Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

LEAD

EC Number: 231-100-4
CAS Number: 7439-92-1

CLH-O-0000002512-83-02/A1

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

5 December 2013

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: LEAD

EC Number: **231-100-4**

CAS Number: **7439-92-1**

Index Number: **none**

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	**Lead**
EC number:	**231-100-4**
CAS number:	**7439-92-1**
Annex VI Index number:	
Degree of purity:	**80-100%**
Impurities:	

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**	**Specific Concentration Limits**	**Notes**
Current entry in Annex VI, CLP Regulation	Not classified	Not classified	-	-
Current proposal for consideration by RAC	Repr. 1A (H360DF)	Repr. Cat. 1; R60-61	0.03%	-
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Repr. 1A (H360DF)	Repr. Cat. 1; R60-61	0.03%	-

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Repr. 1A; H360DF. May damage fertility. May damage the unborn child.

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	-	-	-	Conclusive but not sufficient for classification
2.2.	Flammable gases	-	-	-	n/a
2.3.	Flammable aerosols	-	-	-	n/a
2.4.	Oxidizing gases	-	-	-	n/a
2.5.	Gases under pressure	-	-	-	n/a
2.6.	Flammable liquids	-	-	-	n/a
2.7.	Flammable solids	-	-	-	Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	-	-	-	Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	-	-	-	n/a
2.10.	Pyrophoric solids	-	-	-	Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	-	-	-	Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	Conclusive but not sufficient for classification
2.13.	Oxidizing liquids	-	-	-	n/a
2.14.	Oxidizing solids	-	-	-	Conclusive but not sufficient for classification
2.15.	Organic peroxides	-	-	-	Conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	-	-	-	Conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	-	-	-	Conclusive but not sufficient for classification
	Acute toxicity - dermal	-	-	-	Conclusive but not sufficient for classification
	Acute toxicity - inhalation	-	-	-	Conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	-	-	-	Conclusive but not sufficient for classification

3.3.	Serious eye damage / eye irritation	-	-	-	Conclusive but not sufficient for classification
3.4.	Respiratory sensitization	-	-	-	Conclusive but not sufficient for classification
3.4.	Skin sensitization	-	-	-	Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity	-	-	-	Conclusive but not sufficient for classification
3.6.	Carcinogenicity	-	-	-	Conclusive but not sufficient for classification
3.7.	Reproductive toxicity	**1A (H360DF)**	**0.03 %**	**not classified**	-
3.8.	Specific target organ toxicity –single exposure	-	-	-	Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	Conclusive but not sufficient for classification
3.10.	Aspiration hazard	-	-	-	n/a
4.1.	Hazardous to the aquatic environment	-	-	-	Conclusive but not sufficient for classification
5.1.	Hazardous to the ozone layer	-	-	-	Conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Pictogram: GHS8

Signal word: Danger (Dgr)
Hazard statements: H360DF; May damage fertility. May damage the unborn child.

Proposed notes assigned to an entry: None

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	-	-	-	conclusive but not sufficient for classification
Oxidizing properties	-	-	-	conclusive but not sufficient for classification
Flammability	-	-	-	conclusive but not sufficient for classification
Other physico-chemical properties	-	-	-	conclusive but not sufficient for classification
Thermal stability	-	-	-	conclusive but not sufficient for classification
Acute toxicity	-	-	-	conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	-	-	-	conclusive but not sufficient for classification
Repeated dose toxicity	-	-	-	conclusive but not sufficient for classification
Irritation / Corrosion	-	-	-	conclusive but not sufficient for classification
Sensitization	-	-	-	conclusive but not sufficient for classification
Carcinogenicity	-	-	-	conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity	-	-	-	conclusive but not sufficient for classification
Toxicity to reproduction – fertility	**Cat. 1; R60**	-	**Not classified**	-
Toxicity to reproduction – development	**Cat. 1; R61**	**0.03 %**	**Not classified**	-
Toxicity to reproduction – breastfed babies. Effects on or via lactation	-	-	-	conclusive but not sufficient for classification
Environment	-	-	-	conclusive but not sufficient for classification

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: **T**
R-phrases: **R60, R61**
S-phrases: **S1, S2, S13, S35, S45, S53,**

2 BACKGROUND TO THE CLH PROPOSAL

While preparing this CLH proposal for lead; all relevant information from the Reach registration dossiers has been considered.

2.1 History of the previous classification and labelling

Lead is a well-known human toxicant and lead poisoning has been documented way back in history from ancient Rome, Greece and China. Despite the well-known and extensively studied toxic properties of lead, there is currently no harmonized classification for lead in its metallic form, though lead compounds listed in annex VI, table 3.1 of the CLP-regulation have previously all been classified as category 1A reproductive toxicants. It is also specified that "lead compounds with the exception of those specified elsewhere in this annex" are also classified in category 1A for reproductive toxicity, thus placing *all* lead compounds Repr. Cat. 1A.

2.2 Short summary of the scientific justification for the CLH proposal

Lead is a well-known toxic heavy metal that causes harm to several organ systems in the body. In this CLH-report, we have focused on the reproductive toxicity of lead, proposing a classification of lead in category 1A for reproductive toxicity.

Many studies have evaluated the negative impacts of lead on fertility, and human evidence concludes that lead can negatively affect male fertility by causing decreased sperm quality and testicular atrophy.

Lead also causes neurodevelopmental effects. Pre- and perinatal lead exposure is toxic to the developing nervous system and IQ is one of the major parameters found to be negatively affected. It appears that lead-associated IQ deficits are significantly greater at lower blood lead concentrations and no threshold has yet been identified for lead-induced developmental neurotoxicity. Therefore no safe exposure level can be established.

Taken together, a large body of evidence from human studies concludes that lead is indeed toxic for reproduction; therefore it should be classified in category 1A (H360DF) for reproductive toxicity under the CLP-legislation, and the available data justify a specific concentration limit of 0.03%.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Not classified.

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Not classified.

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Industrial self classification:

Lead metal massive: **no classification**

Lead metal powder (particle size < 1 mm Ø): **Repr. 1A (H360Df)**

2.4.2 Current self-classification and labelling based on DSD criteria

Industrial self classification:

Lead metal massive: **no classification**

Lead metal powder (particle size < 1 mm Ø): **Repr. 1 (R61, R62)**

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Lead has a CMR property being a reproductive toxicant, and according to CLP legislation, all substances with CMR property should have a harmonized classification.

In 2010, the industry submitted a registration dossier where they self-classified metallic lead as a 1A reproductive toxicant, but proposed that the classification should only apply to lead metal powder with a particle size <1 mm. in diameter. They argued that the risk is very low that larger pieces would be accidentally ingested orally, and if they were, the bio-availability would be negligible, thus posing no risk to human health.

In this CLH-report, we propose the same classification as the industry except that we believe that all lead, regardless of particle size should be classified in category 1A for reproductive toxicity.

The reasons for this are several. First of all; according to the CLP regulation, substances shall be classified after their intrinsic properties (hazard) and not after risk. Secondly, there are numerous cases of lead poisoning described in the literature caused by oral ingestion of a piece of lead (e.g. lead containing jewellery, buttons, etc.), even death has been reported. These case reports prove that pieces of lead ingested orally are indeed bioavailable.

Another important aspect is that the same classification should apply to all physical forms so the Safety Data Sheet can accompany the metal throughout its “life span”; lead could during “reasonably expected use” be processed into several different physical forms, in both industrial settings and in the home environment. A brick or piece of lead could under “reasonably expected use” e.g. be melted; an example is casting of bullets and fishing weights in the home. This type of exposure has been shown to increase blood lead levels *(MMWR 2011).* The metal can also be grinded into smaller pieces or polished; potentially causing small, easily inhalable particles during the process.

In addition, lead is a soft metal that can easily “rub off” on to the skin in the case of dermal contact. Even though absorption directly through the skin is considered negligible, the lead can become systemically available through hand-to-mouth behavior. This route of exposure could be feasible for both children and adults that come in contact with lead containing articles, both at home and in the work place.

Taken together, it is of essence that all physical forms of lead, regardless of particle size, receive the same classification; Repr. 1A (H360: DF).

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	231-100-4
EC name:	Lead
CAS number (EC inventory):	
CAS number:	7439-92-1
CAS name:	Lead
IUPAC name:	
CLP Annex VI Index number:	
Molecular formula:	Pb
Molecular weight range:	207.2 g/mol

Structural formula: n/a

1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Pb (metallic lead)	95%	80-100%	mono constituent substance

Current Annex VI entry: **no current entry**

Table 7: Impurities in lead metal massives, general grade, non-confidential information *(CSR 2010).*

Impurity	Typical concentration	Concentration range	Remarks
Antimony EC no.: 231-146-5		0.0 - 15.0 % (w/w)	
Tin EC no.: 231-146-5		0.0 - 15.0 % (w/w)	
Sulphur EC no.: 231-722-6		0.0 - 10.0 % (w/w)	Only in elemental form
Oxygen EC no.: 231-956-9		0.0 - 10.0 % (w/w)	Only in elemental form
Copper EC no.: 231-159-6		0.0 - 10.0 % (w/w)	
Nickel EC no.: 231-111-4		0.0 - 1.0 % (w/w)	
Aluminum EC no.: 231-072-3		0.0 - 10.0 % (w/w)	
Zinc EC no.: 231-175-3		0.0 - 10.0 % (w/w)	
Iron EC no.: 231-096-4		0.0 - 10.0 % (w/w)	
Selenium EC no.: 231-957-4		0.0 - 5.0 % (w/w)	
Cobalt EC no.: 231-158-0		0.0 - 1.0 % (w/w)	
Chromium EC no.: 231-157-5		0.0 - 10.0 % (w/w)	
Magnesium EC no.: 231-104-6		0.0 - 10.0 % (w/w)	
Manganese EC no.: 231-105-1		0.0 - 10.0 % (w/w)	
Sodium EC no.: 231-132-9		0.0 - 10.0 % (w/w)	
Barium EC no.: 231-149-1		0.0 - 10.0 % (w/w)	
Strontium EC no.: 231-133-4		0.0 - 10.0 % (w/w)	
Indium EC no.: 231-180-0		0.0 - 10.0 % (w/w)	
Gallium EC no.: 231-163-8		0.0 - 10.0 % (w/w)	
Tellurium EC no.: 236-813-4		0.0 - 10.0 % (w/w)	
Calcium EC no.: 231-179-5		0.0 - 10.0 % (w/w)	
Silicon		0.0 - 10.0 % (w/w)	

EC no.: 231-130-8			
Potassium EC no.: 231-119-8		0.0 - 10.0 % (w/w)	
Bismuth EC no.: 231-177-4		0.0 - 2.0 % (w/w)	
Others		Metal impurities in the range <0.25% (w/w): e.g. Pt, Ag, Au; metal impurities in the range <0.1% (w/w): Tl; metal impurities in the range <0.025% (w/w): As, Cd, Hg.	

Current Annex VI entry: **no current entry**

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
n/a				

Current Annex VI entry: **no current entry**

1.2.1 Composition of test material

Lead metal massives (high purity grade) = 99.9% (w/w, average concentration)

Lead metal massives (general grade) = 95.0% (w/w, average concentration)

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	Lead is available on the market in both powder and massive forms. In both forms it is a solid, grey-blue element.		Visual inspection
Melting/freezing point	Melting temperature: 326ºC (599 K)	*Franke (2005b)*	measured
Boiling point	The test item has no boiling point at atmospheric pressure up to the final temperature of 600 °C (873 K)	*Franke (2005b)*	measured
Relative density	Density at 23.8 °C = 11.45 g/cm3 D4R: 11.45	*Smeykal (2005a)*	measured
Vapour pressure	n/a Vapour pressure is only relevant for solids with a melting point above 300 ºC (Lead melts at 326ºC).		
Surface tension	n/a Lead is a solid at ambient temperature (20 ºC).		
Water solubility	185 mg/l [20 °C, at pH = 10.96]	*Heintze (2005)*	measured
Partition coefficient n-octanol/water	n/a The solubility of metallic lead in octanol/water is negligible.		
Flash point	n/a Lead is a solid, flash point is only relevant for liquid substances.		
Flammability	Non flammable	*Smeykal (2005b)*	measured
Explosive properties	n/a Lead is metallic and therefore considered inert.		
Self-ignition temperature	n/a Lead metal powder has been tested to be 'not flammable'. Furthermore, no exothermic decomposition (DSC analysis) was reported up to a temperature of 600 °C. Therefore, it can be assumed that lead metal powder is not ignitable or auto-flammable.		measured
Oxidising properties	n/a		
Granulometry	Lead is placed on the market in both massive and powder forms. The mean particle size of a representative lead metal powder sample has been determined (laser diffraction method): D50 = 12.7 µm. Mass median aerodynamic diameter of airborne fraction (rotating drum method, distribution fitted to cascade impactor data): MMAD = 33.7 µm.	*Franke (2005a), Selck (2003)*	measured

Stability in organic solvents and identity of relevant degradation products	n/a This study is only conducted on organic substances, metallic lead is inorganic.		
Dissociation constant	n/a Lead does not contain relevant functional groups for assessment of a dissociation constant.		
Viscosity	n/a Viscosity is a property of fluids. Lead is a solid at ambient temperature (20 ºC).		

2 MANUFACTURE AND USES

2.1 Manufacture

Lead does occur in its metallic form in nature, but it is rare. Lead is usually found in ore with zinc, silver and (most abundantly) copper, and is extracted together with these metals. The main lead mineral is galena (PbS), which contains approximately 85% lead. Other common varieties are cerussite (PbCO3) and anglesite (PbSO4).

Most ores contain less than 10% lead, and ores containing as little as 3% lead can be economically exploited. Sulfide ores are roasted, producing primarily lead oxide and a mixture of sulfates and silicates of lead and other metals contained in the ore *(Samans 1949).* Lead oxide from the roasting process is then reduced in a coke-fired blast furnace where most of the lead is converted to its metallic form.

The metallic lead can then be further processed to produce e.g. lead batteries, lead sheets, lead powder, leaded steels, lead oxide and other lead compounds, and in the production of other articles containing lead *(see next section 2.2; Identified uses).*

2.2 Identified uses

Lead has a large variety of uses, both for industrial purposes as well as in consumer products. It is used e.g. in lead-acid batteries, bullets- shots and fishing sinkers and in aviation fuel. It is also frequently used in solders and other metal alloys such as “tin soldiers” and in brass; which typically contains around 3 % lead. Brass can be found in various consumer articles such as coffee machines, water faucets and as buttons and zippers on clothing; thus making them lead-containing articles. Examples of other uses for lead are as a constituent in paints, varnishes and crystal glass, in electronics, machinery, and in jewellery.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL HAZARDS

Classification for physico-chemical hazards is not considered in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

The blood lead (or PbB) -level is considered the best biomarker for an exposure to lead, but it does not reflect the whole body burden of lead. The PbB level increases when exposure rises, and stabilizes after a while *(EFSA 2010).* The mean blood lead levels of children in European countries typically range between 2-6 μg/dL for children in areas without significant local sources of lead exposure. For children in areas with local sources of lead exposure, the mean blood levels can reach up to 30 or even 50 μg/dL but the variation is large between countries in Europe *(WHO 2009).*

4.1 Toxicokinetics (Absorption, Metabolism, Distribution and Elimination)

4.1.1 Non-human information

There is an extensive amount of data available on lead toxicokinetics in humans, therefore preference has been given for describing human toxicokinetic data in this CLH-report.

4.1.2 Human information

Absorption

The oral and the inhalation routes are the most significant routes of exposure to lead, whereas dermal absorption is considered as minimal.

Oral absorption rate

Gastro-intestinal (GI) uptake of lead occurs in the duodenum. In this mechanism, both active transport and diffusion through intestinal epithelial cells are involved.

Orally ingested lead is absorbed differently depending on the time duration between the exposure and the last meal; adults who have just eaten a meal absorb 3-15% of the ingested amount of lead, whereas those who have not eaten for a period of 24h absorb about 20-70% *(EFSA 2010).* The mineral content of food is one contributing factor to the decreased absorption of lead when lead is ingested with a meal. A possible mechanism behind this effect could be competition between lead and the minerals for the binding sites that mediate uptake *(VRAR 2008).*

Lead absorption is affected by nutritional calcium and iron status *(Watson et al. 1986).* High levels of calcium and/or iron in the blood stream protects from GI absorption of lead, and a low iron intake and deficient iron status is associated with increased blood lead levels *(Cheng et al. 1998; Bárány et al. 2005*). This information is important to keep in mind since iron deficiency is very common, especially amongst women of child bearing age.

Concerning children, even though data are more limited, an oral absorption rate of 40-50% for lead and its compounds can be determined for non-fasting children from 2 weeks to 8 years of age *(ATSDR 2007; VRAR 2008).* Whether fasting might increase lead uptake in young children is not known; uptake rates are only available for dietary lead sources.

There have been a number of clearly identified cases of lead poisoning resulting from the misuse of lead-containing jewels, most often by children who have swallowed or repeatedly mouthed them *(CDC 2006; CDC 2004; Levin et al. 2008; Jones et al. 1999; Canada Gazette 2005; InVS 2008; KEMI 2007).* The observed symptoms of these cases go from headaches and diarrheas to death. One report of a fatal case of lead poisoning describes the death of a 4 year old boy in the USA after he ingested a bracelet charm containing 99 % lead *(CDC 2006).* The initial symptoms of poisoning manifested as

vomiting, abdominal pain and fatigue, and the child had a final PbB level of 180 μg/dL at the time of death.

Inhalation rate

For the very small particles (up to to 0.5 μm), a dissolution occurs in the lungs and the lead will be available for systemic absorption. More than 90% of these very small particles are completely absorbed after deposition in the lower respiratory tract *(VRAR 2008).*

Particles between 0.5-10 μm are partially absorbed in the lung; the non-absorbed parts will be transported up to the mouth via the respiratory tract and then swallowed.

Larger particles over 10 μm will mainly be swallowed and then absorbed via the GI tract.

Dermal absorption

The dermal absorption of lead trough unabraded (non irritated) skin has been established as less than 0.1% (ranging from 0.01% to 0.18% in studies), and is considered to be of much less significance than absorption via the respiratory or gastro-intestinal routes *(VRAR 2008).*

Lead is a soft metal that can easily "rub off" on to the skin in the case of dermal contact. Even though absorption directly through the skin is considered negligible, the lead can become systemically available through hand-to-mouth behavior *(VRAR 2008)*. This route of exposure is feasible for both children and adults that come in contact with lead containing articles, both at home and in the work place. Especially older and thus oxidized lead surfaces can transfer significant quantities (potentially hundreds or thousands of μg's) of lead to the hands via dermal contact *(Klein and Weilandics 1996).* In the workplace, personal habits such as frequent hand-to-mouth activity, smoking, and eating all provide opportunities for lead ingestion. The intensity of exposure resulting from such habits varies as a function of personal hygiene (e.g. hand washing frequency) and the magnitude of direct lead contact and lead contamination (e.g. dust) on surfaces *(VRAR 2008).*

Metabolism

The inorganic lead ion is not known to be metabolized or biotransformed in the body though it does form complexes with a variety of proteins and non-protein ligands. It is primarily absorbed, distributed, and then excreted, often in form of a complex.

Inorganic lead is not converted in the body. Unabsorbed lead which is ingested orally is expelled through the faeces, while absorbed lead that is not retained in the body is released again via the kidneys *(WHO 2003).*

Distribution

Once it is absorbed, inorganic lead appears to be distributed to both soft tissues (blood, liver, kidney, etc.) and mineralizing systems (bones, teeth) in a similar manner regardless of the route of absorption.

The distribution of lead seems to be similar in children and adults, but in adults a larger fraction of lead is stored in skeletal tissue. More than 90% of the total amount of accumulated lead ends up in bone and tooth in adults, while in children, 75% is accumulated in bones *(VRAR 2008).*

The distribution of lead in the body is initially dependent on the rate of delivery by the bloodstream to the various organs and tissues. A subsequent redistribution may then occur, based on the relative affinity of particular tissues for the element and its toxicodynamics there *(ATSDR 2007).*

Lead concentration is related to calcium status; stored lead can therefore be released from bone tissue into the blood stream in situations where a person suffers from calcium deficiency or osteoporosis *(VRAR 2008).*

It should be noted that lead is easily transferred to the foetus via the placenta during pregnancy. The foetal/maternal blood lead concentration ratio is approximately 0.9 *(Carbone et al. 1998; Goyer 1990; Graziano et al. 1990),* i.e. the foetus actually has a slightly higher blood lead level than its mother.

Elimination

Lead has a different half-life in different tissue pools. Blood lead and lead in soft tissue is considered the most labile compartment with a half-life of approximately 40 days, while bone lead is very stable with a half-life of several decades *(ATSDR 2007).*

In lead exposed infants and children, lead is progressively accumulated in the body and is mainly stored in skeletal tissue. As mentioned previously, lead is very slowly eliminated from bone; the half-life can be 10 to 20 years or more. In this way, lead can lead to an internal exposure long after the external exposure has ended, by redistribution between different tissue pools *(VRAR 2008).*

Elimination takes place mostly via urine (> 75%), and 15-20% is excreted via bile and faeces *(TNO 2005).*

4.1.3 Summary and discussion on toxicokinetics

Lead is most easily taken up into the body through inhalation or ingestion, dermal uptake makes a negligible contribution to systemic lead levels. The efficiency of oral uptake of lead can vary depending on e.g. particle size and shape (surface area), amount of time spent in the GI tract, concurrent food intake and the iron- and calcium status of the individual. A number of case reports prove that even one larger piece of lead ingested orally can create sufficient systemic exposure to produce clinical lead intoxication or even death. Therefore lead of all particle sizes should be considered a potential health hazard. As a worst case assumption, one can assume that the bioavailability of metallic lead is equivalent to that of soluble lead compounds such as e.g. lead acetate.

Once taken up into the body, lead is not metabolized. However, it will distribute to various tissue compartments such as blood, soft tissue and bone. The half-life of lead in the body varies depending on body compartment. Blood lead has a half life of around 40 days and measurement of lead in blood can thus provide an estimate of average lead exposure (via all routes) over the preceding month.

Lead is retained far longer in bones, up to several decades. Such lead can both serve as a source of endogenous lead exposure and as a cumulative index of exposure over a time frame of years. Lead excretion takes place primarily via the urine.

4.2 Acute toxicity

Classification for acute toxicity is not considered in this dossier.

4.3 Specific target organ toxicity – single exposure (STOT SE)

Classification for specific target organ toxicity is not considered in this dossier.

4.4 Irritation

Classification for irritation is not considered in this dossier.

4.5 Corrosivity

Classification for corrosivity is not considered in this dossier.

4.6 Sensitisation

Classification for sensitisation is not considered in this dossier.

4.7 Repeated dose toxicity

Classification for repeated dose toxicity is not considered in this dossier.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Classification for specific target organ toxicity is not considered in this dossier.

4.9 Germ cell mutagenicity (Mutagenicity)

Classification for mutagenicity is not considered in this dossier.

4.10 Carcinogenicity

Classification for carcinogenicity is not considered in this dossier.

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

The following section (4.11.1; Effects on fertility) has partly been based on data from the 'Voluntary Risk Assessment Report on Lead and some inorganic Lead compounds' *(VRAR 2008)* and the 'Chemical Safety Report on Lead' *(CSR 2010)* submitted by Industry. Discussions and conclusions are our own (i.e. belong to the dossier submitter).

4.11.1.1 Non-human information

Impacts of lead upon reproduction have been evaluated in a large number of animal studies documenting the negative effects of lead upon fertility. Lead acetate has been used to create lead exposure in a majority of the animal studies mainly because of its ease of use; e.g. it dissolves easily in water that the animals can drink and has good oral bioavailability. Well in the body, it is the actual lead ion itself that is toxic; making it unimportant which type of lead source is really causing the exposure. What matters is the actual lead concentration in blood/soft tissue/bone or whatever compartment that is of interest.

Animal studies have mainly been conducted to confirm the results of observational studies in humans and for elucidation of mechanisms of action. Extrapolation from experimental animal data to humans is generally unnecessary since large amounts of human data are already available, therefore making extrapolation from animals unnecessary.

In this CLH-report we have chosen to focus on human data, hence only a small subset of animal studies are presented below. Study summaries of *Sokol et al. (1994)*, *Chowdhury et al. (1984*) and *Foster et al. (1998)* can be found in table 10 below.

Sokol et al. (1994) found that lead exposure could negatively affect the ability of sperm to penetrate and fertilize the egg. Male rats were given 0.3% lead acetate in drinking water with *ad libitum* access, this produced PbB-levels of 33, 36 and 46 µg/dL after 14, 30 or 60 days respectively. Sperm was harvested from lead-exposed male rats and eggs from non-exposed females were fertilized *in vitro*. Lead exposure significantly decreased the number of eggs penetrated and fertilized compared to controls (p=0.001). Epididymal sperm counts were also significantly decreased (p=0.02) in the lead-treated group (though sperm counts were controlled for and adjusted prior to *in vitro* fertilization).

Chowdhury et al. (1984) found pronounced testicular atrophy along with cellular degeneration in the testes of rats fed lead acetate; 90 mg/kg BW/day which produced a blood lead level of 143 µg/dL. The lead acetate was administered via the drinking water and the animals were exposed for 60 days. Rats in the 45 mg/kg BW/day dose group (blood lead 72 µg/dL) had significantly decreased Leydig cell numbers. Spermatid- and spermatocytes were also significantly reduced in number and found to be in a degenerative condition.

The effect of lead exposure on sperm production and damage to testicular tissue has also been studied in primates. Exposure from infancy (blood lead 35 µg/dL) was associated with ultrastructural changes affecting the architecture of tissues within the testes during adulthood *(Foster et al. 1998).*

The combined animal evidence strongly suggests that lead will have negative impact upon sperm production and cause histopathological changes in testicular tissue.

Table 10: Overview of the effects of lead compounds upon the fertility of experimental animals ***(modified from CSR 2010)***

Method	**Results**	**Remarks** ***(CSR 2010)***	**Reference**
100 day old male Sprague Dawley rats	Results: Lead disrupted the ability of sperm harvested from lead-exposed	2 (reliable with restrictions)	*Sokol et al. 1994*

Fertility/Spermatogenesis evaluation Rats where administered water *ad libitum* either lead free or containing 0.3% lead acetate for 14, 30 or 60 days (n=7 per time point), the three treated groups produced PbB-levels of 33±5, 36±4 and 46±2.8 µg/dL blood lead respectively ($p<0.02$ compared to controls). Endpoint: Parameters included epididymal sperm concentration, ability of sperm to fertilize ova in vitro, ultrastructural organization of spermatozoa, and measurement of spermatogenesis by DNA flow cytometry.	animals to penetrate or fertilize eggs harvested from non-exposed females in vitro. Lead also decreased epididymal sperm count. Lead did not affect the weight of the right cauda epididymi and it did not induce any ultrastructural changes in spermatazoa or any DNA histogram abnormalities in testicular cells.	Weight of evidence Experimental result Test material: lead acetate. CAS #51404-69-4	
70-80 g male Swiss Albino rats Fertility/Spermatogenesis evaluation Male rats (15 per treatment group) were administered lead acetate in drinking water at concentrations of 0, 0.25, 0.5, and 1 g/L which is equivalent to 0, 22, 45 and 90 mg/kg BW/day respectively. The 22, 45 and 90 mg/kg/day dose groups acquired blood lead levels of 54, 72 and 143 µg/dL respectively. After 60 days the animals were sacrificed and biochemical and histopathological analyses were performed on the testes. Endpoint: Animals were sacrificed by cervical dislocation, and testes were weighed and used for determining testicular concentrations of lead, ascorbic acid, and cholesterol. Testes were also fixed and sectioned for histopathological and histometric analyses.	Body weight was statistically significantly decreased at all tested doses. Testicular weight was statistically significantly decreased at 1 g/L. There were statistically significant increases in blood and testicular lead concentrations, urinary δ-aminolevulinic acid (ALA), and testicular cholesterol at all tested doses. There was a statistically significant decrease in testicular ascorbic acid at all tested doses. There were statistically significant decreases in seminiferous tubule diameter and spermatid count at 0.5 g/L and above, and in spermatogenic count and Leydig cell number and nuclear diameter at 1 g/L. Spermatocytes and spermatids were in degenerative condition, and the lumen of the seminiferous tubules was filled with cellular debris at 0.5 g/L. At 1 g/L, the cellular pattern of the seminiferous tubules was disintegrated, spermatogenic inhibition was at the stage of spermatogonia, and Leydig cells were in atrophic condition. The reproductive NOAEL and systemic LOAEL from this study were both 0.25 g/L.	2 (reliable with restrictions) Weight of Evidence Experimental Study Test material: lead acetate. CAS #51404-69-4	*Chowdhury et al. 1984*
Cynomolgus monkeys Fertility/ulstrastructural changes in the testis was evaluated Cynomolgus monkeys were administrated lead acetate orally (1500 µg/kg BW/day) in a vehicle in	At age 10 years, blood lead concentrations in lifetime and postinfancy-dosed monkeys were approximately 35 µg/dL, and in control and infancy animals the concentrations were < 1.0 µg /dL. Sertoli and spermatogenic cells of dosed monkeys from the infancy and	Weight of Evidence Experimental Study Test material: lead acetate. CAS #51404-69-4	*Foster et al. 1998*

the following groups: from birth to 10 years (lifetime), postnatal day 300 to 10 years (postinfancy), and postnatal day 0-400 (infancy); monkeys in the control group received only the vehicle (95% glycerol and 5% distilled water). Effects of chronic lead exposure on the ultrastructure of the testis were evaluated.	lifetime groups revealed injuries. Chronic exposure to lead, which resulted in moderate blood lead concentrations induced persistent ultrastructural alterations in the cynomolgus monkey testis.		

4.11.1.2 Human information

A large number of studies have been conducted in occupationally exposed workers to assess the negative impacts of lead on male reproductive function. Common work places with potential lead exposure are e.g. lead-acid battery plants, metal foundries and smelters. Research on lead exposure & male fertility has also been conducted on study populations from fertility clinics, hospitals and firing ranges. Study summaries for several of these studies can be found in table 11 below.

Table 11: Overview of Studies of Lead Impacts Upon Human Male Fertility ***(modified from CSR 2010)***

Study Population	**Exposure and confounder assessment**	**Results**	**Remarks (*CSR 2010)***	**Reference**
Battery facility, lead smelter, University hospital, Cu alloy foundry. 503 men employed by 10 companies in the UK, Italy and Belgium with a mean age range from 36-40 years	The mean PbB concentration was 31.0 µg/dL (range 4.6-64.5) in 362 workers exposed to lead and 4.4 µg/dL in reference workers. Confounders: Age, genital disorders, smoking, marijuana, alcohol, other metals, radiant heat and working in hot environment.	Mean sperm concentration reduced 49% at PbB levels > 50 µg/dL. The threshold slope least square regression identified a PbB concentration of 44 µg/dL (B=-0.037, F=4.35, p=0.038) as a likely threshold.	2 (reliable with restriction) Key Study	*Bonde et al. (2002)*
Firing range Case report: One individual aged 41 years	The individual had a PbB level of 88 µg/dL and had been exposed for two years. He was not able to conceive a child in his second marriage but had done so in his first marriage. Confounders: Extent of data collection on confounders unclear.	The patient was initially infertile but chelation therapy decreased his blood lead level from 88 to 35 µg/dL, while his sperm count rose from 9.6 to 158 million/ml. The patient fathered a healthy child shortly thereafter.	3 (not reliable) Weight of evidence	*Fisher-Fischbein et al. (1987)*
Battery facility 100 lead workers exposed 1-23 years and 50 office workers employed 1-27 years	Mean PbB of lead poisoned workers was 74.5 µg/dL; 52.8 µg/dL for moderately exposed; 41 µg/dL for slightly exposed group and 23 µg/dL for office workers. Confounders: Alcohol, smoking, and duration	Lead poisoned and moderately exposed workers had increased frequency of asthenospermia, hypospermia and teratospermia resulting in decreased fertility.	3 (not reliable) Weight of evidence Deficiencies include problems in matching of	*Lancranjan et al. (1975)*

	of exposure		controls, exposure misclassification and lack of individual data on age.	
Battery facility 18 lead exposed workers and 18 cement workers with a mean age of 40-41 years	Exposed worker mean PbB was 61 ± 20 µg/dL and 18 ± 5 µg/dL for cement workers. Duration of employment in battery factory was 1-10 years (mean 5 ± 5 years). Confounders: Age, alcohol, cigarette and coffee consumption, frequency of intercourse and days of abstinence prior to semen donation.	Battery workers had significantly shifted (p=0.025) frequency distribution of sperm counts (median count 45 vs 73 X 106 cells/cc, respectively).	2 (reliable with restrictions) Weight of evidence	*Assennato et al. (1987)*
Battery facility, brass foundry, painter 7 lead intoxicated workers aged 22-43 years (mean of 35 years)	Blood lead levels ranged from 66-139 µg/dL. Duration of exposure ranged from 5 weeks to 15 years. Confounders: Diabetes, alcohol and medications.	Heavy occupational exposure to lead associated with disturbances of endocrine and reproductive functions in men. Both oligospermia and azospermia reported to occur.	2 (reliable with restrictions) Weight of evidence	*Cullen et al. (1984)*
Fertility clinic 18 fertile and 172 infertile men of unknown age	The mean seminal fluid lead concentration in infertile men was 11.18 +/- 14.37 µg/dL and 5.61 +/- 0.53 µg/dL in fertile men. + 0.62 µg/dL. Confounders: Extent of data collection on confounders unclear.	The difference in semen lead levels in the infertile groups was significantly higher (p=<0.006).	2 (reliable with restriction) Weight of evidence	*Jockenhövel et al. (1990)*
Battery facility 38 male workers (mean age 36 years) & 30 controls (mean age 35 years)	The mean PbB of lead exposed workers ranged from 48.6-86.6 µg/dL with an average duration of exposure of 11.7 years. The mean PbB for controls was 23.5 µg/dL. Confounders: Age, social and economic status, cigarette and drug consumption, exposure to ionising radiation, general health, sexual history and fertility.	Semen volume, sperm count & necrospermia were lower in the exposed group than the controls. Pathological effects most frequent were asthenospermia and teratospermia.	2 (reliable with restrictions) Weight of evidence	*Lerda (1992)*
Lead/Zinc smelter 152 workers including 119 who	The mean PbB level of all employees was 42.4 µg/dL and 39.7 µg/dL for sperm donors.	Workers with current PbB 40 µg/dL had increased risk of below normal sperm counts (OR 8.2, 95% CI,	2 (reliable with restrictions)	*Alexander et al. (1996)*

provided sperm samples with a mean age of 42.7 years	Confounders: Age, alcohol consumption, smoking, presence of other metals in blood and abstinence before sample collection.	1.2-57.9) and total sperm count (OR 1.6 , 95% CI: 0.4-15.7.	Weight of evidence	
Battery facility and printing house 24 male workers aged 20-40 years plus 24 controls	The mean urine lead levels, in exposed workers, were 87.6 µg/dL and 41.9 µg/dL in controls. Confounders: Age, smoking and alcohol use	Lead workers had high rate of teratospermia, sperm density & motility	3 (not reliable) Weight of evidence Occupational histories are lacking and no PbB data.	*Hu et al. (1992)*
Industrial facilities 98 moderately exposed workers and 51 reference subjects aged 20-43 years	The mean PbB of occupationally exposed men was 38.7 (range 11.9-65.9) µg/dL and 10.9 (6.7-20.8) µg/dL for the control group and in present place of work for≥ 2 years. Confounders: Age, smoking and alcohol habits, social and economic status and exposure to other factors influencing reproductive parameters.	A significant (p=0.05) correlation with PbB and decrease in sperm density, count, motility and viable sperm and abnormal sperm head morphology.	2 (reliable with restrictions) Weight of evidence Associations with certain reproductive parameters also reported for BCd, smoking, alcohol and age.	*Telisman et al. (2000)*
U.S. hospital clinic 64 healthy men aged 21-25 years	Seminal plasma lead levels in µg/dL grouped by sperm viability (%) were 12.5 ± 8 for <25%; 10.8 ± 5.0 25-50% and 6.0 ± 2.0 >50%. Confounders: Medical history, tobacco and drug use, alcohol and caffeine consumption and reproductive history.	Significant differences were observed between high and low sperm groups for lead (p=0.01).	2 (reliable with restrictions) Weight of evidence	*Dawson et al. (1998)*
Fertility clinic 58 men with a mean age of 32.3 ± 4.4 years (range 23-44 years)	Seminal fluid lead concentration in infertile men was 3.6 ± 3.2 µg/dL (p=0.001) than in fertile men whose mean concentration was 1.7 ± 1.0 µg/dL. Confounders: Extent of data collection on confounders unclear.	Did not observe relationships between seminal fluid lead and sperm density or morphology.	2 (reliable with restrictions) Weight of evidence	*Saaranen et al. (1987)*
Andrology clinic patients 40 men of unknown age	The mean PbB concentration was 0.60 µmol/L in the study group and 0.53 µmol/L in the referent group.	No toxic influence of lead on sperm morphology could be demonstrated in this study.	3 (not reliable) Weight of evidence	*Swart et al. (1991)*

	Confounders: Extent of data collection on confounders unclear.			
Andrology clinic patients 35 men with a mean age of 37.7 years ±5.5 years	The mean blood lead concentration was 6.5 ± 5.4 µg/dL. Confounders: Extent of data collection on confounders unclear.	The concentration of lead in blood or seminal plasma did not appear to have any correlation with sperm density, motility, morphology or viability.	2 (reliable with restrictions)	*Chia et al. (1992)*
Occupationally unexposed to lead volunteers 22 men aged 21-50 years	The mean concentration of lead in semen was 9.8 ± 6.5 (range 3.5-28.1) µg/dL. In seminal plasma the mean lead level was 7.7 + 5.6 (range 3.5-21.7) µg/dL. Confounders: Extent of data collection on confounders unclear.	There was no correlation between semen quality and semen or semen plasma levels.	3 (not reliable) Weight of evidence	*Noack-Füller et al. (1993)*
Post mortem investigations 41 post-mortem men in rural and urban areas with a median age of 40 years	The PbB level of the urban men was 10.7 µg/dL and 6.7 µg/dL in the rural subjects. Confounders: Occupation and place of residence.	While lead was found in all reproductive organs there was no strong support for lead involvement in the aetiology of male infertility.	2 (reliable with restrictions) Weight of evidence	*Oldereid et al. (1993)*
Andrology clinic patients 221 men mean age of 34.8 years (range 24-54 years)	The mean PbB concentration was. 7.7 ± 3.1 µg/dL. Confounders: Age, alcohol, smoking, metals, living habits and general health.	The concentration of lead in blood or seminal plasma did not appear to have any correlation with sperm density, motility, morphology or viability.	2 (reliable with restrictions) Weight of evidence	*Xu et al. (1993)*
Environmental and occupationally exposed men 15 occupationally exposed and 15 environmentally exposed aged 20-40 years	The mean PbB level of infertile occupationally exposed workers was 37 (15-70) µg/dL and 27 (15-39) µg/dL for fertile workers. The mean PbB for infertile environmentally exposed was 29 (6-46) µg/d and 17 (6-29) µg/dL for fertile. Confounders: Age, residence, smoking, alcohol intake, drug use, surgical history and mode of transportation.	Infertile subjects in both groups had similar sperm motility, higher level sperm count and slightly greater proportions of abnormal sperm but concluded Pb had little impact on reproductive function.	2 (reliable with restriction) Weight of evidence	*El-Zohairy et al. (1996)*
Lead/Zinc smelter 134 workers classified as to ALAD genotype with a mean age	The mean PbB level of all employees was 42.4 µg/dL and 39.7 µg/dL for sperm donors. Confounders: Age and period of abstinence.	The association between PbB concentration and sperm count and concentration were more evident in ALAD1 genotype and at PbB levels ≥ 40	2 (reliable with restrictions) Weight of evidence	*Alexander et al. (1998).*

range of 39-40 years		µg/dL.		
Refinery and polyolefin factory 27 occupationally exposed workers and 27 volunteers	The seminal plasma lead in the refinery, polyolefin and controls in mg/kg were 0.03 ± 0.02; 0.02 ± 0.01 and 0.03 ± 0.03, respectively. Confounders: Disorders possibly affecting fertility, consumption of alcohol and smoking.	Concentrations of lead were low and did not show any correlation with parameters of semen analysis.	3 (not reliable) Weight of evidence	*Hovatta et al. (1998)*
General population 30 fertile men and 30 infertile men aged 20-45 years (mean 35.2 ± 8.3)	The concentration of lead in the fertile men averaged 6.4 µg/dL and 6.5 µg/dL in the infertile men. Confounders: Extent of data collection on confounders unclear.	There was no significant difference between fertile and infertile groups for average concentration of lead (p=>0.05) and therefore did not vary as a function of fertility status.	2 (reliable with restriction) Weight of evidence	*Seren et al. (2002)*
Battery facility 16 exposed workers 18-61 years of age and 23 controls matched to age ethnic & social factors	16 lead exposed men with mean PbB of 46.1 µg/dL and 23 exposed with a mean PbB of 21.1 µg/dL. Confounders: Extent of data collection on confounders unclear.	No differences between groups on sperm count, over-all sperm morphology, prostatic function and vesicular function. Lead exposed had higher sperm count & number of live spermatozoa than controls.	2 (reliable with restrictions) Weight of evidence	*Wildt et al. (1983)*
Metal foundry 19 men age 27-57 years (mean 40.3)	Of the 19 men 7 had PbB levels exceeding 60 µg/dL; 7 men had PbB of 50-60 µg/dL and 5 had PbB of 30-50 µg/dL and had been employed from 1-24 years (mean 9.2 years). Confounders: Extent of data collection on confounders unclear.	Lead exposure had no effect on semen values.	2 (reliable with restrictions Weight of evidence	*Tuohima and Wickmann (1985)*

Alterations in semen quality are the most commonly observed effects in the occupational setting and can be documented with precision. The decrements in semen quality associated with high blood lead levels are expected to have an impact upon the fertility of normal, healthy individuals.

The following conclusions can be made based on the studies in table 11:

The available data show that moderate to high lead exposure can have a marked adverse impact upon semen quality. Aberrant sperm morphology, decreased sperm count and decreased sperm density have all been demonstrated in exposed individuals.

Bonde et al. (2002) conducted a cross sectional study of 503 men employed by 10 different companies in the UK, Italy and Belgium. Among other things, semen volume and sperm concentration were measured. The study group was of sufficient size to model dose-effect

relationships and **indicated a threshold for an effect upon semen quality at 45 µg/dL of concurrent PbB.** As blood lead levels increase above 50 µg/dL, progressively greater impact on fertility can be expected.

Some of the studies presented in table 11 have *not* found an adverse effect of lead upon male fertility. In these studies, the measured blood lead levels are generally relatively low and below the threshold effect level of 45 µg/dL blood lead suggested by *Bonde et al. 2002* for effects on male fertility. In addition, many of the negative studies have been conducted using very small study populations and confounders have not always been taken into account which can further compromise the study results.

Female fertility:

Historical human data, and animal data, suggest fertility effects in females are probable as well, but fertility effects in women can not be estimated with precision.

Effects of lead on female reproduction have been observed in numerous animal species. These effects include alterations in sexual maturation, hormone levels, reproductive cycles, impaired development of the fertilized egg as well as decreases in fertility *(VRAR 2008*). Effects on female reproduction in animal studies are usually not apparent at the blood lead levels that impair male fertility; higher blood lead levels are generally needed to see an adverse effect on the fertility of females. In addition, human data are inconsistent and can not be estimated with precision, therefore **female fertility has not been evaluated in this dossier.**

4.11.2 Developmental toxicity

The following section (4.11.2; Developmental toxicity) has partially been based on data from the 'Voluntary Risk Assessment Report on Lead and some inorganic Lead compounds' *(VRAR 2008)* and the 'Chemical Safety Report on Lead' *(CSR 2010)* submitted by Industry. Discussions and conclusions are our own (i.e. belong to the dossier submitter).

4.11.2.1 Non-human information

The developmental toxicity of lead has been extensively characterised in humans, therefore animal studies are only briefly summarized below.

As a short summary; a large number of animal studies support the human findings in this area. In primates, rats and mice with *in utero* lead exposure; learning disabilities, altered activity levels, effects on social behaviour and visual and spatial discrimination have been demonstrated. In addition, other developmental effects have also been found in the offspring such as decreased birth weight and size, delayed sex organ development and puberty onset, and delayed sexual maturation *(VRAR 2008).*

4.11.2.2 Human information

The nervous system is the main target organ for lead toxicity. The developing foetus and young children are most vulnerable to lead induced neurotoxicity, their nervous system is still under development and therefore more vulnerable to toxic insults. The immaturity of the blood-brain barrier may contribute to the vulnerability, as well as the lack of high-affinity lead binding proteins in the brain that trap lead ions in adults *(Lindahl et al. 1999).* Young children often exhibit hand-to-mouth behavior and also absorb a larger percentage of orally ingested lead than adults, thus leading to a greater systemic exposure *(EFSA 2010).*

Several epidemiological studies have been conducted examining the impacts of pre-natal lead exposure upon birth outcome and neurobehavioral development in children. Note that the prospective studies have detailed their results in multiple publications and findings are easiest to present by study location as opposed to individual publications. The main prospective studies are listed below along with publications that describe relationships between prenatal lead exposure and different outcomes.

Table 12: Overview of Studies of Lead Impacts Upon Human Developmental Toxicity (modified from *CSR 2010*)

Study Location	Publications
Boston	• Needleman et al. 1984 • Bellinger et al. 1991 • Bellinger et al. 1992 (included in the pooled analysis by Lanphear et al. 2005)
Cleveland	• Ernhart et al. 1985 • Ernhart et al. 1986 • Ernhart et al. 1988 • Ernhart et al. 1989 (included in the pooled analysis by Lanphear et al. 2005) • Ernhart and Greene 1990 • Greene and Ernhart 1991
Cincinnati	• Dietrich et al. 1986 • Dietrich et al. 1987 • Bornschein et al. 1989 • Shukla et al. 1991 • Dietrich et al. 1993 (included in pooled analysis by Lanphear et al. 2005)
Mexico City	• Rothenberg et al. 1989 • Rothenberg et al. 1994 • Rothenberg et al. 1995 • Rothenberg et al. 1999 • Torres-Sanchez et al. 1999 • Rothenberg et al. 2000 • Schnaas et al. 2000 (included in pooled analysis by Lanphear et al. 2005) • Schnaas et al. 2006
Port Pirie	• McMichael et al. 1986 • Baghurst et al. 1987 • Baghurst et al. 1992 (included in pooled analysis by Lanphear et al. 2005)
Sydney	• Cooney et al. 1989
Yugoslavia	• Factor-Litvak et al. 1991 • Wasserman et al. 1994 • Wasserman et al. 1997 (included in pooled analysis by Lanphear et al. 2005) • Wasserman et al. 2000
Rochester, New	

York	• Canfield et al. 2003 (included in pooled analysis by Lanphear et al. 2005)

The relationship between maternal or cord blood lead levels and IQ deficits has been evaluated in several prospective studies.

The Boston study reported an adverse prenatal effect upon Mental Development Indices (MDI) up to 24 months of age in children with blood lead levels between 10 and 25 µg/dL. This effect was no longer statistically significant at 57 months of age *(Bellinger 1991)* or at 10 years *(Bellinger et al. 1992).* However, attenuation of this association varied as a function of social class standing and postnatal lead exposure profiles. Lack of attenuation was most evident in children of low social standing whose pre-natal (cord blood) measures had been in excess of 10µg/dL. Bellinger proposed that environmental enrichment facilitated recovery from early effects of lead.

The Yugoslavia study *(Wasserman et al. 1994),* noted a weak effect on the four-year GCI (General Cognitive Index). Global IQ had not yet been measured in this study and there was some question as to whether there might be some confounding from ethnicity differences and other exposures at the smelter site. The study cohort was derived from two towns – one with a smelter and elevated lead exposures (average cord blood lead of 22 +/- 8 µg/dL) and one without a smelter (average cord blood lead of 5.5 +/- 3.3 µg/dL). The presence of the smelter provided employment and a social environment more favourable to child development outcomes.

After adjustment for covariates, an adverse impact of lead was observed. *Wasserman et al. (2000)* examined the timing of lead exposure on early intelligence and found that **a 50% rise in prenatal blood lead was associated with a 1.07-point decrement in IQ at 5 and 7 years of age. This effect was approximately one-third of the impact of post-natal lead exposure**. It should be noted that the average blood lead levels in the residents of the smelter were very high compared to the other cohort, and there were also geographic and social differences between the high and low exposed groups. These differences could make it difficult to adequately control for confounding factors.

The Mexico City study: Using data from the cohort in Mexico City, *Schnaas et al. (2006*) used generalized linear mixed models with random intercept and slope to analyze the effects of lead on child IQ from pregnancy through 6-10 years of age. A cohort of 175 children, 150 of whom had completed data for all included covariates attended the National Institute of Perinatology in Mexico City from 1987 through 2002. Geometric mean blood lead during pregnancy was 8.0 µg/dl, from 1 through 5 years it was 9,8 µg/dl, and from 6 through 10 years was 6.2 µg/dl. IQ at 6-10 years decreased significantly only with increasing natural-log third trimester PbB, controlling for other PbB and covariates. The dose-response for the PbB-IQ relationship was log-linear, not linear-linear. The authors conclude that lead exposure around 28 weeks gestation is a critical period for later child intellectual development, with **lasting and possibly permanent effects being associated with maternal blood lead levels less than 10 µg/dL.**

Lanphear et al. (2005) examined data collected from 1,333 children who participated in seven international population-based longitudinal cohort studies (those included in table 13 except for the Sydney Study). This meta-study is a highly valued key study and is put forward by *EFSA (2010)* as being of great importance when investigating lead´s toxicity on the developing nervous system.

The children in the cohorts were followed from birth or infancy until 5–10 years of age. The objective of the study was to examine the association between intelligence test scores and blood lead concentration, especially for children who had blood lead levels under 10 µg/dL. The full-scale IQ score was the primary outcome measure. The geometric mean blood lead concentration of the

children peaked at 17.8 µg/dL and declined to 9.4 µg/dL by 5–7 years of age; 244 (18%) children had a maximal blood lead concentration < 10 µg/dL, and 103 (8%) had a maximal blood lead concentration < 7.5 µg/dL. After adjustment for covariates, the authors found an inverse relationship between blood lead concentration and IQ score. Using a log-linear model, they found a 6.9 IQ point decrement [95% confidence interval (CI), 4.2–9.4] associated with an increase in concurrent blood lead levels from 2.4 to 30 µg/dL. The estimated IQ point decrements associated with an increase in blood lead from 2.4 to 10 µg/dL, 10 to 20 µg/dL, and 20 to 30 µg/dL were 3.9 (95% CI, 2.4–5.3), 1.9 (95% CI, 1.2–2.6), and 1.1 (95% CI, 0.7–1.5), respectively. For a given increase in blood lead, the lead-associated intellectual decrement for children with a maximal blood lead level < 7.5 µg/dL was significantly greater than that observed for those with a maximal blood lead level ≥7.5 µg/dL (p = 0.015).

The lead-associated **IQ deficits** observed in this pooled analysis **were significantly greater at lower blood lead concentrations.** The larger sample size of the pooled analysis permitted the authors to show that the lead-associated intellectual decrement was significantly greater for children with a maximal blood lead of < 7.5 µg/dL than for those who had a maximal blood lead of ≥7.5 µg/dL. The authors conclude there is **no evidence of a threshold for negative effects caused by lead exposure, thus no level of lead exposure can be considered as safe.**

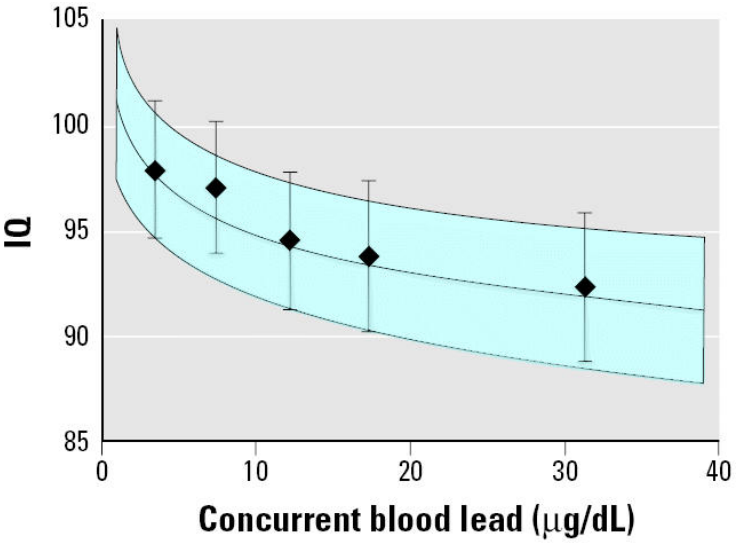

Figure from Lanphear et al. 2005; *Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environmental Health Perspectives, 113, 894-899.*

Log-linear model (95% CIs shaded) for concurrent blood lead concentration, adjusted for HOME score, maternal education, maternal IQ, and birth weight. The mean IQ (95% CI) for the intervals < 5 µg/dL, 5–10 µg/dL, 10–15 µg/dL, 15–20 µg/dL, and > 20 µg/dL are shown.

It should be mentioned as well that there are some studies, most of them not so recent, which do *not* find an association between perinatal lead exposure and IQ measures. These studies are not presented in this dossier. Factors such as co-exposure to other chemicals can potentially affect the toxicity of lead. In a very recent publication, not evaluated and presented further in this dossier, Henn et al. (2012) found evidence of synergism between lead and manganese, whereby lead developmental toxicity was increased among children with high manganese co-exposure.

There are several plausible reasons why certain studies have failed to show causality, one important factor to consider is sample size. Lead´s negative effect upon IQ is not detectable on a one-on-one, individual level but becomes highly significant on a community level. To demonstrate the effect on IQ, a larger cohort is needed and thus studies with a small number of participating individuals could fail to demonstrate causality simply because of the sample size.

Another factor that is important to keep in mind is that lead-associated IQ-deficits are significantly greater at lower blood lead concentrations, and the largest decline in IQ takes place when blood lead

rises from ≥0 up to10 µg/dL *(see the figure from Lanphear et al. 2005)*. Many, especially older studies have evaluated IQ effects in children with much higher overall blood lead levels, e.g. a "lead exposed group" with 50 µg/dL blood lead is compared to a "control group" with blood lead around 30 µg/dL. In this range (between 30-50 µg/dL), the decline in IQ is *much* smaller and very hard to detect. Even if the cohort was quite large, an effect on IQ would not be demonstrated when focusing on these higher blood lead levels. If a study of the same size had compared a "lead exposed group" with 20 µg/dL blood lead with a "control group" with blood lead levels under 5 µg/dL, a significant decline in IQ should be found in the lead exposed group.

The fact that most of the older studies have tried to find IQ effects at higher blood lead levels could be due to several reasons. Firstly, there have previously been technical limitations when it comes to measuring very low blood lead levels with accuracy. Secondly, average blood lead levels were higher than they are today, thus naturally having a higher blood lead level in the "control group" than we would today.

In addition, before anything was known about the nature of the dose-response curve for lead-induced IQ-deficits, it would be natural to presume that if any IQ-effects were to be found, they would be discovered (in the least) at higher blood lead levels, not "hidden" at high blood lead levels and most easily detected at blood lead levels under 10 µg/dL like the case is here.

When taking these factors into account, it is understandable why lead-induced IQ-deficits have not been scientifically proven before quite recently when considering how long the general toxicity of lead has been known to man.

4.11.3 Other relevant information

None.

4.11.4 Summary and discussion of reproductive toxicity

Studies in both humans and experimental animals provide strong evidence that lead causes negative impacts upon male fertility (e.g. semen quality) and neurodevelopmental effects in the offspring such as IQ-deficits after perinatal lead exposure.

Fertility – summary and discussion

The available data indicate that moderate to high lead exposure can have a marked adverse impact upon semen quality. Aberrant sperm morphology, decreased sperm count and decreased sperm density have all been demonstrated in lead exposed individuals.

Bonde et al. (2002) conducted a large cross sectional study of men employed in three different countries. Among other things, semen volume and sperm concentration were measured. The study group was of sufficient size to model dose-effect relationships and indicated a threshold for an effect upon semen quality at 45 µg/dL of concurrent blood lead. As blood lead levels increase above 50 µg/dL, progressively greater impact on fertility can be expected.

Development – summary and discussion

Negative effects of perinatal lead exposure upon neurobehavioural performance have been demonstrated both in experimental animals as well as in human prospective studies. The nervous system is the main target organ for lead toxicity and the developing foetus and young children seem to be the most vulnerable to lead induced neurotoxicity.

Several prospective studies have been conducted examining the impacts of pre- and perinatal lead exposure upon neurobehavioral development in children, and IQ has been one of the major endpoints found to be negatively affected. It appears that lead-associated IQ deficits are significantly greater at lower blood lead concentrations and there is no evidence of a threshold for negative effects. This concludes that no threshold has yet been identified for lead-induced developmental neurotoxicity and therefore no safe exposure level can be established.

4.11.5 Comparison with criteria

According to CLP; classification in category 1A is appropriate when there is "sufficient human evidence" to prove the toxicity of the substance. Lead clearly fulfils these criteria for reproductive toxicity and should therefore be classified in category 1A (H360: DF) for reproductive toxicity.

Category 1B should not be considered as there is an overwhelming amount of human evidence to support a classification in Repr. category 1A according to CLP legislation, or to the equivalent category 1 according to the old DSD legislation.

In 2010, the industry submitted a registration dossier for metallic lead, including a self-classification of lead metal powder (particle size <1 mm. Ø) for the endpoints reproductive toxicity, specific target organ toxicity after repeated dosing (STOT RE), and aquatic toxicity. No classification was proposed for metallic lead with a particle size larger than 1 mm in diameter.

In the registration dossier, the industry have motivated why, in *their* opinion, only lead particles smaller than 1 mm in diameter should be classified and not larger 'pieces' of metal. The following arguments were put forward:

1. *The main exposure routes of lead that can lead to significant systemic exposure are via either inhalation or oral ingestion of small particles. Only small particles are bioavailable and have the properties (large surface area vs. mass) that can lead to sufficient dissolution to cause significant systemic uptake.*

2. *The risk is very low that larger pieces of lead would be accidentally ingested orally. But if this were to happen, the metal piece would move quickly through the GI-tract and be excreted via the faeces without causing any significant systemic uptake, thus posing a low risk to human health.*

The CLP guidance that further explains article 5 and 6 of the CLP regulation states that:

"It is assumed that classification for human health hazards takes into account all the potential hazards which are likely to be faced for all forms or physical states in which the substance is placed on the market and can reasonably be expected to be used.

Reasonably expected use of a substance is as follows:

- *Any process, including production, handling, maintenance, storage, transport or disposal.*
- *All technical operations/manufacturing activities like e.g. spraying, filing, and sawing.*
- *Any putative consumer contact through e.g. do-it-yourself or household chemicals.*
- *All professional and non-professional uses including reasonably foreseeable misuse, but not abuse such as criminal or suicide uses.*

Reasonably expected use is also related to any consumer disposal or any work in which a substance or mixture is used, or intended to be used irrespective of its present limited use or use pattern. Thus, use should not be mixed up with usage category."

The overall conclusion is that powder formed during "reasonably expected use" (i.e. manufacturing, processing or other activities) demonstrates intrinsic properties of the substance, i.e. the original compound – the massive form. The different physical forms thus all reflect the manifestations of the substance's intrinsic properties.

In this CLH-dossier, we propose that metallic lead shall be classified as a reproductive toxicant in category 1A regardless of particle size. First of all; according to the CLP regulation, substances shall be classified after their intrinsic properties and not after risk of exposure. Secondly, there are numerous cases of lead poisoning described in the literature stemming from oral ingestion of a piece of lead (e.g. lead containing jewellery, buttons, etc.), even death has been reported. These case reports prove that pieces of lead ingested orally are indeed bioavailable and can cause systemic exposure.

Another important aspect is that the same classification should be allocated to all physical forms of lead so that the Safety Data Sheet can accompany the metal throughout its "life span", which could include processing into several different physical forms. Processing could take place in industrial settings but also in the home. A brick or piece of lead could under "reasonably expected use" e.g. be melted; an example is casting of bullets and fishing weights in the home. This type of exposure has been shown to increase blood lead levels *(MMWR 2011).* The metal can also be grinded into smaller pieces or polished; potentially causing small, easily inhalable particles during the process.

Taken together, it is of essence that all physical forms of lead, regardless of particle size, receive the same classification; Repr. 1A (H360: DF).

Justification of Chosen Specific Concentration Limit

Lead is a potent developmental neurotoxin, as little as a couple of µg/dL of blood lead can affect children's IQ negatively and no threshold has yet been identified for lead-induced developmental neurotoxicity. According to the newly updated CLP guidelines (see reference list), when human data is available; the Specific Concentration Limit (SCL) should be determined by assigning the substance to the appropriate group; low, medium or high potency. To qualify to be placed in the high potency group, the ED_{10} value (basically lowest dose that induces reprotoxic effects) should be equivalent to, or less than 4 mg/kg bw/day.

For children, the oral absorption rate of lead is approximately 40-50% *(ATSDR 2007; VRAR 2008).* A calculation based on a "best-case scenario" can be made, where the absorption rate is 40% and the blood lead level needed to impair IQ is a 10 µg/dL. A child weighing 12 kg has approximately 1 litre of blood *(Internetmedicin).* Using the following equation we can calculate the exposure in µg/kg needed to produce a sufficiently high blood lead level to impair IQ:

Exposure in µg/kg = (blood lead conc. in µg/L * blood volume in L)/(body weight in kg * absorption rate)

This gives: ***Exposure in µg/kg = (100 µg/L * 1 L)/(12 kg * 0.4) = <u>20.8 µg/kg</u>***

Making the equivalent calculation for a "worst-case scenario" we can set the absorption rate to 50% and assume that the blood lead level needed to impair IQ is 5 µg/dL.

This gives: ***Exposure in µg/kg = (50 µg/L * 1 L)/(12 kg * 0.5) = <u>8.3 µg/kg</u>***

The cut-off for a substance to be placed in the high potency group is **4 mg/kg.** This number greatly exceeds both our worst- and best-case scenarios, thus clearly illustrating the high potency of lead. Therefore, lead should be placed in the high potency group and be assigned the lowest **Specific Concentration Limit of 0.03%.**

4.11.6 Conclusions on Classification and Labelling

There is a large body of evidence from human studies showing the adverse effects of lead on both fertility and development; lead impacts negatively on male fertility causing testicular atrophy and decreased sperm quality. Lead is also very toxic to the developing nervous system, causing IQ deficits in children that are pre- and/or postnatally exposed to lead. No threshold has yet been identified for lead-induced developmental neurotoxicity and therefore no safe exposure level can be established.

Thus, in this CLH-report we propose that lead shall be classified in category 1A (H360) for reproductive toxicity.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

Fertility: Effects of lead exposure on fertility have been examined in both animal and human studies. Due to the wealth of information on human fertility effects, the DS focused on the human data but summarised three animal studies, all of which exposed the test animals to (water soluble) lead acetate. A rat drinking water study exposing animals to 0.3% lead acetate for 14-60 days (resulting in Pb blood levels of 33-46 µg/dl; Sokol et al. 1994) reported decreased sperm counts and lower fertilisation rates *in vitro*. A drinking water study exposing rats to lead acetate resulted in Pb blood levels of 54-143 µg/dl (Chowdhury et al. 1984) and showed testicular atrophy and lower spermatid and spermatocyte counts. A primate study with lifetime oral administration of lead acetate showed ultrastructural changes to testis tissue at Pb blood levels of 35 µg/dl (Foster et. Al 1998).

A large number of human studies on lead-exposed workers and patients at fertility clinics exist. The CLH dossier includes summaries of 23 studies, one of which is considered a key study (Bonde et al. 2002). A further 16 studies are considered reliable with restrictions and 6 studies are considered unreliable but used in a weight of evidence approach. Bonde et al. (2002) conducted a cross-sectional study of lead-exposed workers, establishing a threshold level for effects on semen quality of 45 µg/dl Pb in blood.

Effects of lead exposure on female fertility were not evaluated in the CLH report.

Development: No specific animal studies were presented in the CLH report. The DS referred to the Voluntary Risk Assessment Report on Lead and some inorganic Lead compounds (VRAR 2008) and stated that a large number of animal studies showed findings in humans, including: learning dysfunction, altered activity, delayed sex organ development and sexual maturation upon pre-natal lead exposure.

Several publications from eight epidemiological studies (defined by the region where the studies were carried out) are referenced in the CLH report. Three of these studies are summarised in more detail (Boston, Yugoslavia and Mexico City). Furthermore, a meta-analysis of seven studies is also summarised (Lanphear et al. 2005). The Boston study reported mental deficiencies in children up to 24 months of age associated with Pb blood

levels of between 100 and 250 µg/l, becoming no longer significant at 57 months.The lack of attenuation of this association was most evident in children of low social standing whose pre-natal (cord blood) lead levels had been in excess of 100 µg/L. In the Yugoslavia study, higher Pb levels in umbilical cord blood were associated with a lowering of IQ in children at 5 and 7 years of age, while in the Mexico City study, higher blood lead levels during pregnancy and in early life were associated with a lower IQ in children at 6-10 years of age and a critical exposure period was identified at around 28 weeks of pregnancy, with permanent cognitive effects associated with maternal lead blood levels below 100 µg/l.

Lanphear et al. (2005) analysed publications from seven international population-based longitudinal cohort studies and this data was presented as a key study by the DS. Having analysed 1,333 children, followed from birth or infancy to 5-10 years of age, the authors found an inverse relationship between blood lead levels and IQ. The relationship was not a linear one, with proportionally greater loss of IQ at lower blood lead levels and no apparent threshold effect. This could explain previous negative studies where control groups had higher blood lead levels than more recent studies.

Based on the wealth of human data associating elevated lead blood levels with adverse effects in testes and on neurodevelopment in infants and children, the DS proposed to classify lead as a reproductive toxicant in category Repr. 1A – H360FD according to the CLP regulation (Repr. Cat 1; R60-61 according to DSD). The DS also proposed that metallic lead should be classified as a reproductive toxicant in category 1A regardless of particle size, as substances are classified on the basis of their intrinsic properties and not according to the potential for exposure.

There are numerous cases of lead poisoning described in the literature stemming from oral ingestion of a piece of lead (e.g. lead-containing jewellery, buttons, etc.). These case reports prove that pieces of lead ingested orally are bioavailable and can cause systemic exposure. The DS also remarked that the same classification should be allocated to all physical forms of lead because small particles may be formed during “reasonably expected use” (e.g. melting, grinding and polishing) of the original compound i.e. an ingot or piece of lead.

The DS assumed an oral absorption rate of 40% for lead and used a blood lead level of 100 µg/l as clearly indicating impairment of IQ in children. The DS concluded that lead is a potent developmental neurotoxin as concentrations in the very low µg/l range of blood lead can affect children’s IQ negatively and no threshold has yet been identified for lead-induced developmental neurotoxicity. As a result, the DS considered lead to be of high-potency and proposed a Specific Concentration Limit of 0.03%

Comments received during public consultation

Forty nine comments were received during the public consultation and included. Member States (MS) Competent Authorities, Industry associations, companies and individuals.

Comments were received from seven MSs, who all expressed agreement with the proposal and provided some with additional comments. One MS, later supported by the DS proposed to consider classification for lactation, citing an evaluation conducted by the Netherlands Health Council (2003). Another expressed a wish to consider STOT RE for lead but as this was outside the scope of the CLH proposal, it was not considered further by RAC.

The International Lead Association (ILA) and several member companies submitted substantial comments on the CLH proposal. The main points addressed were the scope

of the proposal, application of read-across and the bioavailability of metallic lead. Several Industry members also raised concerns on the derivation of SCLs in the CLH proposal. The accuracy of the calculation of the SCL (which was derived from an ED_{10} calculation) and the rationale with which a 10-fold lower value than the generic concentration limit of 0.3% was derived were all questioned. The DS noted that there is no specific guidance on how to set a SCL based on human data so that any ED_{10} should be seen as an indication that lead is highly potent. However, the DS recommended that RAC should discuss the setting of an appropriate SCL based on human data. All comments as well as the specific responses by the DS and the RAC are compiled in the RCOM in Annex I to the RAC Opinion.

Assessment and comparison with the classification criteria

The DS justified their proposal to classify all physical forms of lead as a reproductive toxicant in category 1A – H360FD by providing evidence from animal and human data that lead exposure impairs male fertility and neurodevelopment of children. These conclusions are supported by previous evaluations by EFSA (2010) (Scientific opinion on lead in food. EFSA Journal 2010, 8(4):1570) and the previous opinions of RAC and SEAC on the restriction of lead in jewelry (2012). The RAC fully agreed with these opinions and their conclusions as well as with the proposed classification and labelling (Repr. 1A – H360DF (CLP) and Repr. Cat. 1; R60-61 (DSD).

Clear adverse effects on semen quality have been observed at elevated blood lead levels (>45 µg/dl) in humans as well as testicular atrophy in experimental animals. RAC therefore agreed with the DS that classification for fertility is warranted.

There is clear evidence that pre- and post-natal lead exposure impairs neurodevelopment. This has been demonstrated by animal experiments and more importantly by epidemiological studies as described by the DS.

Thus, the RAC agreed with the assessment provided by the DS on the neurotoxicity of metallic lead. Specifically IQ impairment following elevated blood lead levels during pregnancy and the observation that all forms of metallic lead are bioavailable justify the C&L of metallic lead as a developmental toxicant. Although pre-natal exposure clearly leads to developmental neurotoxicity, young children are also particularly sensitive to this effect, given that their central nervous system is still under development. RAC also noted that no threshold for the adverse effect has been identified in humans so that RAC considers that any pre- and post-natal exposure presents a hazard.

During public consultation the question was raised as to whether the CLP criteria for developmental toxicity also apply to post-natally induced neurotoxicity. This reflects the difficulty to differentiate between the health consequences of pre- and post-natal exposure of children in general as described in the different epidemiological studies. However, in their response, the DS referred to Davison and Dobbing (1968), who concluded that the nervous system is still under development for several years after birth and that clear effects on the mental development as indicated by lower IQ in young children has been demonstrated (see e.g. Lanphear et al. (2005)). Referring to the CLP Regulation section 3.7.1.4.

> "*Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or post-natally, to the time of sexual maturation…*"

the DS concluded that post-natal effects also justified the classification as a

developmental toxicant. Section 3.7.1.4 further states:

> "*… However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure …*"

Although the emphasis is placed on pre-natal effects, the criteria do not exclude adverse effects from post-natal exposure. However, lead clearly demonstrates adverse effects on neurodevelopment after pre-natal exposure and classification for developmental toxicity is considered justified.

Classification for lactation

According to the CLP criteria classification for lactation is recommended when "absorption, metabolism, distribution and excretion studies indicate the likelihood that the substance is present at toxic levels in breast milk." An evaluation by the Netherlands Health Council (2003) referenced several human studies which showed lead levels in breast milk of up to 350 µg/l. These levels far exceeded the FAO/WHO acceptable level of 16 µg/l and further studies support the information that children can be exposed to lead via breast milk (Ettinger et al. 2004a, Ettinger et al. 2004b). RAC therefore proposed that metallic lead should additionally by classified for effects on or via lactation (Lact. - H362 (R64).

Setting of specific concentration limits

In the EFSA (2010) risk assessment, a lowered benchmark dose level (BMDL01) of 0.5 µg Pb/kg bw/day was derived as a dose descriptor for the potential adverse effects of lead on children. This corresponded to an increase in blood level of 12 µg Pb/l and an IQ loss of 1 point. 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 per day (e.g. from the diet and background environmental exposure). This already exceeds the BMDL01 level of 0.5 µg Pb/kg bw/d, and therefore any additional lead exposure would on average be expected to further increase a typical child's exposure above the dose descriptor level. This clearly indicates that lead exposure impairs neurodevelopment at very low doses and justifies the derivation of a SCL.

Although specific guidance for setting specific concentration limits for reproductive toxicity using human data is lacking, SCLs can still be set using expert judgment. Article 10 of the CLP Regulation states: '*where adequate and reliable scientific information shows that the hazard of a substance is evident when the substance is present at a level below the concentrations set for any hazard class in Part 2 of Annex I or below the generic concentration limits set for any hazard class in Parts 3, 4 and 5 of Annex I*'. In order to determine SCLs, the relative potency of lead compared with other reproductive toxicants needs to be determined. Although blood lead levels can be correlated with adverse effects in humans, extrapolation from these blood levels to the oral/external dose of metallic lead required is challenging.

In order to evaluate whether the setting of a SCL was appropriate, RAC considered the following:

The DS proposed to set a SCL of 0.03% for developmental effects for all forms of lead. The potency of lead was estimated based on the children's blood level of 100 µg/l that is needed to impair IQ (based on the assumption of ATSDR (2007) that 100 µg/l increase in blood lead level causes the IQ score to decrease by 1-5 points) and the assumption of an

oral absorption rate of 40% (considered a best case scenario by the DS, see Eq. 1).

According to section 3.7.2.5 of the CLP Guidance the lowest ED_{10} for the effect that fulfills the criteria for classification shall be used to determine the potency group. The estimation of the ED_{10} value(s) is usually based on reproductive (here developmental) toxic effects in animals. The guidance emphasizes that the use of human data for ED_{10} calculation has several drawbacks because data on exposure, the size of exposed population and information on the most critical time window for developmental effects are generally limited. If the ED_{10} concept (referring to a 10% effect level of incidence or magnitude of the adverse effect, after correction for spontaneous incidence) is transferred to the available human data, this would mean that the concentration with a drop of 10 IQ points (related to the mean IQ of 100 in the population) would be the starting point for calculation. This effect size appears to be very severe. Based on the meta-study of Lanphear et al. (2005) an ED_{10} level (reduction of about 10 IQ scores) is to be expected at a blood concentration of >300 µg/l (as indicated by the log-linear model for blood lead concentration, see the figure from Langhear et al. 2005 in the CLH report). RAC agreed with the DS proposal to use the estimate of 100 µg/l increase in blood lead level causing adverse effects as an ED_{10} equivalent (and which corresponds to the LOAEL that justified classification). In contrast to what was proposed by the DS however, 50% was used as absorption rate by RAC (see Eq. 5), since there is no justification to apply the lowest observed absorption rate. As shown in adults, it cannot be excluded that the absorption is even higher in a non-fasting condition in children as well.

Children:

Eq.1 (DS proposal): *Exposure in µg/kg = (blood lead conc. in µg/l * blood volume in L)/(body weight in kg * absorption rate)*

*This gives: Exposure in µg/kg = (100 µg/l * 1 l)/(12 kg * 0.4) = 20.8 µg/kg*

This exposure value is in the range of JECFA's estimation that 1 µg/kg bw of lead in diet results in an increase of 10 µg/l blood level (see EFSA, 2010).

Given that 73% of the lead body burden is deposited in the bones of children (ATSDR, 2007) and the blood lead corresponds to 27% of the total burden (neglecting the distribution to other organs for this calculation), the external dose is 77 µg/kg bw (reflecting the total body burden and using the same calculation as above), which is still below 4 mg/kg bw (see Eq. 2).

Considering that 20.8 mg/kg represents 27% of lead in blood, plus 73% of lead deposited in bones:

Eq. 2: *20.8 µg/kg/0.27= 77 µg/kg.*

The calculated external doses of 20.8 µg/kg or 77 µg/kg are clearly below the boundary for high potency (≤4 mg/kg) and thus would indicate high potency and support a specific concentration limit of 0.03%.

Pregnant women:

The ED_{10} equivalent estimation for the oral exposure of young children covers the postnatal period of the developing nervous system only. Uncertainties regarding the prenatal exposure as a critical window that may show higher vulnerability of neonates and a lower absorption rate for adults (3-10%, derived for soluble lead compounds) should be noted. However in the absence of robust data to prove higher sensitivity, guidance recommends to assume equivalent sensitivity. Applying an absorption rate of 3% as a best case for pregnant women (assuming comparable sensitivity to children at comparable blood levels in the fetus, a maternal body weight of 70 kg and a blood

volume of 7 l at delivery) the calculation would result in an external exposure of pregnant women to 0.33 mg/kg bw leading to blood lead levels of 100 µg/l in the mother (see Eq. 3).

Eq. 3: *(100 µg/l * 7 l)/(70 kg * 0.03) = 333 µg/kg*

In adults, 94% of the total body burden of lead is found in the bones. Assuming 6% of the lead burden in the blood, the corrected external dose is 5.5 mg/kg (see Eq. 4).

Eq. 4: *333 µg/kg/0.06 = 5,550 µg/kg.*

The latter value is above the limit of 4 mg/kg for setting an SCL. However, a 94% deposit in bones may be an overestimation as lead mobilisation from bone during pregnancy has been reported. Also, the 3% absorption rate (derived from the lowest estimate for the absorption from soluble lead compounds, taking into consideration that the absorption rate of metallic lead is generally lower than the rates for soluble lead compounds) may be an underestimate.

Animal data:

The CLP Guidance (see 3.7.2.5.3.5) recommends evaluating human data together with animal data. With regard to the animal data, the CLH dossier refers to the documentation of animal studies in the VRAR (2008, see Table 4.203). However the animal data are neither complete nor are they documented in such a way that would allow the estimation of an ED_{10} based on the NOAEL/LOAEL for the effects of concern. The effect size (incidence or magnitude of the effects) for parameters relevant for classification were not given, the parameters selected were different in the available studies for the tested species, and would require analysis of the original publications/reports. ATSDR (2007) concluded that many of the behavioral deficits observed in children exposed to lead have been reproduced in studies in animals, particularly monkeys, and at similar blood lead levels. This is in line with Davis et al. (1990) who stated that neurobehavioral effects were seen at comparable blood levels in children, primates and rodents. However it must be noted that neurobehavioral testing in animals covers some but not all aspects of neurobehavioral function in the developing organism and animal data are thus not fully equivalent to the testing of IQ deficits, the most sensitive neurodevelopmental effect in humans.

Taking into consideration the available absorption data on metallic lead further corrections on the calculations may be needed:

During the discussions at RAC-26 it was questioned whether the chosen gastrointestinal absorption rate of 40-50% for children is overestimated with regard to metallic lead. In the CLH Report the DS referred to the absorption rate of water soluble lead reported in ADSDR (2007). The (absolute) absorption rate for metallic lead remains to be determined. In comparison to lead acetate as the reference compound, it was found that the relative absorption rate in rats receiving a diet containing 0.075% lead was 14% for metallic lead for particles with a mean size of 180-250 µm (Barltrop and Meek, 1979a) and 10% if corrected for 4% lead absorbed by rats receiving the control diet. Tissue and blood concentrations were inversely related to the particle size and tissue concentration was 5-fold (blood conc. 3-fold) higher for particles with a mean size of 6 µm (Barltrop and Meek, 1979b). A factor of 0.10 for 10% relative absorption and an additional factor of 5 (for a 5 fold higher kidney concentration for small (6 µm) particles compared to 180-250 µm particles) were applied to calculate the corrected absorption rate. The higher (5-fold) increase in kidney concentration compared to the 3-fold increase for blood was considered as a conservative approach with which to make this adjustment.

Children, using an adjustment to cover absorption of metallic lead:

Using the small particle size (6 µm) as a worst case, the corrected absorption rate for

metallic lead is 50% *0.10*5 = 25%. Using the same calculation as in Eq.1), this results in an external dose of

Eq. 5: *(100 µg/l * 1l)/(12 kg * 0.25) = 33 µg/kg (child)*

It was also mentioned during the RAC discussion that the total external dose (after correction for tissue distribution) may be higher due to an overestimation of the blood concentration of 27%. 73% of the body burden is found in the children's bones (ATSDR) and the remaining lead is distributed in the blood and soft tissues (liver>skeletal muscle>skin>fat>kidney>lung>aorta>brain, without any data on the percentage in total blood). RAC members assumed that 27% blood lead concentration is too high; using 10% lead in blood would result in a corrected value for external exposure of 330 µg/kg (total body burden) (see Eq. 6).

The 33 µg/kg from Eq. 5 is assumed to be distributed as 10% in the blood, plus 73% in the bone plus the remaining 17% in soft tissues, thus:

Eq. 6: *33 µg/kg/0.1= 330 µg/kg (child, corrected for tissue distribution)*

In order to demonstrate at which level of absorption, no SCL needs to be considered, the following equation is given:

Eq. 7: *(100 µg/l * 1l)/(12 kg * 0.02)/0.1 = 4,166 µg/kg (child, corrected for tissue distribution).*

The (absolute) absorption rate which corresponds to an external dose of 4 mg/kg for children should then be demonstrated to be lower than 2%.

Pregnant women using an adjustment to cover absorption of metallic lead:

As in Eq. 3, applying an absorption rate of 3% (best case), a blood volume of 7 l for pregnant women, and taking into account the rat data indicating a 10% relative absorption of metallic lead and 6 µm particles (factor of 5) (see Eq. 8), then:

Eg. 8: *(100 µg/l * 7l)/(70 kg * 0.03*0.1*5) = 666.7 µg/kg (pregnant women).*

In adults, 94% of the total body burden of lead is found in the bones. Assuming 6% of the lead burden in the blood, the corrected external dose is 11.1 mg/kg (see Eq. 9).

Eq. 9: 666.7 µg/kg/0.06 = 11,111 µg/kg *(pregnant women, corrected for tissue distribution, disregarding lead mobilisation from bone during pregnancy).*

The RAC recognised that the above mentioned reasoning with regard to the estimations of the external dose of metallic lead contain some uncertainties as the level of oral bioavailability is dependent on several factors. The purpose of these calculations is to demonstrate that even with different input values, they still result in a range of low external concentrations for particulate metallic lead in small children, e.g. using either worse case assumptions, a) a starting point of 40% absorption for metallic lead as estimated for soluble lead particles in the DS proposal without any reflection on a putative lower absorption for metallic lead, or b) presuming a much lower absorption rate of particulate metallic lead (as indicated by the rat data on metallic lead particles of 6 µm in the studies of Baltrop and Meek, 1979a,b) and correcting the dose for tissue distribution.

On the one hand the DS proposal resulted in an external dose of 20.8 µg/kg (Eq. 1) and

on the other the corrected calculations resulted in an external dose of 330 µg/kg (Eq. 6) for children. Based on the available information even the 'best case estimates' for the external dose in small children (as the most sensitive individuals compared to pregnant women) are significantly below 4 mg/kg and in the view of the RAC warrant the setting a SCL of 0.03% for lead.

The calculation for pregnant women resulted in an external dose of 11.1 mg/kg (that reflects the increase in mother's lead blood level of 100 µg lead/l) taking the following assumptions into account: a 0.3% absorption rate for metallic lead, a factor of 5 for 6 µm particles and a 94% accumulation of lead in the bone However, during pregnancy the bone lead is mobilised and therefore the actual external dose needed to reach the 100 µg/l lead blood level is likely to be lower, although its extent cannot be estimated. Moreover, under certain conditions (e.g. fasting), the maximum oral absorption was reported to be 70% leading to much lower external doses.

The CLP Guidance (3.7.2.5.5.6) advises that the bioaccumulation of a substance should be taken into account when determining the potency group. Lead is known to bioaccumulate (half-life in bone up to decades) and the actual dose for pregnant women needed in the critical time window for developmental effects to occur may be lower than those estimated in Eq. 9 (11.1 mg/kg). Even when the estimates for pregnant women are above a limit dose of 4 mg/kg, the bioaccumation of lead supports the need for a SCL. Bioaccumulation leading to additional blood lead from bone resorption appears to be less relevant for the lead blood level in children, as bone production is higher in growing children than in adults.

RAC noted that following the CLP Guidance strictly, the small size of the external dose in children (range of 20.8 µg/kg – 330 µg/kg; Eq. 1 and 6) that corresponds to the ED_{10} equivalent can also justify a lower SCL than 0.03% and a SCL of 0.003% was suggested by some RAC members. However, based on the scientific information and expert judgement, RAC agreed that the developmental effects of metallic lead are of high potency to children and to set an SCL of 0.03%. A lower SCL was not considered as justified taking into account the remaining uncertainties of the available information and the fact that sufficient data on the absolute bioavailability of metallic lead at different particles sizes are not available.

With regard to the question whether a limit for the particle size can be set, RAC considered the following:

Industry proposed to set the SCL only for particle sizes below 1 mm. For metallic lead, Barltrop and Meek (1979b) demonstrated that the particle size (tested range 6- to 200 µm as mean particle size) was shown to be inversely related to the absorption rate. IND's suggestion to set the SCL only for particles smaller than 1 mm was based on the observations of Barltrop and Meek and on calculations predicting that relative bioavailability of particles > 1 mm will be below 1%. They postulated that no relevant absorption will occur from particles >1 mm. RAC is not aware of data that confirm the non-bioavailability of lead from particles of sizes >200 µm and takes into account that in general a dust/powder consists of a distribution of different particle sizes. This is assumed for particles produced during normal handling and use. Thus a setting of an upper limit of the particle size is not justified.

The RAC therefore recommended that all physical forms of metallic lead should be classified equally: lack of bioavailability was not demonstrated for lead in its solid form. Taking the available information into account, RAC concluded that particulate metallic lead is a highly potent developmental toxicant. Considering Art. 9(5) of CLP, the RAC concluded that during reasonably expected use (such as grinding, filing, sawing, melting, or soldering of massive lead) small and potent particles that are ingestible and/or inhalable can be released from massive forms. In addition, lead oxide may be formed on the surface. The RAC therefore concluded that the suggested SCL of 0.03% for

developmental toxicity is justified for metallic lead in all its physical forms.

SCL for effects on sexual function and fertility: The DS did not provide a specific argumentation for a SCL for effects on sexual function and fertility but concluded that the same SCLs should apply to both specific effects. However, the CLP Guidance states that SCLs for developmental toxicity and fertility effects should be determined separately. The RAC noticed that the lowest effect level for fertility effects is higher than the critical effect dose for developmental toxicity. The lead blood level of 500 µg/l based on semen quality was used as an ED_{10} surrogate and revealed external doses above 4 mg/kg/day. Thus the RAC agreed that no SCL is warranted for this endpoint.

Conclusion

In conclusion, the RAC agreed with the DS that all physical forms of metallic lead should be classified as Repr. 1A – H360DF (Repr. Cat 1; R60-61). In addition, the RAC concluded that classification as Lact. – H362 (Xn; R64) under DSD was appropriate. According to the criteria in the CLP Guidance (3.7.2.5), the RAC agreed that the generic concentration limit would underestimate the hazard of lead. The RAC concluded that the metallic lead should be assigned a specific concentration limit of 0.03% for developmental toxicity (H360D, C ≥ 0.03%).

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4.12 Other Effects

Not evaluated in this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier.

6 OTHER INFORMATION

Certain data this CLH-report has been derived from the 'Voluntary Risk Assessment Report on Lead and some inorganic Lead compounds' *(VRAR 2008),* the 'Chemical Safety Report on Lead' *(CSR 2010)* submitted by Industry, and The Scientific Opinion on Lead in Food *(EFSA 2010)*.

Please note that the original reference(s) have not always been examined when reference has been made to these sources.

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