Substance Name:
Lead(II)bis(methanesulfonate)

EC Number: 401-750-5

CAS Number: 17570-76-2

SUPPORT DOCUMENT FOR IDENTIFICATION OF

LEAD(II) BIS(METHANESULFONATE)

AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS CMR[1] PROPERTIES

[1] CMR means carcinogenic, mutagenic or toxic for reproduction.

CONTENTS

TABLES

Substance Name(s): Lead(II) bis(methanesulfonate)

EC Number(s): 401-750-5

CAS number(s): 17570-76-2

The substance is identified as substance meeting the criteria of Article 57 (c) of Regulation (EC) 1907/2006 (REACH) owing to its classification as toxic for reproduction category 1 A[2].

It is proposed to identify the substance(s) as substance(s) of equivalent concern according to Article 57 (c).

Summary of how the substance meets the criteria as category 1B reproductive toxicant.

Lead(II) bis(methanesulfonate) (EC Number: 401-750-5, CAS number: 17570-76-2) is covered by index number 082-008-00-4 in Regulation (EC) No 1272/2008 and classified in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as toxic to reproduction, Repro. 1A (H360-Df: 'May damage the unborn child. Suspected of damaging fertility'). The corresponding classification in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is toxic to reproduction category 1 (R61: "May damage the unborn child. Suspected of damaging fertility').

Therefore, this classification of Lead(II) bis(methanesulfonate) in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic to reproduction in accordance with Article 57 (c) of REACH.

Registration dossiers submitted for the substance? Yes

2 Classification in accordance with Regulation (EC) No 1272/2008 Annex VI, part 3, Table 3.1 List of harmonised classification and labelling of hazardous substances.

JUSTIFICATION

1 Identity of the substance and physical and chemical properties

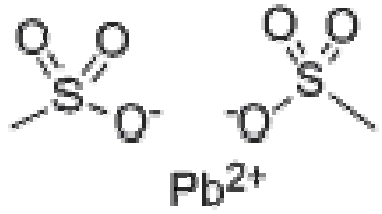
1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	401-750-5
EC name:	lead(II) bis(methanesulfonate)
CAS number (in the EC inventory):	17570-76-2
CAS number:	149864-43-7
CAS name:	Methanesulfonic acid, lead(2+) salt (2:1)
IUPAC name:	Lead(II) bis(methanesulfonate)
Index number in Annex VI of the CLP Regulation	082-008-00-4
Molecular formula:	C2 H6 O6 Pb S2
Molecular weight range:	Ca. 397.4
Synonyms:	Methanesulfonic acid, lead(2+) salt Lead methane sulphonate Lead salt FP (trade name) Methanesulfonicacid,lead(2+)salt Lead Methane Sulfate lmethanesulfonic acid, lead(II) salt Lead methyl sulfonate

(Registration dossier 2011)

Structural formula:



(ChemicalBook 2011)

1.2 Composition of the substance

Name: Lead(II) bis(methanesulfonate)

Description: lead salt

Degree of purity: Confidential information

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
Lead(II) bis(methanesulfonate)	Confidential information		

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
Confidential information			

(Registration dossier 2011)

Additives

Confidential information

1.3 Physicochemical properties

Table 4: Overview of physicochemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	Solid, crystalline powder	
Melting/freezing point	360 ºC	
Boiling point		Test not conducted in view of high melting point.
Vapour pressure	4.3 x10-5 Pa at 25°C	
Water solubility	> 200 g/l at 25°C	.
Partition coefficient n-octanol/water (log value)	< -4.1 at 21°C	
Dissociation constant		
Relative density	3.31 at 20°C	

(Registration dossier 2011)

2 Harmonised classification and labelling

2.1 Classification and labelling according to CLP / GHS

According to Regulation (EC) No 1272/2008 Annex VI Table 3.1:

Classification: Repr. 1A, Acute Tox. 4, STOT RE 2, Skin Irrit. 2, Eye Dam. 1

Hazard Statement: H360Df: May damage the unborn child. Suspected of damaging fertility.

H332: Harmful if inhaled.

H302: Harmful if swallowed.

H373: May cause damage to organs through prolonged or repeated exposure.

H315: Causes skin irritation.

H318: Causes serious eye damage.

Note 1 to Table 3.1: The concentration stated or, in the absence of such concentrations, the generic concentrations of this Regulation (Table 3.1) or the generic concentrations of Directive 1999/45/EC (Table 3.2), are the percentages by weight of the metallic element calculated with reference to the total weight of the mixture.

2.2 Classification and labelling in Annex I of Directive 67/548/EEC

According to Regulation (EC) No 1272/2008 Annex VI Table 3.2:

Classification: Repr. Cat 1; R61, Repr. Cat. 3; R62, Xn; R20/22-48/20/22, Xi; R38-41, N; R58, R33

Risk phrases: R61: May cause harm to the unborn child.

R62: Possible risk of impaired fertility.

R20/22: Harmful by inhalation and if swallowed.

R33: Danger of cumulative effects.

R38: Irritating to skin.

R41: Risk of serious damage to eyes.

R48/20/22: Harmful: danger of serious damage to health by prolonged exposure through inhalation and if swallowed.

R58: May cause long-term adverse effects in the environment.

Note E to Table 3.2: Substances with specific effects on human health (see Chapter 4 of Annex VI to Directive 67/548/EEC) that are classified as carcinogenic, mutagenic and/or toxic for reproduction in categories 1 or 2 are ascribed Note E if they are also classified as very toxic (T+), toxic (T) or harmful (Xn). For these substances, the risk phrases R20, R21, R22, R23, R24, R25, R26, R27, R28, R39, R68 (harmful), R48 and R65 and all combinations of these risk phrases shall be preceded by the word "Also".

Note 1 to Table 3.2: The concentration stated or, in the absence of such concentrations, the generic concentrations of this Regulation (Table 3.1) or the generic concentrations of Directive 1999/45/EC (Table 3.2), are the percentages by weight of the metallic element calculated with reference to the total weight of the mixture

(EU, 2008)

3 Environmental fate properties

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (c).

4 Human health hazard assessment

See section 2 on Harmonised Classification and Labelling.

For details on the relevant Human Health endpoints see Annex 1.

5 Environmental hazard assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (c).

6 Conclusions on the SVHC Properties

6.1 PBT, vPvB assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (c).

6.2 CMR assessment

Lead(II) bis(methanesulfonate) (EC Number: 401-750-5, CAS number: 17570-76-2) is covered by index number 082-008-00-4 in Regulation (EC) No 1272/2008 and classified in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as toxic to reproduction, Repro. 1A (H360-Df: 'May damage the unborn child. Suspected of damaging fertility'). The corresponding classification in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is toxic to reproduction category 1 (R61: "May damage the unborn child. Suspected of damaging fertility').

Therefore, this classification of Lead(II) bis(methanesulfonate) in Regulation (EC) No 1272/2008 shows that the substance meets the criteria for classification as toxic to reproduction in accordance with Article 57 (c) of REACH.

6.3 Substances of equivalent level of concern assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (c).

7 References

(Background document 2011) Background document to the opinions on the Annex XV dossier proposing restrictions on Lead and its compounds in jewellery (2011), Committee for Risk Assessment (RAC), Committee for Socio-economic Analysis (SEAC), ECHA/RAC/RES-O-0000001304-85-03/S1, ECHA/SEAC/RES-O-0000001304-85-04/S1, http://echa.europa.eu/doc/reach/restrictions/background_doc_lead_and_its_compounds.pdf

(EU, 2008). Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packing of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Union, L353: 1-1355.

(ChemicalBook 2011) ChemicalBook http://www.chemicalbook.com. Accessed 12th October 2011.

(IARC 2006) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, VOLUME 87, Inorganic and Organic, Lead Compounds WORLD HEALTH ORGANIZATION INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

ANNEX 1 RELEVANT HUMAN HEALTH ENDPOINTS

Main concern for Lead(II) bis(methanesulfonate) is for workers exposure. Consumer exposure to the substance itself is negligible; however, exposure to lead is still possible.

1 Toxicokinetics (absorption, metabolism, distribution and elimination)

No data on Lead(II) bis(methanesulfonate) toxicokinetics have been found. Based on 28 days repeated dose toxicity study with Lead(II) bis(methanesulfonate) it is concluded, that this substance is bioavailable and the effects observed are related to ionic lead. Therefore information on toxicokinetics of inorganic lead is given instead.

1.1 Non-human information

1.1.1 Absorption

Ingestion

Absorption of lead from the gastrointestinal tract in experimental animals is age-dependent and is influenced by the amount of food intake.

Prior to weaning, rodents absorbed from 50% to more than 80% of a single oral dose of radiolabelled lead, while older rodents absorbed < 1–15%.

In non-human primates, the absorption of lead ranged from 38–65% in young animals and from ca. 3–40% in mature animals. Fasted young monkeys (Macaca fascicularis; 10 days of age) absorbed 64.5% of an oral dose of 10 µg/kg bw 210Pb-lead nitrate, while only 3.2% was absorbed by fasted mature adults. Similarly, the gastrointestinal absorption of an oral dose of 72.6 µg 206Pb-lead acetate (352 nmol) in 12 mL apple juice was ~65% in fasted infant rhesus monkeys.

Skin absorption

After application of a solution of lead acetate or nitrate (6.4 mg of lead) to the skin of female BALB/c mice, an analysis of the organs, faeces and urine showed that 0.4% of the applied dose was absorbed through the skin and entered the circulatory system. In less than 24 h significant increases in lead concentrations were observed in the skin, muscle, pancreas, spleen, kidney, liver, caecum, bone, heart and brain but not in the blood.

1.1.2 Distribution

Experimental studies have shown that lead is rapidly distributed into soft and mineralizing tissues after acute and chronic exposures. The initial distribution of lead into soft tissues has a half-life of 3.5 days in rats

After acute exposure by inhalation, lead content expressed as percentage of the dose in rats has been shown to be highest in kidneys, liver and lung, with concentrations increasing in bone as those in soft tissues declined and stabilized. After oral exposure, lead concentrations in rats were highest in kidneys. After intravenous injection of 203Pb-lead chloride to rats, 20% of the

dose was found initially in the kidney; subsequently, long-term deposition of 25–30% occurred in bone. At steady state, the pattern of distribution of lead is bone > kidney > liver > brain.

1.1.3 Excretion

Excretion of lead occurs mainly in the faeces and urine (WHO, 1985). Adult mice were found to excrete about 62% of intravenously injected lead within 50 days; cumulative lead concentrations in faeces were 25–50% of the administered dose. Adult rats excreted 24.4% and 9.5% of intravenously injected lead in faeces and urine, respectively, within 48 h. Five days after a single intravenous dose of 203Pb in rats, total lead excretion was found to amount to 53%, with similar amounts being excreted in urine and faeces, except on day 2 (ratio faeces:urine, 2). Studies on dogs after intravenous administration of 210Pb showed that 56–75% of the total dose of lead was excreted in the faeces.

In rats and monkeys exposed by inhalation to lead oxide (21.5 µg/m³) for 1 year, lead excretion was greater in faeces than in urine, but wide variations between individual animals were noted. Studies on rats exposed for 30–45 min to an 'urban-like' aerosol of 210Pb-dibenzoylmethane (added to gasoline and burned in a tubular furnace heater at 600 °C) showed that, 6 days after inhalation, less than 1% of the total absorbed dose of lead was retained in lung, 40% had been eliminated in faeces and 15% in urine, 40% was fixed in the skeleton and 4–5% in soft tissue.

Adult monkeys have been shown to excrete more absorbed lead in faeces than young animals (13% versus 3.45%), while urinary excretion was similar (5.31% versus 3.84%). In rodents, lead is transferred across the placenta to fetuses and during lactation to the litter.

(IARC 2006)

1.2 Human information

1.2.1 Absorption

Absorption of lead is influenced by the route of exposure, the physicochemical characteristics of the lead and the exposure medium, and the age and physiological status of the exposed individual (e.g. fasting, concentration of nutritional elements such as calcium, and iron status). Inorganic lead can be absorbed by inhalation of fine particles, by ingestion and, to a much lesser extent, transdermally.

Inhalation exposure

Smaller lead particles (< 1 µm) have been shown to have greater deposition and absorption rates in the lungs than larger particles. In adult men, approximately 30–50% of lead in inhaled air is deposited in the respiratory tract, depending on the size of the particles and the ventilation rate of the individual. The proportion of lead deposited is independent of the absolute lead burden in the air. The halflife for retention of lead in the lungs is about 15 h. Once deposited in the lower respiratory tract, particulate lead is almost completely absorbed, and different chemical forms of inorganic lead seem to be absorbed equally.

Dermal exposure

Little information is available regarding absorption of lead in humans after dermal exposure. The percentage of absorption was estimated by measuring the 203Pb activity in blood samples, by counting over the subject's calf region using a whole-body monitor, and also by counting 24-h and 48-h urine samples. Absorption through intact skin was 0.18 ± 0.15% of the dose applied; that through scratched skin was 0.26 ± 0.46%..

Oral exposure

Gastrointestinal absorption of water-soluble lead appears to be higher in children than in adults. Estimates derived from dietary balance studies conducted in infants and children (ages 2 weeks to 8 years) indicate that approximately 40–50% of ingested lead is absorbed. In adults, estimates of absorption of ingested water-soluble lead compounds (e.g., lead chloride, lead nitrate, lead acetate) ranged from 3 to 10% in fed subjects.

1.2.2 Distribution

Lead enters and leaves most soft tissues reasonably freely. The clearance from the blood into both soft tissues and bone dominates lead kinetics during the first few weeks after an exposure, with an apparent half-life of several weeks. Once an approximate equilibrium is reached between soft tissues and blood, the concentration of lead in blood is determined almost entirely by the balance among absorption, elimination, and transfer to and from bone. In the absence of continuing exposure, the whole-body half-life represents the loss of lead from bone. Lead enters and leaves bone by physiologically-distinguishable mechanisms, which include rapid exchange between blood plasma and bone at all bone surfaces, incorporation of lead into forming bone and its loss during bone resorption, and very slow diffusion of lead throughout undisturbed bone. Slow diffusion accounts for the gradual build-up of large quantities of bone-seeking elements such as lead in quiescent, largely cortical bone.

1.2.3 Metabolism

Ionic lead in the body is not known to be metabolized or biotransformed. It does form complexes with a variety of proteins and non-protein ligands.

1.2.4 Excretion

Lead in the faeces includes both lead that has not been absorbed in the gastrointestinal tract and lead excreted in the bile (endogenous faecal excretion). When lead exposure is by ingestion, more than 90% of excreted lead is found in the faeces. Biliary clearance is also a major route of excretion of absorbed lead. Excretion of lead does not appear to depend on exposure pathway, but the ratio of urinary to faecal excretion is variable. Values of from 1:1 to 3:1 have been reported for the ratio of urinary lead clearance to endogenous faecal lead clearance in adult humans after injection, inhalation or ingestion of 203Pb-lead

Excretion of lead through sweat is a minor process

(IARC 2006)

1.3 Summary and discussion on toxicokinetics

Inorganic lead can be absorbed following inhalation, oral, and dermal exposure, but the latter route is much less efficient than the former two. Inorganic lead in submicron size particles can be almost completely absorbed through the respiratory tract, whereas larger particles may be swallowed. The extent and rate of absorption of lead through the gastrointestinal tract depend on characteristics of the individual and on physicochemical characteristics of the medium ingested. Children can absorb 40–50% of an oral dose of water-soluble lead compared to 3–10% for adults. Gastrointestinal absorption of inorganic lead occurs primarily in the duodenum by saturable mechanisms. The distribution of lead in the body is route independent and, in adults, approximately 94% of the total body burden of lead is in the bones compared to approximately 73% in children. Lead in blood is primarily in red blood cells. Conditions such as pregnancy, lactation, menopause, and osteoporosis increase bone resorption and consequently also increase lead in blood. Lead can be transferred from the mother to the fetus and also from

the mother to infants via maternal milk. Metabolism of inorganic lead consists of formation of complexes with a variety of protein and nonprotein ligands. Lead is excreted primarily in urine and feces regardless of the route of exposure. Minor routes of excretion include sweat, saliva, hair, nails, and breast milk. The elimination half-lives for inorganic lead in blood and bone are approximately 30 days and 27 years, respectively.

Effects observed are strongly related to the blood lead concentrations.

(ATSDR 2007)

2 Repeated dose toxicity

2.1 Non-human information

Repeated dose toxicity: oral

Lead(II) bis(methanesulfonate) has been shown to give dose-related haematological effects and effects on relative kidney and liver weight. An increase in red blood cell counts by 11% was found at 250 mg/kg bw/d (highest dose) accompanied by a reduction in haemoglobin concentration of 12%. A dose-related decrease in mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentration at 80 and 250 mg/kg bw/d was found in males and females.

Relative kidney and liver weights were significantly increased in males, kidney weight also in females. The cortical tubulus of the kidney showed eosinophilic deposits in the lumen. In the liver of all males minimal hypertrophy of centrilobular hepatocytes occurred. At the highest dose (250 mg/kg bw/d) relative spleen weight was increased by 83% in males accompanied by extramedullary haematopoiesis. Females showed a lesser increase (42%) in relative spleen weight and no effect on extramedullary haematopoiesis.

According to the UKCA the observed effect on red blood cells seen at 80 mg/kg bw/d and above are consistent with a lead-induced microcytic anaemia. Lead is known to damage kidney tubules and therefore, kidney effects may have been due to the effect of ionic lead. The effects on spleen are considered as a secondary response to the effects on the red blood cells.

The effects seen in the study are considered to be related to the exposure of ionic lead. The NOAEL was determined at < 25 mg/kg bw/d for males and 25 – 80 mg/kg bw/d for females.

(Registration dossier 2011)

2.2 Human information

No data on Lead(II) bis(methanesulfonate) repeated dose toxicity to humans have been found. Data on lead poisoning is given instead, as it was proven in 28-days toxicity study that Lead(II) bis(methanesulfonate) is bioavailable and the toxic effects observed were due to ionic lead.

Lead interferes with numerous physiological processes. In the haeme biosynthetic pathway, it inhibits δ-aminolevulinic acid dehydratase (also known as porphobilinogen synthase), probably through its high affinity for the zinc-binding site in the enzyme.

Although lead displaces zinc more readily in one of the alloenzymes of the protein, the relationship between δ-aminolevulinic acid dehydratase genotype and sensitivity to lead at different blood lead concentrations is at present unclear. Lead also causes an increase in zinc

protoporphyrin, by a mechanism which is not fully established. Lead inhibits pyrimidine-5'-nucleotidase, resulting in accumulation of nucleotides, and subsequent haemolysisand anaemia.

Renal manifestations of acute lead poisoning include glycosuria, aminoaciduria and phosphaturia. Chronic exposure to low concentrations of lead is associated with increased urinary excretion of low-molecular-weight proteins and lysosomal enzymes. Chronic exposure to high concentrations of lead results in interstitial fibrosis, glomerular sclerosis,tubular dysfunction and, ultimately, in chronic renal failure. Lead has also been implicatedin the development of hypertension secondary to nephropathy.

A considerable body of evidence suggests that children are more sensitive than adults to the neurotoxic properties of lead. Although clinical symptoms of toxicity generally become apparent at blood lead concentrations of 70 µg/dL, many important disturbances occur at much lower concentrations. These include electrophysiological anomalies of evoked brain potential in response to auditory stimuli and reduced peripheral nerve conduction.

Exposure to lead is associated with cardiovascular effects and with changes in endocrine and immune functions.

(IARC 2006)

Measurement of ***Blood Lead Concentration*** (PbB) is the most widely used biomarker of lead exposure. Elevated blood lead concentration (e.g., >10 µg/dL) is an indication of excessive exposure in infants and children and is considered to be excessive for women of child-bearing age. The biological exposure index (BEI) for lead in blood of exposed workers is 30 µg/dL. The NIOSH recommended exposure limit (REL) for workers (50 µg/m3 air, 8-hour TWA) is established to ensure that the blood lead concentration does not exceed 60 µg/dL

Table A1: Blood and Bone Lead Concentrations Corresponding to Adverse Health Effects

Age	Effect	Blood lead[a] (µg/dL)
Children	Depressed ALAD	<5
Children	Neurodevelopmental effects	<10
Children	Sexual maturation	<10
Children	Depressed vitamin D	>15
Children	Elevated EP	>15
Children	Depressed NCV	>30
Children	Depressed hemoglobin	>40
Children	Colic	>60
Adults (elderly)	Neurobehavioral effects	>4
Adults	Depressed ALAD	<5
Adults	Depressed GFR	<10
Adults	Elevated blood pressure	<10
Adults	Elevated EP (females)	>20
Adults	Enzymuria/proteinuria	>30
Adults	Peripheral neuropathy	>40
Adults	Neurobehavioral effects	>40
Adults	Altered thyroid hormone	>40
Adults	Reduced fertility	>40
Adults	Depressed hemoglobin	>50

[a]Concentration range associated with effect.
ALAD = δ-aminolevulinic acid dehydratase; EP = erythrocyte protoporphyrin; GFR = glomerular filtration rate; NCV = nerve conduction velocity
(ATSDR 2007)

2.3 Summary and discussion of repeated dose toxicity

Levels of lead exposure resulting in relatively low levels of lead in blood (e.g., <20 µg/dL) are associated with adverse effects in the developing organism is a matter of great concern. Most of the information gathered in modern times regarding lead toxicity comes from studies of workers from a variety of industries and from studies of adults and children in the general population. The most sensitive targets for lead toxicity are the developing nervous system, the hematological and cardiovascular systems, and the kidney.
(ATSDR 2007)

3 Toxicity for reproduction

No data on reproductive toxicity of Lead(II) bis(methanesulfonate) were found. Data on general lead reproductive toxicity profile is given instead, as it was proven in 28-days toxicity study that Lead(II) bis(methanesulfonate) is bioavailable and the toxic effects observed were due to ionic lead.

In humans, there are clear indications that high levels of lead cause adverse effects on both male and female reproductive functions. Less is known concerning reproductive effects following a chronic exposure to low levels. However, if the PbB level is above 200 µg/L, an abortion or still-born baby risk exists and several studies reported that the length of gestation is affected at PbB level of 150 µg/L and above. It was reported in 1999 that the risk of spontaneous abortion nearly doubles for every 5 µg/dL increase in blood lead levels.

Effects on sperm may start to appear at blood lead levels of 400 µg/L. Moreover, a Finnish study has observed a significant increase of the risk of spontaneous abortion among the wives of men whose PbB level was 300 µg/L or higher during spermatogenesis.

Since lead is able to cross the blood-placental barrier, it can induce a developmental neurotoxicity. It has been demonstrated that both maternal plasma and whole blood lead during the first trimester (but not in the second or third trimester) were significant predictors ($p<0.05$) of poorer Mental Developmental Index (MDI) scores. As a possible explanation, it is speculated that lead might be affecting the process of neuronal differentiation, which is primarily a first-trimester event.

Another recent study reported an association between prenatal lead exposure and intellectual function. According to the authors, IQ of 6 to 10-year-old children decreased significantly only with increasing natural-log third trimester PbB, but not with PbB at other times during pregnancy or postnatal PbB measurements. However, because their observations began after the 12th week of pregnancy, the effects of the first trimester PbB could not be examined. As with other studies, the dose-response PbB-IQ function was log-linear, with a steeper slope at PbB <100 µg/L.

Lead poisoning in pregnant women

Since lead can easily cross the placental barrier, the exposure of children starts *in utero* and lasts during the lactation period. PbB level is correlated to the serum calcium: the demineralization of the skeleton observed during pregnancy and lactation induces a migration of the lead accumulated in the mother's bone to the fetus and the infant. This transferred

amount of lead is directly linked to lead accumulated by the mother (resulting from a cumulated exposure) rather than to the maternal exposure during pregnancy.

The maternal and the fetal PbB levels are quite identical. The teratogenic effects observed in animals were not noted for humans, but it seems that the risk of spontaneous abortions, growth retardation and premature delivery appear when PbB level is above 250 µg/L.

Table A2: Summary of the effects of an exposure to lead in children

	PbB (µg/L)					
	No threshold	56	100	400	700	800
Hematological effects			Inhibition of ALAD (i.e. haeme synthesis) : used as biomarker of lead exposure (LDAI 2008a)	↓ hemoglobin production in children (LDAI 2008a)	Anaemia (LDAI 2008a)	
Effects on kidney			Affection of the biological function Animals/humans : nephropathy (tubular atrophy) (LDAI 2008 a)			
Developmental neurotoxicity	Possible reduced IQ (WHO, 2003 ; JECFA, 2010 ; EFSA, 2010)					Encephalopathy Effect on the cognitive functions (development, maturation) (LDAI, 2008a)

Overall conclusion: According to all the effects observed in children and particularly effects on the neurodevelopment which seem to occur with no threshold, it should be considered that a threshold for the effects of lead on children could not be identified. The effects of lead on the neurodevelopment of children would be then considered as the most relevant effect in order to perform the risk assessment.

(Background document 2011)

3.1 Effects on fertility

3.1.1 Non-human information

Male fertility

Many studies in experimental animals have generated results that are consistent with direct toxic effects of lead on seminiferous tubules or Leydig cells, but one study reported simultaneous impairment of spermatogenesis and reduced pituitary content of FSH, which points to a primary action at the extratesticular level. The male reproductive organs of Sprague-Dawley rats and NMRI mice are apparently rather resistant to the toxicity of inorganic lead. However, several studies of other rat strains and other rodent species indicate fairly consistently that exposures to lead that result in blood lead concentrations > 30–40 µg/dL for

at least 30 days are associated with impairment of spermatogenesis and reduced concentrations of circulating androgens. The great variations in hormone concentrations, whether they are circadian, age-related, seasonal, individual or even strain-related make it difficult to draw valid conclusions on hormonal effects.

Age and sexual maturity of the animal may have a bearing on the results in several ways. It has been shown that prepubertal rats are less sensitive to the toxic effects of lead on testosterone and sperm production than animals exposed to lead after puberty.

Marked differences in lead distribution were found in suckling rats compared with adult rats. Age-related changes should also be considered: it was showed that up to 7% of rats maintained for 52 weeks showed spermatogenesis not proceeding beyond the spermatocyte stage. At 104 weeks, 20% of rats had developed atrophy of the seminiferous epithelium.

It was shown that mice are more vulnerable to the toxic effects of lead on reproduction than rats. Exposure of sexually-mature animals to lead caused varying degrees of impaired spermatogenesis, premature acrosome reaction and reduction of fertility or hormonal disorders at widely varying (30–187 µg/dL) blood lead concentrations.

Changes in levels of enzymatic activity and ATP in testicular homogenate were reported in rats given 0.2 and 20 mg/kg bw solutions of lead acetate, over a 4-month period.

Testicular atrophy and cellular degeneration was found in rats with blood lead concentrations > 70 µg/dL, but not in rats with blood lead concentrations of 54.0 µg/dL.

A comprehensive study in rabbits estimated a threshold for effects on total sperm count of 23.7 µg/dL lead in blood.

Groups of cynomolgus monkeys with mean blood lead concentrations of 10 ± 3 µg/dL (n = 4) and 56 ± 49 µg/dL (n = 7) after treatment with lead acetate from birth to the age of 15–20 years had increased abnormal sperm chromatin as expressed by the αT distribution (shift from green to red fluorescence) with a larger SD αT when compared with a referencegroup with blood lead < 1 µg/dL. However, there were no effects of treatment on parameters of semen quality such as sperm count, viability, motility.

The results of studies on the lead content of testicular or seminal fluid are inconclusive. Although a relation between testicular lead content and histopathological changes has been noted, the lack of uniformity regarding age of the animals, duration of exposure, assessment of internal doses, identification of reproductive end-points, and methods to measure effect indicators, makes it impossible to draw any clear conclusions on mechanisms and dose–response relationships.

(IARC 2006)

3.1.2 Human information

Male fertility

Studies have focused mainly on the quality of semen, endocrine function and birth rates in occupationally-exposed subjects, and have shown that concentrations of inorganic lead > 40 µg/dL in blood can impair male reproductive function by reducing sperm count, volume and density, and by affecting sperm motility and morphology.

Dose–response relationships, in particular at a threshold level, are poorly understood, and site, mode or mechanism of action are often unknown. Also, the effects were not always the same or associated in the same way, although the prevalent effects were on sperm count and concentration.

Several studies reported effects on testicular function in groups of men with mean blood lead concentrations above 40–50 µg/dL. These results are consistent with a likely threshold of about 45–55 µg/dL. In contrast, the findings of a study of semen in 97 men employed in a South African lead–acid battery plant, with blood lead concentrations ranging from 28–93 µg/dL, did not support an effect of lead on sperm concentration and total sperm count. However, the authors noted that their results should be interpreted with caution because of the relatively high range of current blood lead concentrations, the high prevalence of abnormalities in semen quality and the lack of a control population.

In a cross-sectional survey of workers exposed to lead and non-occupationally exposed controls, a significant negative association was found between sperm count and mean blood lead concentrations in six subgroups stratified by blood lead concentration. The mean blood lead concentrations in the six subgroups ranged from 5–35 µg/dL. In contrast, in a longitudinal study of battery workers in Denmark, no improvement was found in sperm concentration or in the proportion of morphological abnormalities with a decline in blood lead concentration from about 40 to 20 µg/dL.

A cross-sectional survey was undertaken on some fertility parameters of 503 workers employed by 10 companies in Belgium, Italy and the United Kingdom, as part of the ASCLEPIOS project. Volume of semen and concentration of sperm were determined. Measurement of dose indicators in blood and seminal fluid and its fractions and the sperm chromatin structure assay were performed The mean blood lead concentration was 31.0 µg/dL (range, 4.6–64.5 µg/dL) in 362 workers exposed to lead and 4.4 µg/dL (range, below the detection limit to 19.8 µg/dL) in 141 workers not exposed to lead. The median sperm concentration was reduced by 49% in men with blood lead concentrations > 50 µg/dL. The findings were consistent across the three centres and the sample size was larger than in earlier studies thus strengthening the findings.

The concentration of inorganic lead in blood may not reflect the concentration in the target organs and therefore lead measured in seminal fluid and its fractions might be better correlated with testicular lead and histopathological alterations. A high content of lead within spermatozoa and a low concentration in seminal fluid was found, indicating that lead is either taken up by spermatozoa or is incorporated into the sperm cells during spermatogenesis.

Zinc contributes to sperm chromatin stability and binds to protamine 2. It has recently been shown that lead competes with zinc and binds human protamine 2 (HP2) causing conformational changes in the protein. This decreases the extent of HP2-DNA binding, which probably results in alterations in sperm chromatin condensation. Alteration of sperm chromatin structure by increased in-situ denaturation is strongly correlated with the presence of sperm DNA strand breaks and is associated with reduced fecundity in humans.

A retrospective study on time to pregnancy was conducted among the wives of men (502 couples) who had been monitored for lead to assess whether paternal occupational exposure to inorganic lead was associated with decreased fertility. The fecundability density ratios, adjusted for potential confounders, were 0.92 (95% CI, 0.73–1.16), 0.89 (95% CI, 0.66–1.20), 0.58 (95% CI, 0.33–0.96) and 0.83 (95% CI, 0.50–1.32) for blood lead categories in men of 0.5–0.9, 1.0–1.4, 1.5–1.8 and ≥ 1.9 µmol/L, respectively. This study provided limited support for the hypothesis that paternal exposure to lead is associated with decreased fertility.

In a study performed as part of the ASCLEPIOS project, a total of 1104 subjects in four European countries took part, of whom 638 were occupationally exposed to lead at the relevant time. Blood lead concentrations were mainly < 50 µg/dL. No consistent association between time to pregnancy and lead exposure was found in any of the exposure models. It may be concluded from this multicentric survey that there are no detectable effects on male fertility at the levels of lead exposure currently measured in European worksites.

Lead may be determined in Leydig cells, thus in possible relation with testosterone levels in serum. Lead may also be detected in germ cells, demonstrating that it passes through the blood–testis barrier, which is functionally very similar to the blood–brain barrier, and affects

the germ cells at different degrees of differentiation (spermatogonia, primary spermatocytes, spermatids or spermatozoa). In this regard, it is still an open question whether lead in cells or in fluids is a result of a breakdown of the blood–testis barrier or whether lead normally passes this barrier.

(IARC 2006)

3.2 Developmental toxicity

3.2.1 Non-human information

Many early studies identified effects on spermatogenesis in rats exposed to lead and also indicated that high exposure of dams to lead can reduce numbers and size of offspring. There may also be paternally-transmitted effects resulting in reductions of litter size, weights of offspring and survival rate. Other important topics are the exposure periods, the sites of action, and growth and development.

Lead (as lead acetate) was administered to mouse dams via the drinking-water (at 10 mg/mL) during three periods: (1) when target mice were born (postnatal); (2) after conception of target mice (gestational); or (3) during the mothers' own pre-weaning age (premating). These experiments showed variable effects of lead exposure on brain weight, DNA per brain and protein per brain.

Exposure of female rats to lead produced irregular estrous cycles at blood lead concentrations of 30 µg/dL and morphological changes in ovaries including follicular cysts and reduction in numbers of corpora lutea at blood lead concentrations of 53 µg/dL.

It was also reported delayed vaginal opening in rats whose mothers were given 25, 50 and 250 ppm lead in drinking-water. The vaginal opening delays in the 25-ppm group occurred in the absence of any growth retardation or other developmental delays and were associated with median blood lead concentrations of 18–29 µg/dL.

Testicular homogenates from 2–3-week-old male offspring of lead-exposed female rats (mean blood lead concentration in the pups, 6.3 µg/dL) showed decreased ability to metabolize progesterone.

Sprague-Dawley dams were given lead acetate (0.1%) in drinking-water from day 14 of gestation until parturition to determine whether exposure of the fetus to elevated lead concentrations during a period of rapid differentiation of the hypothalamic–pituitary–gonadal (HPG) axis would disrupt HPG function in adulthood. Female offspring from lead-treated dams were found to have a significant delay in the day of vaginal opening and prolonged and irregular periods of diestrous accompanied by an absence of observable corpora lutea at 83 days of age. Male offspringfrom these dams were found to have decreased sperm counts at 70 and 165 days of age, exhibit enlarged prostates at 165 days and 35% reduction in the volume of the sexually dimorphic nucleus of the preoptic area of the hypothalamus. Pulsatile release of gonadotropins, measured in castrated male and female adult animals, revealed irregular release patterns of both FSH and LH in some lead-treated animals which were not observed in controls. The overall pattern of data suggested to the authors that multiple functional aspects of the HPG axis can be affected by exposure to lead during a period of gestation when structures related to the HPG axis are undergoing rapid proliferation.

The reproductive toxicity and growth effects of lead exposure in developing rats have also been assessed. Lead exposure was initiated *in utero*, prepubertally, or postpubertally. In male animals, weights of testis and all secondary sex organs were significantly decreased in animals exposed prepubertally. Serum testosterone levels were significantly suppressed, most severely in animals exposed *in utero*. In female animals exposed prepubertally, delayed vaginal opening

and disrupted estrous cycling was observed in 50% of the animals. The group treated *in utero* had suppression of circulating estradiol accompanied by significant decreases in both circulating LH concentrations and pituitary LH protein concentration, but no effect on LHβ mRNA was observed. These findings suggested to the authors a dual site of action for lead: (a) at the level of the hypothalamic pituitary unit; and (b) at the level of gonadal steroid biosynthesis. Prepubertal growth in both sexes was suppressed by 25% in the group exposed *in utero*. The effects of lead on growth are possibly due to a delay in the development of sex-specific pituitary growth hormone secretion rather than a persistent developmental defect.

Studies on female monkeys have shown that pre- and/or postnatal exposure to lead can affect pubertal progression and hypothalamic–pituitary–ovarian–uterine functions. Chronic exposure to lead of nulliparous female monkeys, resulting in blood concentrations of approximately 35 µg/dL, induced subclinical suppression of circulating LH, FSH and estradiol without producing overt effects on general health and menstrual function

(IARC 2006)

3.2.2 Human information

Effects of lead during pregnancy

Placental lead concentrations was studied in a series of births in Birmingham, United Kingdom, classified by stillbirth, neonatal death or survival beyond one week. Average results showed higher lead concentrations in those neonates who failed to survive both birth and the neonatal period. There was no association of placental lead with impaired birth weight among survivors.

Placental transfer of lead and its effects on newborns were examined. The mean blood lead concentrations were 41.2 µg/dL and 37 µg/dL for maternal blood and cord blood, respectively, with a significant correlation (r = 0.77, p < 0.001). The increased lead transfer, however, did not appear to affect adversely birth weight or red cell values of the newborn.

Frequencies of congenital malformations was studied in the offspring of female employees at a smelter in northern Sweden and in a reference population near the smelter. In the population of the area, no significant variation in the total frequency of malformations or in any particular group of malformations was found. Among the women who worked at the smelters, the risk for malformations was about two times as high and the risk for multiple malformations about four times as high as in the reference population.

In another study lead was found to be associated, in a dose-related fashion, with an increased risk for minor anomalies, but the risk for major malformations was not increased.

A study on the relationship between prenatal low-level lead exposure and fetal growth in 4354 pregnancies, showed that the risk for adverse fetal growth is not increased at cord blood lead concentrations < 15 µg/dL but that modest increases in risk may be associated with concentrations ≥ 15 µg/dL.

A hypothesis tested that exposure to lead during pregnancy is associated with reduced intrauterine growth and an increase in preterm delivery. Mean blood lead concentrations at mid-pregnancy were 0.92 µmol/L (± 0.38, n = 401) in women in the exposed town and 0.26 µmol/L (± 0.09, n = 506) in women in the comparison town. The authors concluded that exposure to environmental lead does not impair fetal growth or influence length of gestation.

The relation between paternal occupational exposure to lead and low birth weight/prematurity was also examined in a retrospective cohort study. Birth weight and gestational age, obtained from New York State birth certificates (1981–92), were compared for children born to lead-exposed and non-exposed workers. The exposed group (n = 4256) consisted of births to male workers of reproductive age reported to the New York State Heavy Metals Registry. The control group (n = 2259) consisted of the offspring of a random sample of male bus drivers, frequency

matched by age and residence. There were no statistically-significant differences in birth weight or gestational age between the exposed and the control groups. However, workers who had elevated blood lead concentrations for more than 5 years had a higher risk of fathering a child of low birth weight (risk ratio, 3.40; 95% CI, 1.39–8.35) or who was premature (risk ratio, 3.03; 95% CI, 1.35–6.77) than did controls after adjustment for paternal age, low maternal education, race, residence, gravidity, maternal spontaneous abortion history, perinatal complications, adequacy of prenatal care and sex of the infant.

The effect of maternal bone lead on length and head circumference of newborns and infants aged one month was evaluated. Birth length of newborns was found to decrease as tibia lead concentrations increased. Patella lead was positively and significantly related to the risk of a low head circumference score; this score remained unaffected by inclusion of birth weight.

Effects of lead on abortion

The available data shows that the effects of lead on fertility and abortion were not always the same either morphologically or quantitatively, neither did they always vary in the same direction. Those on sperm count and concentration were the most frequent in showing effects of lead. It is not yet clear whether the mechanism is a direct effect of lead on reproductive organs or on the endocrine control of reproduction, or both. The mechanism for inducing pregnancy loss is also not clear. Besides preconceptional chromosomal damage to the sperm or a direct teratogenic effect on the fetus, interference with the maternal–fetal hormonal environment is possible, as endocrine-disrupting activity associated with lead has been observed in rodents, primates, and humans. Vascular effects on the placenta are also plausible, given the literature on lead and hypertension. Developmental toxicity to the fetus is also possible.

Effects on stature and growth

The effects of low to moderate prenatal and postnatal lead exposure on children's growth in stature were studied in 235 subjects assessed every 3 months for lead exposure (blood lead concentration) and stature (recumbent length) up to 33 months of age. Fetal lead exposure was indexed by maternal blood lead concentration during pregnancy. Adverse effects of lead on growth during the first year of life were observed. Mean blood lead concentrations during the second and third years of life were negatively associated with attained height at 33 months of age (p = 0.002), but only among those children who had mean blood lead concentrations above the cohort median (> 10.77 µg/dL) during the 3–15-month period. The results suggest that the effects of lead exposure (*in utero* and during the first year of life) are transient provided that subsequent exposure to lead is not excessive. An average blood lead concentration of 25 µg/dL or higher during the second and third year of life was detrimental to the child's attained stature at 33 months of age. Approximately 15% of this cohort experienced these levels of lead exposure.

The relationship between blood lead concentration and stature was evaluated for a group of 1454 Mexican-American children (age, 5–12 years), from data sets of the 1982–84 Hispanic Health and Nutrition Examination Survey. An inverse relationship was found between blood lead concentration in the range 0.14–1.92 µmol/L [3–40 µg/dL] and stature, which suggests that growth retardation may be associated even with moderate concentrations of blood lead.

The possible role of environmental pollutants in the incidence of intrauterine fetal growth retardation IUGR in India was investigated by measurement of lead and zinc concentrations in blood collected at parturition from mothers and neonates. There was a weak but significant inverse relationship between cord blood lead concentrations and birth weight of newborns (r = –0.23, p < 0.05).

(IARC 2006)

3.3 Summary and discussion of reproductive toxicity

Studies on the reproductive and developmental toxicity of lead did not show consistent effects, morphologically or quantitatively, on markers of male fertility. It is not clear whether the effects are caused by a direct interaction of lead with the reproductive organs, or by modulation of the endocrine control of reproduction, or both.
There is consistent evidence in humans, in the form of case series and epidemiological studies, that the risk for spontaneous abortion (pregnancy loss before the 20th week of gestation, but after the stage of unrecognized, sub-clinical loss) is increased by maternal exposure to high concentrations of lead.
In humans, prenatal lead exposure is associated with an increased risk for minor malformations, low birth weight and reduced postnatal growth rate. The effect on postnatal growth rate is apparent only in those children with continuing postnatal lead exposure.
Differences in reproductive end-points between species make it unlikely that useful conclusions can be extrapolated from animals to humans.

(IARC 2006)

4 Neurotoxicity

A considerable body of evidence suggests that children are more sensitive than adults to the neurotoxic properties of lead. Although clinical symptoms of toxicity generally become apparent at blood lead concentrations of 70 µg/dL, many important disturbances occur at much lower concentrations. These include electrophysiological anomalies of evoked brain potential in response to auditory stimuli and reduced peripheral nerve conduction. Both cross-sectional and prospective studies of children have found impairments in cognition, attention, and language function at concentrations of lead previously thought to be harmless. In studies with larger samples, better measures of lead burden and neurobehavioural function, and more advanced statistical techniques, effects are detectable at blood lead concentrations below 10 µg/dL. The relative effect is greater below 10 µg/dL than above this level. Recently, attention has shifted from the impact of lead on cognition to its effects on behaviour. Exposure to lead has been found to be associated with attentional dysfunction, aggression and delinquency.

(IARC 2006)

5 Other endpoints

Exposure to lead is associated with cardiovascular effects and with changes in endocrine and immune functions.

(IARC 2006)