



EUROPEAN COMMISSION

DIRECTORATE-GENERAL JRC  
JOINT RESEARCH CENTRE

Institute for Health and Consumer Protection  
Toxicology and Chemical Substances (& ECB)

Ispira, 15/05/2008

**Opinion of the TC NES on the Industry Voluntary Risk Assessments  
(Human Health) on Lead and Lead compounds**

**1. Background**

The Lead industry committed to undertake a Voluntary Risk Assessment (VRA) for **lead** and inorganic **lead compounds** produced in the EU or imported into the EU in volumes exceeding 1,000 tonnes per year: **lead oxide, lead tetroxide, dibasic lead phthalate, basic lead sulphate, tribasic lead sulphate, tetrabasic lead sulphate, neutral lead stearate, dibasic lead stearate, dibasic lead phosphite, polybasic lead fumarate, basic lead carbonate, dibasic lead sulphite**. This initiative was endorsed by the EU Competent Authorities in 2001. The whole process was managed by the Lead Development Association International (LDAI). The VRA was compiled in co-operation with expert consultants from the ILZRO (International Lead Zinc Research Organization) for human health toxicity, consumer and indirect exposure. EBRC Consulting was responsible for the sections covering occupational exposure. The reviewing country was the Netherlands.

The Industry voluntary risk assessment on Lead and Lead compounds was intended to follow the EU Technical Guidance Document (TGD) on Risk assessment and the voluntary development of additional detailed guidance for the risk assessment of metals (MERAG and HERAG projects). The procedure was discussed at the 11<sup>th</sup> Joint CA meeting in Helsinki (16-17 June 2005). Industry had expressed that they favour a final endorsement of the results of the assessments by the Technical Committee on New and Existing Substances (TC NES) and CAs, in the same way as done for the regulatory Risk Assessments under Reg. 793/93. At the 13<sup>th</sup> Competent Authorities meeting, it was agreed to request the TC NES to discuss, comment and develop an opinion on the Voluntary Risk assessment, and thereafter to forward the VRA along with the TC NES opinion to the Scientific Committee on Health and Environmental risks (SCHER).

Some Member States (MS) expressed their reservation on the process followed. The risk assessment was a very complex document of more than 800 pages as a consequence of the extensive data available on lead and its compounds. In 1999 the Competent Authorities, and the Netherlands in particular as reviewing country, had made a commitment to review the outcome of the Industry risk assessments. The Commission (DG Environment and DG Enterprise) supported this activity, since there was seen to be a need to have a high quality, scientifically sound risk assessment on certain lead compounds to underpin decision-making on various issues related to lead at Community level. Nevertheless, it was acknowledged that the preparations towards REACH and the fulfillment of legal obligations under the current Existing Substances risk assessment program had made it very difficult to commit resources in order to comment in-depth on all parts of the VRA. Consequently the Member States requested to be stated that lack of comments to any part of the risk assessment did not indicate

acceptance of that part of the VRA. Nevertheless for those sections which had been commented, LDAI had addressed all comments raised.

The TC NES was requested to develop an opinion on the assessment answering the following two questions:

- Is the assessment in line with the methodology in the TGD or has adequate justification been given for major deviations or modifications?
- Are the conclusions of the assessment plausible and can they be supported, based on the assumption that the methodology, including details thereof is adequate and the information presented is correct?

## **2. Commentary of the review process**

The VRA report on lead and lead compounds was first presented to TC NES II 05. The first in depth discussion took place at TC NES I 06 followed by a discussion at TC NES II 06. IND revised the report in light of the discussions at TC NES level and the revised report was brought forward at TC NES I 07. Based on the last discussion and comments received in writing IND revised the VRA report which was distributed to TC NES III 07 in September 2007 where a short presentation on the status of the VRAR under "outcome of written process was given. A revised report was distributed thereafter in October 2007 and a final version in February 2008. The following opinion relates to the February 2008 version of the VRA on lead and lead compounds.

## **3. Summary of the conclusions of the RAR**

### *3.1 Exposure assessment*

Exposure of humans to lead metal and/or inorganic lead compounds can take place in the workplace, from consumer products, indirectly via the environment and in the vicinity of local (point) sources.

The processes that have been identified for estimating **workers** exposure include: production of lead metal (primary and secondary), lead sheet production, battery production, production of lead oxides and stabiliser compounds, production of lead crystal glass and ceramic ware, PVC processing, exposure in demolition and scrap industries and further occupational exposure scenarios (like bronze and brass foundries, stained glass workshops, use of lead ammunition, incineration plants, construction and iron workers, monumental masonry workers, soldering of electronic circuit boards, printing and paint manufacturing and others).

Exposure was measured when possible and given priority to modelled data. Exposure data were obtained from surveys in companies (customized questionnaires) and biomonitoring (measurements of blood lead levels); read across to other substances such as Zinc oxide for which an extensive data base on dermal and inhalation exposure is also available was not necessary in view of the extensive database on inhalation and dermal exposure in a wide range of lead producing and consuming industries.

No separate exposure assessment was carried out for female workers because no data were available that would enable doing so. Thus, the risk evaluation for female workers was carried out based on exposure estimates for the entire workforce (predominantly male workers, but also including small numbers of females).

In contrast to other EU risk assessment reports, use of personal protective equipment and other measures in occupational hygiene have been taken (implicitly) into account in the exposure assessments and in the risk evaluation. In situations where the use of such measures was unclear, scenarios without exposure reducing measures were considered.

The major sources of exposure for **consumers** are from historical applications that may still pose a risk like lead water pipes, lead-soldered food cans and lead-based paints. Exposure from current applications of lead in consumer products evaluated in the report include candles with lead wick cores, hair dye, children's costume jewelry, lead shot and bullets, weights/sinkers, artist materials/paints, lead sheet, ceramics and crystal. No routes of consumer exposure were identified for other products such as batteries, radiation shielding, and consumer electronics.

Exposure of adult **humans exposed via the environment** is predominantly mediated by the lead content of food and beverages. For young children, ingestion of soil and dust is a significant determinant of exposure even in the absence of point source emissions. However, it has to be considered that the earlier use of lead in gasoline still may explain the presence of lead in soil.

### *3.2 Effects assessment*

The most significant endpoints in relation to human health for the lead compounds covered by the risk assessment are repeated dose toxicity, carcinogenicity and reproductive toxicity.

Lead compounds are classified in Annex I to Dir. 67/548/EEC (19<sup>th</sup> Adaptation to progress)

Repr. Cat. 1: R61 (May cause harm to the unborn child)

Repr. Cat 3: R62 (Possible risk of impaired fertility)

Xn; R20/22: Harmful by inhalation and if swallowed

R33: Danger of cumulative effects

The VRA report proposes to change the current classification. This proposal has not been discussed at the Technical Committee for Classification and Labelling.

Repr. Cat. 1; R61: May cause harm to the unborn child

Repr. Cat 1: R60: May impair fertility

Carc. Cat. 3: R40: Limited evidence of a carcinogenic effect – for all inorganic lead compounds but not to lead metal.

Xn; R48/20/22: Harmful: Danger of serious health effects by prolonged exposure through inhalation and if swallowed

In addition classification of dibasic lead phosphate as “R11: Highly flammable” is proposed.

In the effects assessment clear preference has been given to the large number of human studies over those in animals. Animal data was used primarily for purposes of classification and labeling and for mechanistic studies.

The oral and the inhalation route present the most significant **routes of exposure**. The pattern of deposition in the respiratory tract and the systemic uptake of lead compounds depend on the mean mass aerodynamic diameter of inhaled particulate matter. For small particles that can enter the deep lung (alveolar fraction) systemic uptake approaches 100 %. Particles that are deposited in the upper airways (extrathoracic and tracheobronchial region) are subject to mucociliary clearance and transfer to the gastrointestinal system. For the risk assessment purposes an absorption factor of 10% for the inhalation route is used for all lead compounds.

Gastrointestinal uptake of lead occurs primarily in the duodenum and appears to involve both active transport and diffusion through intestinal epithelial cells (transcellular uptake) or between cells (paracellular uptake) and may involve ionized lead and/or inorganic or organic complexes of lead. For gastrointestinal absorption a factor of 8% for adults is used for the risk characterization; it appears to be higher in children (40 – 50%). Dermal absorption through human skin is considered to be minimal, a value of <0.01% is estimated and used for the risk characterization.

Once absorbed, inorganic lead appears to be distributed to both soft tissues (blood, liver, kidney, etc) and mineralizing systems (bone, teeth) in a similar manner, regardless of the route of absorption. In the body, the inorganic lead ion is not known to be metabolized or biotransformed. However it may form complexes with a variety of proteins and non-protein ligands and is primarily absorbed, distributed and then excreted in a complexed form. Lead is eliminated from the body in both urine and faeces. Lead not absorbed in the gastrointestinal tract is excreted in the faeces. Blood lead not retained in the body is excreted in the kidney through the urine or excreted through biliary clearance, some in the form of glutathione conjugates, into the gastrointestinal tract and then through the faeces.

Two pharmacokinetic models have been used for systemic exposure assessment. For the evaluation of lead exposure for children the IEUBK model (Integrated Exposure Uptake Biokinetic Model developed by US EPA) and for modeling of adult lead exposures the O'Flaherty PBPK (Physiologically-based pharmacokinetic modelling) were used to confirm that available blood lead data are consistent with monitoring data for lead in environmental media. The MPPDep (Multiple-Path Particle Deposition) model (v1.11) was used to predict fractional deposition behaviour in the human respiratory tract for workers.

For the various toxicological endpoints for which this is relevant, NOAELs have been derived mainly via meta-analysis and combined analysis of all available relevant studies. These are expressed as blood lead levels, which is in line with the way exposure assessment to lead is historically dealt with in medical surveillance and epidemiological studies.

Based on the data presented in the section on **acute** inhalation, dermal and oral **toxicity**, no acute effects are anticipated up to the limit dose for any of the lead compounds covered under the risk assessment. No irritating effects on skin, eye and respiratory tract and no sensitising effects on skin and respiratory tract have been reported for any of the lead compounds covered under the risk assessment.

The most significant effects to lead appear after **repeated exposure**. These effects were described and discussed in different sections: haematological effects, renal system effects, cardiovascular effects, nervous system effects, immune system effects and endocrine system effects. The lowest NOAEL derived for male adults is 40 µg/dL for nervous system effects. For female adults a NOAEL of 30 µg/dl was derived based on reproductive impacts. For children a NOAEL of 10 µg/dL is derived for nervous system effects in an individual child and of 5 µg/dl for a population based child limit; a societal NOAEL which is different from a traditional human health NOAEL that guards against health impairment that manifests at the level of the individual.

Lead compounds appear to express **genotoxicity** in vitro, but at high concentrations and via mechanisms that appear to lack physiological relevance. Some in vivo mutagenicity studies are positive but those conducted using physiological relevant exposure are generally negative. Based upon a weight of evidence evaluation, genotoxicity was not regarded by the rapporteur to be a relevant toxicological hazard to be carried forward to risk characterisation.

As regards **carcinogenicity**, animal studies have demonstrated positive effects of several soluble lead compounds; human epidemiology studies at occupational exposure levels are

generally negative. Kidney cancers observed in rodents were not seen in human epidemiology studies. Limited epidemiological evidence suggests a possible relationship between occupational exposure to lead and stomach cancer, but there is lack of evidence for stomach cancer induction in animals. The risk assessment concludes with no concern for kidney cancer for workers and a need for further information (conclusion (i)) for stomach cancer risk in the occupational setting. The IARC has classified lead in category 2A (probable human carcinogen) based on observations of cancer in animals and limited epidemiological findings of stomach cancer for inorganic lead compounds.

For **reproductive effect** the lowest NOAELs derived are 45 µg/dL for male workers based upon semen quality and 30 µg/dL for “female workers of childbearing capacity” based on weight of evidence evaluation of poorly defined and uncertain results on spontaneous abortions, preterm delivery, gestational age and birth weight. In addition a NOAEL of 10 µg/dL was derived for pregnant women based on nervous system effects on the developing foetus.

### *3.3 Risk characterisation*

Risk characterization for threshold-based toxicological effects is carried out using the Margin of Safety (MOS) Approach as described in the TGD. A reference MOS of 1 is used for all populations (workers, consumers and humans via environment) since the NOAELs used were identified from multiple scientific studies in human populations, covering susceptible subpopulations which makes the use of inter- and intraspecies factors > 1 not necessary. MOS values  $\geq 1$  are considered of no concern (conclusion (ii)) and scenarios with MOS values < 1 are considered of concern (conclusion (iii)).

Risk characterisation shows no risk for **workers** for acute toxicity, irritation, sensitization, mutagenicity and carcinogenicity (exclusive of stomach cancer) for all workplace scenarios and a conclusion (ii) is proposed. For stomach cancer further information requirement are identified and a conclusion (i) is drawn.

A quantitative risk characterization for workers was performed for the endpoints repeated dose toxicity and toxicity for reproduction. MOS values are calculated by comparing typical and worst case exposure values of different scenarios with a NOAEL of 40 µg/dL for repeated dose toxicity (nervous system effects), with a NOAEL of 30 and 45 µg/dL for fertility effects in females and males respectively and of a NOAEL of 10 µg/dL for developmental effects.

For the endpoint repeated dose toxicity there is concern for typical exposure in some subscenarios of lead sheet production. For worst case exposure there is concern for most occupational scenarios, except ceramic ware production and PVC processing. Concerns for effects on female fertility are identified in subscenario(s) of almost all scenarios whereas concerns for effects on male fertility are identified for typical exposure in lead sheet production, for reasonable worst case exposure in at least one subscenario of all scenarios except ceramic ware production and other occupational scenarios. There is concern for developmental effects in almost all subscenarios for both typical and worst case exposure. Some scenarios, especially other occupational scenarios have a requirement for further information on exposure (i.e. conclusion (i)).

For **consumers** MOS values are calculated using a NOAEL of 10 µg/dL based on nervous system effects in individual children and in pregnant women (foetal effects). Concern is identified and conclusion (iii) applies to consumer exposure to illegal ceramics, candles with lead core wicks, lead shot for subsistence hunting, residential lead-based paint, children jewellery and toys containing lead, folk remedies and illegal cosmetics. Products with

inadequate information and product categories that result in exposures that are both difficult to quantify and with a MOS just slightly in excess of 1 are assigned conclusion (i). There is no concern for all other endpoints and for all other consumer products evaluated.

**Indirect exposure via the environment** is compared to an individual and a societal NOAEL to derive individual and societal MOS values. Conclusion (ii) applies to endpoints of acute toxicity, irritation, sensitisation, repeated dose toxicity, genotoxicity, and carcinogenicity. However, it should be noted that this conclusion only applies in countries that have phased out the use of lead in gasoline. Conclusion (iii) for repeated dose toxicity would be probable for young children (impaired cognitive development) and conclusion (iii) likely for pregnant women (adverse effects upon foetal development) in countries with significant consumption of lead in gasoline.

#### 4. Major Comments on the assessment by the TC NES

Comments were received from Member States (BE, SE, NL, UK, DK, HU, SK, FR, PL) and Norway either in writing or during the discussion at TC NES level. General comments concerned the restriction of the risk assessment to some inorganic lead compounds.

As concerns the **classification and labeling** of lead and lead compounds IND proposed to remove the classification for acute effects as the observed intoxication occurred after repeated exposure. Not all MS agreed with this approach and expressed their reservation.

The proposal to remove R33 (Danger of cumulative effects) and replace it by R48 (Danger of serious health effects by prolonged exposure) was supported. There is still disagreement with which R-Phrases R48 should be combined. The proposal in the VRA is: Xn; R48/20/22 (Harmful: Danger of serious health effects by prolonged exposure through inhalation and if swallowed). Some MS (e.g. DK) felt it should be T; R48/23/25 (Toxic: Danger of serious health effects by prolonged exposure through inhalation and if swallowed).

SE and NO did not agree that lead and lead compounds are of no concern with respect to genotoxicity and carcinogenicity and suggested classification for mutagenicity in Cat. 3 and carcinogenicity in Cat. 2. This opinion is principally based on positive results in several *in vivo* mutagenicity studies using doses not inducing unacceptable levels of cytotoxicity in the target tissue (data from effects on mitotic index, ratio of normochromatic to polychromatic erythrocytes or percentage of polychromatic erythrocytes). The results of these studies are ascribed in considerable strength and weight in the weight of evidence evaluation of all available *in vivo* data submitted by SE. IND did not concur with this recommendation, indicating that the studies in question did not actually assess cytotoxicity in target tissues and that conclusions should be drawn from the full set of studies identified for the weight of evidence evaluation.

IND proposed a classification for carcinogenicity in cat. 3 but did not perform a quantitative risk assessment for the endpoint carcinogenicity and concluded with no concern based on the observation that no tumours of the type seen in experimental animals have been seen in humans exposed to lead. For the limited evidence of stomach cancers in epidemiological studies conclusion (i) was drawn.

As regards the **human health effects** part the main problem for MS was the lack of guidance in the TGD on the use of human epidemiological data for the risk assessment. MSs (like SE) questioned the way studies were selected, summarized and concluded by the rapporteur. Some MSs delivered references which were partly included in the RAR. Quality criteria as developed *a priori* by an independent Scientific Review Panel were applied to studies.

The main comments of the MSs in the effects part addressed the determination of NOAELs. Several MS (DK, SE, NO, PL) did not agree with (most of) the NOAELs determined for repeated dose toxicity which were identified by use of epidemiological data. They were of the opinion that in fact they are LOAELs as these effect levels were set at exposure levels, where subclinical signs e.g. enzyme inhibition or small decreases in the IQ of children were seen and did not accept that certain effects were considered as non-adverse. SE consequently proposed to add a factor of 3 to derive a NOAEL. Other MS (NL, UK) however supported the choice of the NOAELs.

Special attention of the discussion was drawn to the neurobehavioural effects in children. The impact on societal resources of effects on the IQ within a large population of individuals should not be disregarded. DK did not agree with the invention of an "epistemic threshold" and a NOAEL of 5 ug/dL as with regard to neurotoxic effects in children and argued that lead should be regarded as a non-threshold substance i.e. any additional exposure would attribute to some impairment of neurobehavioural performance as no threshold for the neurobehavioural effects in children has been identified. SE proposed to add a factor of 10 for the severity of effects with regard to the neuropsychological effects in children.

In the **risk characterization** part the discussion was focused on the reference MOS value of 1. The approach to not use any assessment factor when using human biomonitoring data was not found acceptable by some MS. The justification given in the VRA that the NOAELs used were identified from multiple scientific studies in human populations, covering susceptible subpopulations was not found sufficient by those MS, which argued that the effects seen at the NOAEL is an average effect of an exposed group, and that within that group only the most sensitive persons had developed adverse effects whereas no effects at all may be present in larger part of the population making the study rather insensitive for registration of effects. Consequently some MS (DK, SE) could not agree with a number of conclusions drawn, especially when they are based on a Reference MOS of 1.

IND has taken many comments on board and revised the report. No changes were made on the choice of the NOAELs and MOS values. Argumentation had been added by IND to substantiate the choice of the values.

Some MS (mainly SE and DK) wished to have stated that in relation to this VRA only limited resources have been available among member states for commenting and discussion in the TCNES-group and the conclusion should be seen in that context. Therefore in their opinion these conclusions do not necessarily represent the opinion of all MSs, since lack of comments from a MS to any part of the risk assessment should not indicate acceptance of that part of the RAR.

## 5. Conclusion

The VRA is in line with the methodology of the Technical Guidance Document, but it should be noted that the risk assessment is mainly based on human epidemiological data for which no guidance is available in the TGD. Justification has been given in the VRA for the use of that data.

The conclusions of the VRA are plausible and all concerns can be supported by the majority of the TC NES based on the assumption that the methodology, including details thereof is adequate and the information presented is correct. However some MSs argued for a more conservative approach and did not support all the conclusions of no concern.