Committee for Risk Assessment

RAC

Opinion

proposing harmonized classification and labelling
at EU level of

Lead

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

CLH-O-0000002512-83-02/F

Adopted

5 December 2013

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2 December 2013

CLH-O-0000002512-83-02/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemicals name: Lead

EC number: 231-100-4

CAS number: 7439-92-1

The proposal was submitted by **Sweden** and received by the RAC on **23 October 2013.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

PROCESS FOR ADOPTION OF THE OPINION

Sweden has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **23 October 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **7 December 2012**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Helmut Greim**

Co- rapporteur, appointed by RAC: **Agnes Schulte**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling was reached on **2 December 2013** and the comments received are compiled in Annex 2.

The RAC opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **lead** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Current Annex VI entry	No current Annex VI entry									
Dossier submitters proposal		Lead	231-100-4	7439-92-1	Repr. 1A	H360DF	GHS08 Dgr	H360DF		Repr. 1A; H360DF: C ≥ 0,03 %
RAC opinion		Lead	231-100-4	7439-92-1	Repr. 1A Lact.	H360DF H362	GHS08 Dgr	H360DF H362		Repr. 1A; H360D: C ≥ 0,03 %
Resulting Annex VI entry if agreed by COM	082-013-00-1	Lead	231-100-4	7439-92-1	Repr. 1A Lact.	H360DF H362	GHS08 Dgr	H360DF H362		Repr. 1A; H360D: C ≥ 0,03 %

Classification and labelling in accordance with the DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits
Current Annex VI entry	No current Annex VI entry						
Dossier submitters proposal		Lead	231-100-4	7439-92-1	Repr. Cat. 1; R60-61	T R: 60-61 S: (1/2-)13-35-45-53	Repr. Cat. 1; R60-61: C ≥ 0,03 %
RAC opinion		Lead	231-100-4	7439-92-1	Repr. Cat. 1; R60-61 R64	T R: 60-61-64 S: 45-53	Repr. Cat. 1; R61: C ≥ 0,03 %
Resulting Annex VI entry if agreed by COM	082-013-00-1	Lead	231-100-4	7439-92-1	Repr. Cat. 1; R60-61 R64	T R: 60-61-64 S: 45-53	Repr. Cat. 1; R61: C ≥ 0,03 %

SCIENTIFIC GROUNDS FOR THE OPINION

RAC general comment

There is a wealth of information associating elevated blood lead levels with adverse effects in both animals and humans. Most animal studies are conducted with soluble lead compounds such as lead acetate while human epidemiology studies and case studies often do not report the specific form of lead that the subjects were exposed to. However, according to the dossier submitters (DS) proposal, the classification should apply to all physical forms of metallic lead, regardless of particle size. The DS justified this approach by referring to the CLP Regulation which stipulates that substances shall be classified in accordance with their intrinsic properties (hazard) and not on the basis of considerations of risk. In accordance with Art. 12 of CLP, bioavailability shall only be considered for classification purposes when conclusive scientific experimental data show that the substance is not biologically available and those data have been ascertained to be adequate and reliable. The RAC noted that the *Guidance on the Application of the CLP Criteria,* section 1.3.2.1, refers to a few specific cases in which bioavailability may have an influence on hazard classification, e.g. some metals, where the nature of the physical form (metals in solid form) may limit absorption. In order to conclude that there is a lack of or reduced bioavailability there needs to be a high burden of proof, supported by robust data and expert evaluation.

Information on bioavailability is usually obtained from adequate, reliable, and conclusive toxicokinetic studies for all relevant routes of exposure and all relevant forms or physical states where the substance and/or metabolite(s) of the substance have been quantified in body fluids and/or target organs. Since such data have not been presented by the DS or during the public consultation (PC), the RAC agreed with the DS that the classification should apply to all physical forms of lead, regardless of particle size. This is further justified because upon inhalation and oral ingestion of metallic lead, lead ions become bioavailable as indicated by the data presented by the DS. 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 *(Jones et al. 1999; CDC 2004; Canada Gazette 2005; CDC 2006; KEMI 2007; InVS 2008; Levin et al. 2008).* The observed symptoms of these cases range from headaches and diarrhoea 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 were manifested as vomiting, abdominal pain and fatigue; at the time of death the child had a final PbB level of 1800 µg/l (see CLH Report pp. 18, and opinion on lead in jewelry). In addition, a publicly available study mentioned during the PC investigated the relative absorption of metallic lead compared to lead acetate and the effects of particle size on metallic lead absorption. Particles of elemental lead were supplied in the diet of rats and increased blood and tissue lead levels were measured. Larger (mean) particle sizes lead to a lower relative absorption than small particles, but all particle sizes tested (up to 250 µm) were bioavailable (Barltrop and Meek 1979a). As increased lead levels in blood are associated with adverse effects, exposure to metallic lead is thought to induce the same lead-associated neurodevelopmental and other adverse effects.

Article 5 (1) of CLP on the identification and examination of available information on substances states that "*The information shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used*." In addition, according to Article 9 (5) of CLP the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used should be considered when evaluating the available information for the purposes of classification. In relation to this, metallic lead can be processed into different physical forms in industry and at home e.g. casting bullets and fishing weights. It can be ground or polished potentially causing small, easily inhalable particles.

Although metallic lead is considered to have a low dermal absorption rate, lead oxide formed on the surface of lead can easily rub off on the skin becoming systemically available by hand to mouth contact for both children and adults.

HUMAN HEALTH HAZARD ASSESSMENT

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 authorsfound 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 the 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 the 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 the 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. The 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. The RAC also noted that no threshold for the adverse effect has been identified in humans so that the 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). The 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, The 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). The 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 The 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 µ/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 * 1 l)/(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). The 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 * 1 l)/(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:

Eq. 8:*(100 µg/l * 7 l)/(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.

The 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, the 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. The 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, the 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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ANNEXES

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by the RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs' comments (excl. confidential information).