality criterion in soil.

7.1.1 Quality criterion in soil

Quality criterion (*administrative based*): 40 mg Pb/kg soil.

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Lead and inorganic lead compounds

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to lead and inorganic lead compounds and an estimation of a quality criterion in soil. This resulted in 2004 in the present report which includes an administrative based quality criterion in soil.

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