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Environmental Protection Agency

Lead, inorganic and soluble salts

Evaluation of health hazards and proposal of a health-based quality criterion for drinking water

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Title:

Lead, inorganic and soluble salts. Evaluation of health hazards and proposal of a health-based quality criterion for drinking water

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Content

Preface

This report has been prepared by Elsa Nielsen and John Christian Larsen, Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

In 2002, the European Commission asked EFSA (the European Food Safety Authority) "*… for a scientific opinion on the risks to human health related to the presence of lead in foodstuffs. In particular, the opinion should consider any new developments regarding the toxicity of lead since the SCF (Scientific Committee for Food) opinion of 1992 in order to assess whether the PTWI (Provisional Tolerable Weekly Intake) of 25 µg/kg bw is still appropriate. The opinion should contain an updated exposure assessment for lead, in particular addressing exposure from food (incl. drinking water) and from other non-dietary sources (e.g. air), the exposure situation for specific groups of the population (e.g. infants and children, people following specific diets, smokers, etc.) and an indication of the age group in which children would be most exposed to the toxic effects of lead take into account available biomonitoring data when assessing the exposure and compare the results with the calculated exposure*." The 'Scientific Opinion on Lead in Food' was published in 2010 (EFSA 2010).
The Danish EPA has requested an update of the 2004 report 'Evaluation of health hazards by exposure to lead and inorganic lead compounds and estimation of a quality criterion in soil' (Nielsen 2004) primarily based on the EFSA (2010) opinion. But also the recent opinion from the European Chemicals Agency (ECHA) Committee for Risk Assessment (RAC) 'Opinion on an Annex XV dossier proposing restrictions on lead and lead compounds in jewellery' (ECHA 2011a), as well as the most recent JECFA evaluation on lead (JECFA 2011) should be consulted.

The report has been elaborated according to the general practice laid down in the Danish EPA guidance document for the setting of health-based quality criteria for chemical substances in relation to soil, ambient air and drinking water.

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

- The Danish Nature Agency: Anne Christine Duer
- The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences): Niels Henrik Spliid
- The Danish Veterinary and Food Administration: Gudrun Hilbert
- The National Board of Health, Denmark, medical officer of health: Lene Garsdal
- Danish Regions: Arne Rokkjær,
- The Danish Environmental Protection Agency: Katrine Smith, Poul Bo Larsen, Finn Pedersen, Jette Rud Heltved.

1 General description

The effects of inorganic lead and lead compounds have been studied extensively and thus, numerous data are available regarding adverse health effects of inorganic, soluble lead compounds in humans as well as in experimental animals. The current evaluation will primarily focus on the human data, and is an update of these data in the 2004 report 'Evaluation of health hazards by exposure to lead and inorganic lead compounds and estimation of a quality criterion in soil' (Nielsen 2004). The critical effects of inorganic, soluble lead compounds at low exposure levels are the neurodevelopmental effects, particularly the association with reduced cognitive development and intellectual performance in young children; therefore, this endpoint is the main focus of the current evaluation.

The update is primarily based on the recently published 'Scientific Opinion on Lead in Food' from the European Food Safety Authority (EFSA 2010). Text taken from the Nielsen (2004) report, as well as new information in this update report, is clearly indicated. It should be noted that only the information from the Nielsen (2004) report of relevance for the setting of a health-based quality criterion for inorganic, soluble lead compounds in drinking water is taken over and updated in this report.

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

1.1 Identity and physical / chemical properties

Taken from Nielsen (2004):

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).

1.2 Use

Taken from Nielsen (2004):

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).

New information:

In Denmark, the uses of lead and lead compounds are regulated in a number of different Statutory Orders (MST 2012a). Specific rules for the allowed content of lead have been issued for several specific products or product categories such as, e.g. electrical and electronic consumer products, batteries, vehicles and

ammunition. For products not specifically regulated by year 2000 there is a widespread ban towards import and sale of lead-containing products.

1.3 Environmental occurrence and fate

Taken from Nielsen (2004):

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

Taken from Nielsen (2004):

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

Taken from Nielsen (2004):

Lead is present in tap water 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).

New information:

In Danish groundwater samples taken in the period 1993-2006, lead was found in 406 of 663 (61%) abstraction wells and occurred in concentrations over the drinking water standard (5 µg/l, value at the entrance to the property) in 10 samples (2%). The average concentration was 0.6 µg/l and the maximal concentration measured was 35 µg/l. (GEUS 2007).

In 2010, lead occurred in concentrations over the drinking water standard (5 µg/l, value at the entrance to the property) in four of 238 samples from Danish groundwater (GEUS 2011).

In a screening survey of metal release at consumers' kitchen taps, the release of lead was measured in 51 domestic drinking water installations on Zealand (primarily in the vicinity of Copenhagen), Denmark (FORCE Technology 2008). Water samples were taken in three different ways: A fully flushed sample (A-sample), and two four-hour stagnation samples of 200 ml (B-sample) or 800 ml (C-sample). The three samples were taken in order to represent water from mains, first part of installation (mixer taps, connecting pipe, stop valve) and remaining part of installation (pipes, manifolds, water meter, valves). The concentration of lead was low in the A-samples, and generally increased in the B- and C-samples with average concentrations of 7.3 µg/l in the B-samples and 2.8 µg/l in the C-samples. The maximum concentration of 110 µg/l was found in a B-sample. The authors noted "*The measured concentrations cannot be compared with the parametric value of 10 µg/l as weekly average.*"

1.3.3 Soil

Taken from Nielsen (2004):

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. (WHO 1995, WHO 1996, ATSDR 1999).

1.3.4 Foodstuffs

Taken from Nielsen (2004):

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).

New information:

In Denmark (1998-2003), lead was measured in 96 food items and mainly found in offal (liver, kidney), beverages and vegetables with average concentrations ranging from about 1 to 47 µg Pb/kg fresh weight (Fromberg et al. 2005).

Following an EFSA call for data on lead concentrations in various food commodities and tap water, a total of 94126 results (from 14 Member States (including Denmark) and Norway in the period 2003-2009) were evaluated as being suitable for calculating lead concentrations in various food categories (EFSA 2010). In about two thirds of the samples, the lead level was below the limit of detection (LOD) or limit of quantification (LOQ) (figures not presented here as both LOD and LOQ varied with the analytical technique, the laboratory and the food matrix). The mean lead concentrations in the various food categories are presented in Table 1. Adjustment factors based on detailed food consumption information (or food production in some cases) were used to normalise an unbalanced sampling frequency in order to better reflect products as consumed when aggregating the results into the various food categories.

Table 1. Lower bound (LB) and upper bound (UB) original and adjusted lead mean concentration (µg/kg[1]) in various food categories (EFSA 2010)

EFSA Concise Food Category	**Mean**		**Adjusted mean**	
	LB	UB	LB	UB
Cereals and cereal products	28.6	47.1	21.0	40.7
Sugar and sugar products	33.9	60.2	40.3	64.4
Fats	38.7	63.5	29.2	55.0
Vegetables	73.3	92.2	37.7	53.6
Starchy roots or potatoes	22.3	34.5	24.1	36.4
Fruits	13.7	25.4	10.2	22.0
Juices, soft drinks, bottled water	4.7	10.2	3.0	11.0
Coffee, tea, cocoa	222	237	3.4	4.5
Alcoholic beverages	21.6	31.9	15.5	32.3
Meat and meat products	253	273	20.7	41.2
Fish and seafood	54.3	104	15.6	49.3
Eggs	5.2	25.2	5.2	25.2
Milk and dairy based products	8.9	20.2	10.2	22.0
Miscellaneous products	319	348	324	350
Food for special dietary uses	390	410	490	498
Infant and follow-on formula	4.4	14.3	2.0	4.7
Other infant food	37.0	70.1	8.2	20.3
Tap water	5.2	6.7	5.2	6.7

[1] All concentrations converted to µg/kg fresh weight.

1.4 Human exposure

Taken from Nielsen (2004):

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 bw, 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).

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).

New information:

In Denmark, the dietary intake for adults remained at a stable concentration level during the most recent 5-year period (1998-2003) in comparison with the previous monitoring periods where a decrease was observed (Fromberg et al. 2005): Estimated average dietary intake of 19 µg/day with the 95th percentile being 31 µg/day (1998-2003), average of 18 µg/day and 95th percentile of 28 µg/day (1993-1997), average of 27 µg/day and 95th percentile of 46 µg/day (1988-1992), and average of 42 µg/day and 95th percentile of 76 µg/day (1983-1987). The food groups that contributed mostly to the dietary lead intake were beverages (approximately 9.5 µg/day) followed by vegetables (approximately 1.5 µg/day), bread and cereals (approximately 2.5 µg/day), fruit (approximately 2 µg/day) and sugars (approximately 2 µg/day). It was noted in the report that the high proportion of lead intake from beverages is caused by a high mass of beverages in the total diet combined with the reported concentrations. Furthermore, it was noted that beverages included drinking water (tap water), which generally has a low concentration of lead, but the high consumptions explains why water is of importance for the dietary lead intake.
For children (4-6 years old, N = 230), the estimated average dietary intake was 9.7 µg/day with the 95th percentile being 15.4 µg/day (Fromberg et al. 2005).

In the EFSA 'Opinion on Lead in Food' (EFSA 2010) it is reported that human exposure is mainly via food and water, with some via air, dust and soil.
The mean and 95th percentile lead dietary exposures were calculated separately for each country recorded in the EFSA Concise European Food Consumption Database for the total population as well as for subgroups of the population, including infants, children and vegetarians. The adjusted occurrence results, aggregated at the concise food category level (see Table 1 in section 1.3.4) were used with the individual consumption data for each country separately. Selected results for Denmark and for the total European population are presented in Table 2.

Compared to dietary exposure, non-dietary exposure to lead was considered by EFSA (EFSA 2010) generally to be of minor importance for adults as well as children although it was noted that house dust and soil can be an important source of exposure to lead for young children. The exposure to lead from soil and dust for 2-year old children was estimated to be in the range of 0.18-0.80 μg/kg bw/day based on a mean and high lead content of 23 and 100 mg/kg soil and dust, respectively, and ingestion of 100 mg soil and dust per day by a child weighing 12.5 kg. The exposure to lead from outdoor air (adults) was estimated in the range of 0.001-0.003 μg/kg bw/day based on a mean and high lead content of 0.003 and 0.010 μg/m^3, respectively, and inhalation of 17 m^3 per day by an adult weighing 60 kg.

Table 2. Estimates of mean lead dietary exposure (μg/kg bw/day) (EFSA 2010)

	Mean LB[1]	**Mean UB[2]**	**P95 LB[1]**	**P95 UB[2]**
Denmark				
Adults (N = 4150)	0.56	1.03	0.84	1.61
Women 20-40 years (N = 742)	0.56	1.07	0.86	1.65
Europe				
Adults, minimum[3] (19 countries)	0.36	0.63	0.73	1.26
Adults, maximum[4] (19 countries)	0.74	1.24	1.74	2.43
Women (20-40 years), minimum[3]	0.38	0.64	0.68	1.13
Women (20-40 years), maximum[4]	0.80	1.28	2.03	2.60
Children 4-7 years (10 countries)	1.10	3.10	1.71	5.51
Children 1-3 years (10 countries)	0.80	2.61	1.30	4.83
Formula-fed infants (0-0.5 year)	0.27	0.63	0.40	0.94
	Average		**High consumers**	
Nursing infants (0-0.5 year)	0.21		0.32	

[1] Lower bound
[2] Upper bound
[3] Lower bound for country with lowest average exposure
[4] Upper bound for country with highest average exposure

2 Toxicokinetics

2.1 Absorption, distribution and elimination

Taken from Nielsen (2004):

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

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).

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).

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).

2.2 Mode of action

Taken from Nielsen (2004):

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

Taken from Nielsen (2004):

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

Taken from Nielsen (2004):

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 bw/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).

New information:

In the EFSA 'Opinion on Lead in Food' (EFSA 2010) it is noted that most of the information on human health effects of lead is based on PbB (blood lead level) data. Lead in blood has two main pools, a short-half-life pool (blood and soft tissues with a half-life of 20-40 days) and a long-half-life pool (skeleton with a half-life of 10-30 years). Thus, PbB reflects a combination of recent exposure and that which occurred several years previously. At steady-state, PbB is considered to be the most suitable indicator of the concentration of lead in soft tissues, and hence recent exposure; however, PbB does not necessarily correlate with the total body burden of lead. The lead concentration in bone reflects long-term uptake and the total body burden as more than 90% of the total body burden is in the skeleton.

Most of the lead in blood is present in the red blood cells. The relationship between lead uptake and PbB is curvilinear, i.e. at low lead uptake there is a steady linear increase in PbB with increasing uptake, while at higher lead uptakes the curve flattens out as binding sites in the red blood cells become saturated. (EFSA 2010).

In the most recent JECFA evaluation (JECFA 2011), it is noted that the relationship between dietary exposure to lead and blood lead levels has previously been evaluated by the Committee (JECFA 2000) based on data from a study of a group of Scottish infants exposed to lead from drinking water (Lacey et al. 1985 – quoted in JECFA 2000). The previous evaluation concluded that a range between 0.05 and 0.10 µg/dl per 1 µg/day of dietary exposure was appropriate for low levels of lead exposure. In the present analysis (JECFA 2011), the Committee employed a range of 0.05 to 0.16 µg/dl per 1 µg/day for children.

3.2 Single dose toxicity

Taken from Nielsen (2004):

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

The nervous system is the main target organ for lead 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 effects on the nervous system generally develop at lower PbB levels in children than in adults. As the most critical effect of inorganic, soluble lead compounds at low exposure levels is the association with reduced cognitive development and intellectual performance in young children, this endpoint is the main focus in this section.

3.3.1.1 Behavioural function

Summarised from Nielsen (2004), section 3.3.1.2 and section 6.6.2:

A number of epidemiological studies have been carried out (reviewed in WHO 1995, ATSDR 1999, and/or Banks et al. 1997 as well as recent studies quoted in Toxline 1995-1999/04), 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 (as reviewed in WHO 1995, WHO 1996, ATSDR 1999, and/or Banks et al. 1997) 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 (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; 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-analyses 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 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) and one study (Finkelstein et al. 1998 - quoted from Toxline 1995-1999/04), 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 (Canfield et al. 2003), 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 (disturbances in reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, impaired memory and learning ability, nervousness, mood, or coping ability) at PbB levels from 40 to 60 µg/dl (ATSDR 1999, WHO 1995).

New information:

A pooled analysis of the results of seven studies initiated prior to 1995 was performed by Lanphear et al. (2005 – quoted from EFSA 2010). The three largest studies indicated the strongest support for an association between lead exposure and developmental neurotoxicity, whereas two studies did not indicate any negative effect of lead exposure. The EFSA CONTAM Panel considered, that although the results of the individual studies differed in some respects, the overall evidence strongly supported an association between biomarkers of early-life chronic exposure to lead and lowered IQ and similar neuropsychological measures in children at school age, after adjustment for possible confounders. The geometric mean PbB concentration peaked at 178 µg/l and declined to 94 µg/l by 5-7 years of age. A total of 244 of the children had a maximal PbB concentration below 100 µg/l, with 103 having a maximum below 75 µg/l. The estimated IQ point decrement was 3.9 (95 % CI, 2.4 to 5.3) for an increase in PbB from 24 to 100 µg/l, 1.9 (95 % CI, 1.2 to 2.6) for an increase in PbB from 100 to 200 µg/l, and 1.1 (95

% CI, 0.7 to 1.5) for an increase in PbB from 200 to 300 μg/l. For a given increase in PbB, the intellectual decrement for children with a maximal PbB concentration <75 μg/l was significantly greater (p = 0.015) than that observed for those with a maximal PbB concentration ≥ 75 μg/l. The analysis also showed that the lead-associated deficits at lower exposures had become apparent only in recent studies that included children born in the post-leaded-petrol era. No threshold for these effects has been identified, and the evidence suggests that the response at PbB concentrations below 100 μg/l is steeper than at higher exposure levels.

A discernible impact of PbB on performance on end-of-grade (EOG) testing was found for early childhood blood levels as low as 20 μg/l; a PbB of 50 μg/l was associated with a decline in EOG reading and mathematics scores roughly equal to 15% of the interquartile range (Miranda et al. 2007 – quoted from EFSA 2010).

Jusko et al. (2008 – quoted from EFSA 2010) examined the association between PbB assessed throughout early childhood (from 6 months) and IQ in 194 children at 6 years of age. After adjustment for various potential confounders, lifetime average PbB (mean 72 μg/l; median 62 μg/l) was inversely associated with Full-Scale IQ and Performance IQ Scores. Compared with children who had lifetime average PbB concentrations <50 μg/l, children with lifetime average concentrations between 50 and 99 μg/l scored 4.9 points lower on Full-Scale IQ (p=0.03). Non-linear modelling of the peak PbB concentration revealed an inverse association (p=0.003) with Full-Scale IQ down to a PbB of 21 μg/l.

A possible anatomical basis for the developmental neurotoxicity of lead has been demonstrated by magnetic resonance scanning (Cecil et al. 2008 – quoted from EFSA 2010). Following increased lead exposure during childhood, reductions were documented in adult grey matter volume, especially of the prefrontal cortex that is responsible for executive functions, mood regulation and decision-making.

A recent prospective study (Min et al. 2009 – quoted from EFSA 2010) in children with diverse backgrounds that included maternal illicit drug exposure during pregnancy reported that PbB concentrations (of 50 μg/l and above) at age 4 years was negatively associated with IQ at age 4 through 11 years, while reading, mathematics and verbal scores were affected only at age 11 years, possibly because these functions were not testable at earlier developmental stages. This study therefore emphasises the importance of age at testing, and that the full spectrum of developmental neurotoxicity may not be apparent at preschool ages. Likewise, the time of exposure assessment is important.

In the EFSA 'Opinion on Lead in Food' (EFSA 2010) the available neurodevelopmental data have been concluded as follows: "*In conclusion, developmental lead neurotoxicity has been reported at exposures that correspond to a B-Pb of as low as 20 μg/L. The dose-effect relationship seems to be nonlinear, reflecting a greater relative impact at lower lead concentrations. It is unclear whether this association is due to toxicokinetic properties of lead at these dose levels. It is also possible that the outcome scales are not linearly linked to functional levels. Although the prospective studies provide better evidence, the use of lifetime average or peak exposure levels fail to take into account the age at greatest vulnerability. In addition, some important brain functions that are vulnerable to lead toxicity may not be testable in preschool children. The global tests, such as IQ scales, may not capture deficits that are restricted to certain types of brain function. However, the overall evidence clearly indicates developmental lead neurotoxicity. Lead-related developmental neurotoxicity appears to persist to at least the late teenage years; more severe forms of lead poisoning are known to have effects that are apparent in adulthood.*"

On a request from EFSA, the University of Copenhagen performed a benchmark dose (BMD) analysis of the Lanphear et al. (2005) data based on standard multiple regression models (Budtz-Jørgensen 2010 – as cited in EFSA 2010). The logarithmic model gave the lowest BMD and BMDL (benchmark dose level) with a BMD_{01} of 3.5 µg/l and a $BMDL_{01}$ of 2.6 µg/l, whereas the linear model gave the highest BMD and BMDL with a BMD_{01} of 18.0 µg/l and a $BMDL_{01}$ of 12.0 µg/l. The EFSA CONTAM Panel chose the $BMDL_{01}$ of 12.0 µg/l PbB as the reference point for their risk characterisation for assessing the risk of intellectual deficits in children as measured by the Full Scale IQ. The $BMDL_{01}$ associated with a BMR (benchmark response) of 1% (i.e. a decrease of cognitive ability by 1 IQ point) was chosen to account for the fact that a shift of the distribution of the IQ by 1 IQ point to lower values would have an impact on the socioeconomic status of the population and its productivity. The relationship between dietary lead intake and PbB levels in children up to age seven was estimated using an Integrated Exposure Uptake Biokinetic (IEUBK) model for lead in children and a $BMDL_{01}$ dietary intake value of 0.50 µg/kg bw/day for developmental neurotoxicity was derived. (EFSA 2010).

3.3.1.2 Peripheral nerve function

Summarised from Nielsen (2004), section 6.6.2:

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.

3.3.1.3 Neurological signs and symptoms

Summarised from Nielsen (2004), section 6.6.2:

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.

3.3.1.4 Hearing impairment in children

Summarised from Nielsen (2004), section 6.6.2:

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.

3.3.2 Effects on the haematological system

Summarised from Nielsen (2004), section 6.6.2:

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.

3.3.3 Cardiovascular effects

Summarised from Nielsen (2004), section 6.6.2:

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.

3.3.4 Hepatic effects

Summarised from Nielsen (2004), section 6.6.2:

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.

3.3.5 Renal effects

Summarised from Nielsen (2004), section 6.6.2:

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.

3.4 Toxicity to reproduction

Taken from Nielsen (2004):

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

Taken from Nielsen (2004):

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).

New information:

In the most recent IARC evaluation (IARC 2006) it was concluded: "*Humans occupationally exposed to lead show evidence of genotoxicity as measured in a variety of assays. In some studies, these effects were correlated with blood lead concentrations. However, all the human genotoxicity studies involved co-exposure*

to lead and other compounds, making it difficult to attribute genetic and other effects to lead alone. In a limited number of studies on non-occupationally exposed individuals, no genotoxic effects were found that were correlated with blood lead concentrations."

3.6 Carcinogenic effects

Taken from Nielsen (2004):

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, remark: The IARC 2004 reference is the draft version of the monograph from the meeting held in February 2004, whereas the IARC 2006 reference is the final version of the monograph). 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

Taken from Nielsen (2004):

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

Taken from Nielsen (2004):

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

Taken from Nielsen (2004):

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

Taken from Nielsen (2004):

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).

New information:

In the most recent IARC evaluation (IARC 2006) it was concluded: "*Lead is a toxic metal and one expression of this property is genetic toxicity. There is, however, little evidence that it interacts directly with DNA at normally encountered blood lead concentrations. The genetic toxicity of lead appears to be mediated in part by increases in, and modulation of, reactive oxygen species. In addition, lead interacts with proteins, including those involved in DNA repair. This latter mechanism might be responsible for enhancing the genotoxicity of other agents. These properties could result in mutation, changes in gene expression and cell proliferation, all of which would contribute to a carcinogenic response if exposure is sustained.*"

In the EFSA 'Opinion on Lead in Food' (EFSA 2010) the available data on genotoxicity has been summarised based on the information in the IARC (2006) evaluation. The EFSA CONTAM panel concluded that the data on genotoxicity indicate that lead may be a weak indirect genotoxin.

4.5 Carcinogenic effects

Taken from Nielsen (2004):

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 1987, 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.

New information:

In the most recent IARC evaluation (IARC 2006) the available data on carcinogenicity in experimental animals have been summarised as follows: "*Overall, extensive experimental evidence shows that various water-soluble and -insoluble lead compounds can induce kidney tumours in rodents. In addition, one study showed that renal tumours can occur in the absence of lead-induced nephropathy. It is also noteworthy that the induction of brain gliomas, which are rarely spontaneous, occurred after oral exposure to lead in rats. Lead proved to be an effective renal tumour carcinogen/promoter in rats and mice exposed to various organic renal carcinogens.*" The IARC Working Group concluded that there is sufficient evidence in experimental animals for the carcinogenicity of inorganic lead compounds. Remark: The IARC (2006) monograph is the final version of the IARC (2004) draft monograph from the meeting held in February 2004.

In the EFSA 'Opinion on Lead in Food' (EFSA 2010) the above IARC (2006) summary is reproduced. The EFSA CONTAM panel considered that human

exposure to lead through food is unlikely to represent a significant cancer risk as lead is not a direct acting genotoxin and the doses used to induce tumours in rodents are very high compared to human intake.

5 Regulations

5.1 Ambient air

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

5.2 Drinking water

Denmark: 10 µg Pb/l (tap), 5 µg Pb/l (entrance to the property) (MM 2001).

EU: 10 µg Pb/l (EC 1998).

WHO: 0.01 mg Pb/l (WHO 1996).

The guideline value was retained according to the revised volume 1 (WHO 2004).

In the fourth edition of the Guidelines (WHO 2011), the guideline value of 0.01 mg/l was again retained, but it was made provisional with the following justification: "*There remain uncertainties associated with the epidemiology, which relate to very low blood lead levels and end-points that are affected by many factors. Nevertheless, because lead exposure arises from a range of sources, of which water is frequently a minor one, and as it is extremely difficult to achieve a concentration lower than 10 µg/l by central conditioning, such as phosphate dosing, the guideline value is maintained at 10 µg/l but is designated as provisional on the basis of treatment performance and analytical achievability. It needs to be recognized that lead is exceptional, in that most lead in drinking-water arises from plumbing in buildings, and the remedy consists principally of removing plumbing and fittings containing lead, which requires much time and money. It is therefore emphasized that all other practical measures to reduce total exposure to lead, including corrosion control, should be implemented.*"

US-EPA: MCLG[1]: 0 mg/l (zero)
MCL[2]: -
TT[3] Action Level: 0.015 mg/l
(US-EPA 2012)

[1] Maximum Contaminant Level Goal (MCLG) - The level of a contaminant in drinking water below which there is no known or expected risk to health.
[2] Maximum Contaminant Level (MCL) - An enforceable regulation set for most contaminants, based on the MCLG. MCLs are set as close to the MCLGs as possible, considering cost, benefits and the ability of public water systems to detect and remove contaminants using suitable treatment technologies.
[3] Treatment Technique (TT) – An enforceable procedure or level of technological performance which water systems must follow to ensure control of a contaminant in drinking water. The treatment technique regulation for lead (referred to as the Lead and Copper rule) requires water systems to control the corrosivity of the water. The regulation also requires systems to collect tap samples from sites served by the system that are more likely to have plumbing materials containing lead. If more than 10% of tap water samples exceed the lead action level of 15 parts per billion, then water systems are required to take additional actions.

The MCLG was based on the best available science which shows there is no safe level of exposure to lead (US-EPA 2012).
Because lead contamination of drinking water often results from corrosion of the plumbing materials belonging to water system customers, a Treatment Technique (TT) rather than an MCL for lead has been established.
Health effects - Infants and children: Delays in physical or mental development; children could show slight deficits in attention span and learning abilities.
Health effects - Adults: Kidney problems; high blood pressure.
Sources of contamination: Corrosion of household plumbing systems; erosion of natural deposits.

5.3 Soil

Denmark: 40 mg/kg (MST 1995).

The quality criterion was based on the JECFA PTWI of 25 µg/kg bw (see section 5.8) where 50% of the PTWI value (i.e. 13 µg/kg bw/week) was allocated to known lead sources and where the contribution from food, air and drinking water was estimated to 8 µg/kg bw/ week and the remaining 5 µg/kg bw/week was allocated to intake from soil (MST 2004).

In the report 'Evaluation of health hazards by exposure to lead and inorganic lead compounds and estimation of a quality criterion in soil' (Nielsen 2004), it was concluded that a health-based quality criterion in soil could not be established as 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. Therefore, the quality criterion of 40 mg Pb/kg soil was retained as an administrative based quality criterion in soil.

The cut off criteria is 400 mg/kg. Between the soil quality criteria and the cut off criteria there must be advice on the use of the land for housing and child care center (MST 2012b).

5.4 Occupational Exposure Limits

Denmark: 0.05 mg Pb/m^3, 20 µg Pb/100 ml blood (biological exposure value) (At 2007).

5.5 Classification

Both the classification according to the Dangerous Substances Directive 67/548/EEC (DSD) in the former chemical regulation as well as the classification according to the present CLP-Regulation (EC) No 1272/2008 (CLP: Classification, Labelling and Packaging) are reproduced from the European chemical Substances Information System (ESIS 2012):

Lead compounds with the exception of those specified elsewhere in Annex VI:
DSD: Repr. Cat. 1; R61, Repr. Cat. 3; R62, Xn; R20/22, R33, N; R50-53
CLP: Repr. 1A H360Df, Acute Tox. 4 H302/H332, STOT RE 2 H373, Aquatic Acute 1 H400, Aquatic Chronic 1 H410

5.6 IARC

Inorganic lead compounds are probably carcinogenic to humans, Group 2A (limited evidence in humans, sufficient evidence in experimental animals) (IARC 2006).

5.7 US-EPA

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).

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

5.8 WHO / JECFA

25 µg/kg bw, provisional tolerable weekly intake (PTWI) (JECFA 2000). This PTWI was withdrawn in 2010, see below.

At the 16th meeting (report published in 1972), the JECFA Committee established a provisional tolerable weekly intake (PTWI) of 3 mg Pb per person (50 µg/kg bw), stating that this did not apply to infants and children. At the 22nd meeting (report published in 1978), the PTWI was retained for adults, noting that establishing a PTWI for children was not yet possible owing to the lack of relevant scientific data. The health risks associated with exposure of infants and children to lead were evaluated at the 30th meeting (report published in 1987), and a PTWI of 25 µg/kg bw was established for this population group, based on the information that a mean daily exposure to lead of 3-4 µg/kg bw for infants and children was not associated with an increase in blood lead levels. At the 41st meeting (report published in 1993), the previous PTWI of 50 µg/kg bw for adults was withdrawn and the PTWI of 25 µg/kg bw was extended to all age groups. In these previous evaluations, it was emphasized that the PTWI applied to lead from all sources. At the 53rd meeting (report published in 2000), the risk of dietary exposure of infants and children to lead was assessed and it was concluded that current concentrations of lead in food would have very little impact on the neurobehavioural development of infants and children, but it was stressed that a full risk assessment of lead should take other sources of exposure into account; the PTWI was not reconsidered. (JECFA 2011).

At the 73rd meeting (June 2010), the information on lead was evaluated, in particular for a dose-response analysis below blood lead levels of 10 µg/dl. The recent review of the European Food Safety Authority (EFSA 2010) was used as the starting point for the evaluation, together with newer studies that were considered to be informative. Only brief summaries of the toxicological effects were presented in the report, except for the studies of the effects critical for the risk assessment, which were evaluated in more detail. The main emphasis for this evaluation was on studies in humans.
The Committee noted that impaired neurodevelopment in children is generally associated with lower PbB concentrations than the other effects, the weight of evidence is greater for neurodevelopmental effects than for other health effects and

the results across studies are more consistent than those for other effects. Therefore, the Committee concluded that the effects on neurodevelopment provided the appropriate basis for dose-response analyses regarding blood lead levels and children's IQ. The analyses were based on estimates in the Lanphear et al. 2005 pooled analysis (described in section 3.3.1.1). After initial consideration of six different dose-response models, the bilinear model was chosen for the evaluation because this model represents a more conservative approach at low doses. The chronic dietary exposure corresponding to a decrease of 1 IQ point was estimated to be 12 µg/day (5^{th} to 95^{th} percentile CI 4-145 µg/day), equivalent to 0.6 µg/kg bw/day (5^{th} to 95^{th} percentile 0.2-7.2 µg/kg bw/day) for a 20 kg child (for children, a relationship between dietary exposure to lead and blood lead levels in the range of 0.05 to 0.16 µg Pb/dl blood per 1 µg/day was employed). Based on the dose-response analyses, the Committee estimated that the PTWI of 25 µg/kg bw is associated with a decrease of at least 3 IQ points in children. The Committee therefore concluded that the PTWI could no longer be considered health protective, and it was withdrawn. Because the dose-response analyses did not provide any indication of a threshold for the key effects of lead, the Committee concluded that it was not possible to establish a new PTWI that would be considered to be health protective. (JECFA 2011).

5.9 European Food Safety Authority (EFSA)

The CONTAM Panel in EFSA (EFSA 2010) identified developmental neurotoxicity in young children as the critical adverse effect of lead for the risk assessment with the decrease of (full scale) IQ score as intellectual deficit in children at ages 4 and higher as the most sensitive and most relevant endpoint. The pooled analysis performed by Lanphear et al. (2005, described in section 3.3.1.1) was selected as the database for the dose-response modelling. The CONTAM Panel chose the 95^{th} percentile lower confidence limit of the benchmark dose (BMD) of 1% extra risk ($BMDL_{01}$) of 12 µg Pb/l blood as the reference point for the risk characterisation of lead. The $BMDL_{01}$, associated with a benchmark response (BMR) of 1% (i.e. a decrease of cognitive ability by 1 IQ point), was chosen to account for the fact that a shift of the distribution of the IQ by 1 IQ point to lower values would have an impact on the socio-economic status of the population and its productivity. The relationship between dietary lead intake and PbB levels in children up to age seven was estimated using an Integrated Exposure Uptake Biokinetic (IEUBK) model for lead in children and a $BMDL_{01}$ dietary intake value of 0.50 µg/kg bw/day for developmental neurotoxicity was derived.
The CONTAM Panel concluded that the PTWI of 25 µg/kg bw set by JECFA (withdrawn at the JECFA meeting in June 2010, see section 5.8) and endorsed by the Scientific Committee of Food was no longer appropriate and that it would not be appropriate to derive a PTWI as there is no evidence for a threshold for a number of critical endpoints including developmental neurotoxicity.

5.10 Scientific Committee on Health and Environmental Risks (SCHER)

SCHER has published an opinion regarding the standard of 10 µg/l for lead in drinking water on a request from DG Environment as the rationale for the current 10 µg/l limit has been questioned and the Commission was asked to raise the limit to 15 or 20 µg/l (SCHER 2011).
SCHER concluded that even at PbB levels below 10 µg/dl adverse effects on children's intelligence development can be observed. The SCHER opinion cited the EFSA conclusion that when using a low concentration of lead in drinking water (2.1 µg/l), the dietary exposure of sensitive subgroups (infants and foetal exposure)

to lead results in a Margin of Exposure (MoE) value below 1 indicating that risks to young children regarding neurodevelopmental effects cannot be excluded. The SCHER opinion also noted that in the European Risk Assessment Report of lead (VRAR 2008), a drinking water concentration of 10 µg/l was integrated in the exposure assessment. This resulted in PbB levels above the 'epistemic' threshold of 5 µg/dl (proposed in the VRAR 2008) for impacts of lead upon societal cognitive resources; it was noted (in the VRAR 2008) that effects may occur at PbB levels less than 10 µg/dl and that a 'real' threshold for lead effects cannot be identified. An increase in the drinking water concentrations above 10 µg/l will therefore, further increase exposures and cause additional risk to human health, particularly to the mental and neurological development of children aged 0-14 years. Overall, SCHER concluded that there is no scientific basis to support an increase in the lead drinking water standard; in fact, a further reduction in lead intake is warranted for risk reduction.

5.11 European Chemicals Agency (ECHA)

The ECHA Committee for Risk Assessment (RAC) has published an opinion on an Annex XV dossier proposing restrictions on lead and lead compounds in jewellery (ECHA 2011a). The opinion was based on information related to the identified risk and to the identified options to reduce the risk as documented in an Annex XV dossier submitted by France (ECHA 2011b) and information submitted by interested parties.

RAC expressed their agreement with the assessment from France that developmental neurotoxicity, specifically neurobehavioral effects from repeated lead exposure, is the key effect that the restriction is aimed at protecting against. As children will be particularly sensitive to this hazard, given that their central nervous system is still under development and as no threshold for the adverse effect has been identified in humans, RAC considered that any exposure by released lead from jewellery will present a risk. In consideration of the mouthing behaviour of small children, and the possibility for lead migration, RAC concluded that lead exposure of children from jewellery may occur.

RAC also expressed their support to the risk assessment of EFSA (EFSA 2010), in which a lower benchmark dose level ($BMDL_{01}$, corresponding to a change in the PbB level of 12 µg/l and an IQ loss of 1 point) of 0.5 µg Pb/kg bw/day was derived as a dose descriptor for the potential adverse effects of lead on children. RAC noted that EFSA observed that children in the age group of 1-7 years have mean background lead exposures between 0.8 and 5.5 µg/kg bw/day (e.g. from the diet and background environmental exposure) and that this clearly already exceeds the $BMDL_{01}$ level of 0.5 µg Pb/kg bw/day. Therefore, any additional lead exposure would on average be expected to further increase a typical child's exposure above the dose descriptor level.

Based on the EFSA $BMDL_{01}$ of 0.5 µg Pb/kg bw/day, application of a MoE of 10, and an exposure scenario in which a child (10 kg bw) mouths a jewel for one hour with a surface of 10 cm^2 and a weight of 10 g, a tolerable migration rate from the jewellery of 0.05 µg Pb/cm^2/hr or 0.05 µg Pb/g/hr was estimated. RAC noted that the exposure of 0.05 µg Pb/kg bw/day correlates with an IQ reduction in children of 0.1 points. RAC also noted that any relevant lead exposure should in principle be avoided as no threshold has been found for the harmful effect of lead on the central nervous system, and with a view to background exposure from diet and other environmental sources.

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.

In Danish groundwater samples taken in the period 1993-2006, the average concentration of lead was 0.6 µg/l and the maximal concentration measured was 35 µg/l.

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. In Denmark (1998-2003), lead was measured in 96 food items and mainly found in offal (liver, kidney), beverages and vegetables with average concentrations ranging from about 1 to 47 µg Pb/kg fresh weight.

6.3 Human exposure

In the general non-smoking adult population and older children, the major source of exposure to lead is mainly via food and water. In Denmark, the estimated average dietary intake for adults (1998-2003) was 19 µg/day with the 95th percentile being 31 µg/day. For children (4-6 years old), the estimated average dietary intake was 9.7 µg/day with the 95th percentile being 15.4 µg/day.

In average adult consumers in 19 European countries, the average dietary lead exposure was 0.36-1.24 µg/kg bw/day and 0.73-2.43 µg/kg bw/day for high consumers (lower bound for country with lowest average exposure – upper bound for country with highest average exposure). The dietary exposure was similar for women of child-bearing age. Cereals, vegetables and tap water contributed most to the dietary lead exposure.
For children (4-7 years), the average dietary lead exposure was 0.80-2.61 µg/kg bw/day and 1.30-4.83 µg/kg bw/day for high consumers; for children (1-3 years), the average was 1.10-3.10 µg/kg bw/day and 1.71-5.51 µg/kg bw/day for high

consumers; and for infants fed with ready-to-consume infant formula (3 months), the average was 0.27-0.63 μg/kg bw/day and 0.40-0.94 μg/kg bw/day for high consumers; the intervals are based on lower bound and upper bound assumptions, respectively.
For breast-fed infants (3 months), the average was estimated to be 0.21 μg/kg bw per day and 0.32 μg/kg bw per day for high consumers.

Compared to dietary exposure, non-dietary exposure to lead is of minor importance for the general non-smoking adult population and older children.
House dust and soil can be an important source of exposure to lead for young children. The exposure to lead from soil and dust for 2-year old children has been estimated to be in the range of 0.18-0.80 μg/kg bw/day.

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, lead is transported in the blood primarily within erythrocytes and then transferred to soft tissues, including liver and kidneys, 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, half-lives for inorganic lead in blood and bone are approximately 30 days and between 10 and 30 years, respectively; 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. Enhanced mobilisation of lead from bones occurs during pregnancy.

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 in urine and to a lesser extent by biliary clearance and then in the faeces.

6.5 Mode of action

Many toxic effects of lead can be attributed to the affinity of lead for the sulfhydryl (thiol) group (–SH) and other ligands in proteins. In addition, lead has the ability to substitute for calcium, and perhaps also zinc, and this is also a factor common to many of the toxic actions of lead. Therefore, almost all organs and organ systems may be considered as potential targets for lead toxicity.

6.6 Relationship between lead exposure and blood lead levels

Most of the information on human health effects of lead is based on internal exposure (blood lead (PbB) levels) rather than external exposure. Lead in blood has a short-half-life pool (blood and soft tissues) and a long-half-life pool (skeleton) and thus, PbB reflects a combination of recent exposure as well as exposure several years

previously. At steady-state, PbB is considered to be the most suitable indicator of the concentration of lead in soft tissues, but PbB does not necessarily correlate with the total body burden of lead. The lead concentration in bone reflects the total body burden as more than 90% of the total body burden is in the skeleton.

Most of the lead in blood is present in the red blood cells. The relationship between lead uptake and PbB is curvilinear, i.e. at low lead uptake there is a steady linear increase in PbB with increasing uptake, while at higher lead uptakes, the curve flattens out as binding sites in the red blood cells become saturated. The 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. In the most recent JECFA evaluation (JECFA 2011), a range of 0.05 to 0.16 µg/dl per 1 µg/day for children was employed.

6.7 Human toxicity

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. 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.

The central nervous system is the main target organ for lead toxicity. Lead causes a continuum of effects in children and adults ranging from slowed nerve conduction, behavioural changes, and small decrements in cognitive ability, to mental retardation and encephalopathy. There is considerable evidence demonstrating that the developing brain is more vulnerable to the neurotoxicity of lead than the mature brain. The most critical effect of lead at low exposure levels is the developmental neurotoxicity. Numerous studies have documented that an elevated blood lead level is inversely associated with a reduced IQ score and reduced cognitive functions up to at least seven years of age. There is some evidence that this subsequently leads to a reduced adult grey matter volume, especially of the prefrontal cortex. The dose-effect relationship between blood lead levels and IQ seems to be non-linear reflecting a greater relative impact at lower lead concentrations. Developmental lead neurotoxicity has been reported at exposures corresponding to a PbB level as low as 2 µg/dl and evidence suggests that the responses at PbB levels below 10 µg/dl is steeper than at higher concentrations. Overall, the available studies do not provide definitive evidence of a threshold for the lead induced neurodevelopmental effects.

As the critical effects of inorganic, soluble lead compounds at low exposure levels are the neurodevelopmental effects, particularly the association with reduced cognitive development and intellectual performance in young children, this is the only endpoint summarised in this section. Summaries on adverse effects on other target organs and systems can be found in sections 3.3.2 to 3.3.5 and 3.4.

6.8 Animal toxicity

Lead causes a number of adverse effects in several organs and organ systems in experimental animals, including non-human primates following repeated exposure. 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 bw/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.

6.9 Mutagenic and genotoxic effects

In the most recent IARC evaluation (IARC 2006) it was concluded: "*Lead is a toxic metal and one expression of this property is genetic toxicity. There is, however, little evidence that it interacts directly with DNA at normally encountered blood lead concentrations. The genetic toxicity of lead appears to be mediated in part by increases in, and modulation of, reactive oxygen species. In addition, lead interacts with proteins, including those involved in DNA repair. This latter mechanism might be responsible for enhancing the genotoxicity of other agents. These properties could result in mutation, changes in gene expression and cell proliferation, all of which would contribute to a carcinogenic response if exposure is sustained.*"

In the EFSA 'Opinion on Lead in Food' (EFSA 2010) it was concluded that the data on genotoxicity indicate that lead may be a weak indirect genotoxin.

6.10 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 (2006) has also 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 produced renal tumours at quite high doses (>10 mg/kg bw/day). IARC (2006) and US-EPA (IRIS 2004) have concluded that there is sufficient evidence for the carcinogenicity to experimental animals of exposure to inorganic lead compounds.

In the EFSA 'Opinion on Lead in Food' (EFSA 2010) it was concluded that extensive experimental evidence shows that various water-soluble and -insoluble lead compounds in high doses can induce tumours at different sites in rodents.

6.11 Evaluation

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 the adverse health effects of lead. Many toxic effects of lead are due to the affinity of lead for the thiol group (–SH) and other ligands in proteins as well as the ability of lead to substitute for calcium, and perhaps also zinc. Therefore, almost all organs and organ systems may be considered as potential targets for lead 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.

The central nervous system is a critical target organ for lead toxicity and lead causes a continuum of effects in both children and adults ranging from slowed nerve conduction, behavioural changes, and small decrements in cognitive ability, to mental retardation and encephalopathy. There is considerable evidence showing that the developing brain is more vulnerable to the neurotoxic effects of lead than the mature brain and the most critical effect of lead at low exposure levels is the impaired neurodevelopment in children. Numerous studies have documented that an elevated blood lead (PbB) level is inversely associated with a reduced IQ score and reduced cognitive functions up to at least seven years of age. The dose-response relationship between PbB levels and IQ seems to be non-linear reflecting a greater relative impact at lower lead concentrations. Effects have been reported in children at PbB levels below 10 μg/dl – in the most recent studies at exposure levels corresponding to a PbB level as low as 2 μg/dl, and evidence suggests that the response at PbB levels below 10 μg/dl is steeper than at higher concentrations. Overall, no threshold for the lead induced neurodevelopmental effects can be identified based on the available studies.

Lead affects 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. Other effects observed following long-term oral exposure to lead (cardiovascular, hepatic, renal effects, gastrointestinal, reproductive 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.

Epidemiological studies have either been negative or have shown only small excess mortalities from cancers of the lung, stomach, kidney, and brain / 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.
Studies in experimental animals have shown that inorganic soluble lead compounds administered in food or drinking water cause renal tumours at quite high doses (>10 mg/kg bw/day), dose levels which also caused renal toxicity in rodents. IARC (2006) and US-EPA (IRIS 2004) have concluded that there is sufficient evidence for the carcinogenicity to experimental animals of exposure to inorganic lead compounds; IARC (2006) placed inorganic lead compounds in Group 2A – probable carcinogenic to humans (limited evidence for the carcinogenicity to humans, sufficient evidence to experimental animals).
Data regarding genotoxicity are conflicting. IARC (2006) 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.

EFSA (2010) concluded that the data on genotoxicity indicate that lead may be a weak indirect genotoxin.
Overall, a carcinogenic potential cannot be excluded in relation to ingestion of inorganic soluble lead compounds via food or drinking water; however, the mode of action has not yet been fully understood.

6.11.1 Critical effects, NOAEL / LOAEL, TDI / PTWI

The critical effect following intake of lead at low exposure levels is the impaired neurodevelopment in children, i.e. reduced cognitive development and intellectual performance (most often evaluated by IQ scores) in children exposed pre- and/or postnatally. Effects have been reported in children at PbB levels as low as 2 µg/dl, and evidence suggests that the response at PbB levels below 10 µg/dl is steeper than at higher concentrations.

The available data do not provide evidence of a threshold for the critical effects of lead, i.e. a NOAEL or LOAEL cannot be derived. Therefore, a TDI (or preferable, a tolerable weekly intake (TWI) for cumulative substances such as lead) cannot be established. This conclusion is identical with the conclusion reflected in the 2004 report 'Evaluation of health hazards by exposure to lead and inorganic lead compounds and estimation of a quality criterion in soil' (Nielsen 2004).

This conclusion is also in accordance with the view expressed by major European and international bodies:
The US-EPA has not set an oral Reference Dose (RfD) as *"…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).
The JECFA Committee concluded "*Because the dose-response analyses do not provide any indication of a threshold for the key effects of lead, the Committee concluded that it was not possible to establish a new PTWI that would be considered to be health protective.*" (JECFA 2011).
The EFSA CONTAM Panel concluded *"… as there was no evidence for a threshold for a number of critical endpoints including developmental neurotoxicity and nephrotoxicity in adults, it would not be appropriate to derive a PTWI.*" (EFSA 2010).
The ECHA Committee for Risk Assessment (RAC) concluded "*As children will be particularly sensitive … given that their central nervous system is still under development and as no threshold for the adverse effect has been identified in humans …* " (ECHA 2011a).

6.11.2 Risk characterisation: EFSA, JECFA, ECHA

EFSA (2010) and JECFA (2011) have performed risk characterisations for dietary exposure (food and drinking water) to lead. The reference point for the risk characterisation was derived from dose-response analyses based on estimates from the Lanphear et al. 2005 pooled analysis (described in section 3.3.1.1). It should be noted that the dose-response analyses were performed slightly differently by EFSA and JECFA and thus, the resulting reference points for the risk characterisation are slightly different as well.

ECHA (2011a) has performed a risk characterisation for lead in jewellery.

6.11.2.1 EFSA

As the reference point for the risk characterisation, EFSA (2010) chose the 95th percentile lower confidence limit of the benchmark dose (BMD) of 1% extra risk ($BMDL_{01}$) of 1.2 µg Pb/dl blood. In this case, the $BMDL_{01}$ means the PbB level associated with a benchmark response (BMR) of 1%, i.e. a decrease of cognitive ability by one IQ point. The relationship between dietary lead intake and PbB levels in children up to age seven was estimated using a biokinetic model for lead in children and the PbB level of 1.2 µg/dl was estimated to be equivalent to a $BMDL_{01}$ dietary intake value of 0.50 µg/kg bw/day.

The CONTAM Panel noted that the use of concurrent PbB levels as the dose metric on which to base the $BMDL_{01}$ was such that it accounted for a substantial proportion of inter-individual variation in toxicokinetics. It was therefore concluded that a MOE (Margin of Exposure) of 10 or greater should be sufficient to ensure that there was no appreciable risk of a clinically significant effect on IQ. At lower MOEs (greater than 1.0), the risk was considered likely to be low, but not such that it could be dismissed as of no potential concern.

Estimated dietary exposure (food and drinking water) in children up to age seven (see Table 2 in section 1.4) exceeded the $BMDL_{01}$ intake level of 0.50 µg/kg bw/day for neurodevelopmental effects. The MOE in average 1-3 year old child consumers ranged from 0.16 to 0.45, and was only slightly higher in 4-7 year old children. Therefore, the risk of neurodevelopmental effects in some children cannot be excluded.

Breast-fed 3-month old infants are predicted to have a lead exposure (see Table 2 in section 1.4) that is below the $BMDL_{01}$ intake value of 0.50 µg/kg bw/day for neurodevelopmental effects.

Lead exposure based on lower bound assumptions in both average and high 3-month old infant consumers of infant formula (see Table 2 in section 1.4) is below the $BMDL_{01}$ intake value of 0.50 µg/kg bw/day for neurodevelopmental effects, but may exceed this level, based on upper bound estimates. Therefore, the risk of neurodevelopmental effects to infants cannot be excluded.

Women of 20 to 40 years of age were used as a surrogate for pregnant women to calculate the risk of lead exposure *in utero* on neurodevelopment in the offspring. Estimates of exposure (see Table 2 in section 1.4) were at or above the $BMDL_{01}$ intake value of 0.50 µg/kg bw/day for neurodevelopmental effects. Therefore, the risk of neurodevelopmental effects to the developing foetus through exposure of some pregnant female consumers cannot be excluded.

Based on the risk characterisation for different subgroups of the general populaton the EFSA CONTAM Panel concluded "… *in infants, children and pregnant women, there is potential concern at current levels of exposure to lead for effects on neurodevelopment. Protection of children and women of child-bearing age against the potential risk of neurodevelopmental effects should be protective for all other adverse effects of lead, in all populations.*"

6.11.2.2 JECFA

JECFA (2011) considered six different dose-response models and chose one of these, the bilinear model, for the evaluation. The chronic dietary exposure

corresponding to a decrease of one IQ point was estimated to be 12 μg/day, equivalent to 0.6 μg/kg bw/day for a 20 kg child. Based on the dose-response analyses, it was estimated that the PTWI of 25 μg/kg bw is associated with a decrease of at least three IQ points in children.

The mean dietary exposure estimates for children aged about 1-4 years ranged from 0.03 to 9 μg/kg bw/day.
The health impact at the lower end of this range was considered negligible by the Committee, because it is below the exposure level of 0.3 μg/kg bw/day calculated to be associated with a population decrease of 0.5 IQ point.
The higher end of the exposure range is higher than the level of 1.9 μg/kg bw/day calculated to be associated with a population decrease of 3 IQ points, which was deemed by the Committee to be a concern.

The Committee stressed that these estimates are based on dietary exposure (mainly food) and that other sources of exposure to lead also need to be considered. The Committee concluded " … *in populations with prolonged dietary exposures to lead that are at the higher end of the ranges identified above, measures should be taken to identify major contributing sources and foods and, if appropriate, to identify methods of reducing dietary exposure that are commensurate with the level of risk reduction.*"

6.11.2.3 ECHA

As the reference point for the risk characterisation of lead in jewellery, the ECHA Committee for Risk Assessment (RAC) (ECHA 2011a) chose the EFSA $BMDL_{01}$ intake level of 0.50 μg/kg bw/day for neurodevelopmental effects and applied a MoE of 10 noting that a MoE of 10 according to EFSA (2010) is sufficiently low to ensure no appreciable risk. The resulting exposure of 0.05 μg/kg bw/day is stated to correlate with an IQ reduction in children of 0.1 points.
Considering an exposure scenario in which a child (10 kg bw) mouths a jewel for one hour with a surface of 10 cm^2 and a weight of 10 g, a tolerable migration rate from the jewellery of 0.05 μg Pb/cm^2/hr or 0.05 μg Pb/g/hr was estimated.
Based on this, RAC proposed to restrict the lead content in jewellery articles and any parts thereof to 0.05%, unless it is demonstrated that the migration rate of lead release from jewellery articles does not exceed 0.05 μg/cm^2/hr if measured by surface (or 0.05 μg/g/hr if measured by weight) for both the metallic and the non-metallic parts.

It should be noted that RAC in their opinion stressed that any relevant lead exposure should in principle be avoided as no threshold has been found for the harmful effect of lead on the central nervous system, and with a view to background exposure from diet and other environmental sources.

7 Health-based quality criterion in drinking water

The critical effects following intake of lead at low exposure levels are the neurodevelopmental effects, particularly reduced cognitive development and intellectual performance (most often evaluated by IQ scores) in children exposed pre- and/or post-natally. There is a general worldwide agreement (WHO/JECFA (2011), US-EPA (2004), EFSA (2010), ECHA (2011a), DTU Food (2004, 2012)) that the available data do not provide any indication of a threshold for the critical effects of lead. Therefore, a TDI (or preferable, a tolerable weekly intake (TWI) for cumulative substances such as lead) cannot be established. Consequently, the concentration of lead in drinking-water below which no effects can be observed cannot be determined and thus, a health-based quality criterion for lead in drinking water cannot be established based on the available data. This conclusion is identical with the conclusion regarding a health-based quality criterion for lead in soil as reflected in the 2004 report 'Evaluation of health hazards by exposure to lead and inorganic lead compounds and estimation of a quality criterion in soil' (Nielsen 2004).

The current limit value for lead in drinking water is 10 µg Pb/l (MM 2001).
As no threshold for the critical effects of inorganic lead can be identified, it is recommended that the exposure to lead from all sources, including drinking water, should be as low as possible.

This recommendation is in accordance with the view expressed by major European and international bodies:
The US-EPA has set the MCLG[4] at 0 mg/l (zero) and stated that the MCGL is based on the best available science which shows there is no safe level of exposure to lead (US-EPA 2012).
The SCHER opinion regarding the standard of 10 µg/l for lead in drinking water (SCHER 2011) expressed that an increase in the drinking water concentrations above 10 µg/l will further increase exposures and cause additional risk to human health, particularly to the mental and neurological development of children aged 0-14 years, and concluded that a further reduction in lead intake is warranted for risk reduction.
Based on the risk characterisations for dietary exposure (food and drinking water) to lead, EFSA (2010) and JECFA (2011) concluded that there is potential concern at current levels of exposure to lead for effects on neurodevelopment.

Dietary exposure (food and drinking water) is the major source of lead even in young children living in areas with high soil lead concentrations. In the dietary exposure assessment performed by EFSA (2010) it was noted that tap water is a major contributor to the dietary lead exposure. A similar finding was reported in the most recent Danish Food Monitoring report on chemical contaminants (Fromberg et al. 2005), see section 1.4. These findings also support the recommendation that inorganic lead in drinking water should be as low as possible.

[4] Maximum Contaminant Level Goal (MCLG) - The level of a contaminant in drinking water below which there is no known or expected risk to health.

7.1.1 Health-based quality criterion in drinking water

It is recommended that inorganic lead in drinking water should be as low as possible.

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Lead, inorganic and soluble salts

The Danish Environmental Protection Agency (DEPA) has requested an update of the 2004 report 'Lead and inorganic lead compounds. Evaluation of health hazards and estimation of a quality criterion in soil' primarily based on the EFSA (2010) opinion, but also on the most recent evaluations on lead. Based on the report an administrative based quality criterion in drinking water has subsequently been established.

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