

Committee for Risk Assessment

RAC

**Opinion on scientific evaluation of occupational
exposure limits for**

Lead and its compounds

ECHA/RAC/A77-O-0000006827-62-01/F

11 June 2020

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR LEAD AND ITS COMPOUNDS

Commission request

The Commission, in view of the preparation of the proposals for its amendment of Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work (CAD), and in line with the 2017 Commission Communication '*Safer and Healthier Work for All*' - *Modernisation of the EU Occupational Safety and Health Legislation and Policy*¹, asked the advice of RAC to assess the scientific relevance of occupational exposure limits for some chemical agents.

Therefore, the Commission made a request on 26 March 2019 to ECHA in accordance with the Service Level Agreement (Ares(2019)18725), to evaluate, in accordance with the Directive (98/24/EC), the following chemical agents: **lead and its compounds**.

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission RAC is requested to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for lead and its compounds with a deadline of 26 September 2020.

Chemical name(s): Lead and its compounds

In support of the Commission's request, ECHA prepared a scientific report concerning occupational limit values for lead and its compounds at the workplace.

This scientific report was made publically available² on **17 October 2019** and interested parties were invited to submit comments by **16 December 2019**.

RAC developed its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion, the scientific report was further developed as an Annex to ensure alignment.

The RAC opinion includes a recommendation to the Advisory Committee on Safety and Health at Work (ACSH) in line with the relevant Occupational Safety and Health legislative procedures.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC: **Andrea Hartwig and Dick Heederik**

The opinion was adopted by **consensus** on **11 June 2020** .

¹ <http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes>

² <https://echa.europa.eu/oels-pc-on-oel-recommendation>

RAC Opinion of the assessment of the scientific relevance of OELs for lead and its compounds

RECOMMENDATION

The opinion of RAC on the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for lead and its compounds is set out in the table below and in the following summary of the evaluation, supported by Annex 1.

SUMMARY TABLE

The table presents the outcome of the RAC evaluation to derive limit values for lead and its compounds

Derived Limit Values

OEL as 8-hour TWA:	4 µg lead/m ³ (inhalable fraction) for lead and its inorganic compounds None for organic lead compounds
STEL:	None
BLV:	150 µg lead/L blood for lead and its inorganic compounds None for organic lead compounds
BGV:	45 µg lead/L blood ³

Notations

Notations:	None
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Note

The application of a Biological Limit Value (BLV) is to be preferred over an air limit value since internal lead levels are decisive for the chronic toxicity of lead and its inorganic compounds. Nevertheless, an air limit value complementary to the BLV is also proposed. However, due to the potential additional exposure resulting from ingestion due to hand-mouth behaviour, which could significantly affect internal exposure, the air limit value may not sufficiently protect from exceedance of the BLV.

Since acute toxicity to lead is observed only at considerably higher blood lead levels, i.e. representing very high air levels no STEL is proposed.

³ Neither the proposed BLV of 150 µg/L blood and the proposed air limit value of 4 µg/m³ for lead and its inorganic compounds protects from developmental toxicity. Therefore, RAC recommends to state in the Chemical Agents Directive a recommendation for Groups at Risk, special considerations applying to women of childbearing age, as is mentioned below in this opinion.

It is recommended to add a qualitative statement in the Chemical Agents Directive that the exposure of fertile women to lead should be avoided or minimized in the workplace because the BLV for lead is not protective of the offspring of women of childbearing age.

Due to data limitations, no quantitative scientific evaluation of organic lead compounds is possible and thus no limit values are proposed by RAC.

RAC OPINION

Background

This opinion concerns **lead and its compounds** (See section 1 of Annex 1).

This evaluation takes previous reviews into account, in particular:

- The SCOEL recommendation (2002) and international evaluations such as: AGS, (2017), ATSDR (2007), ATSDR (2019), ANSES (2017a), ACGIH (2017), Safe Work Australia (2014), CLH report for Lead (ECHA, 2012), EFSA (2010, updated 2013), IARC (2006), LDAI, 2008, NTP (2012), US EPA (2013a)
- Annex 1 for the restriction on lead in PVC (ECHA, 2018a)
- REACH registrations

In addition, Annex 1 extensively reports recent primary literature concerning critical aspects such as chronic toxicity, carcinogenicity and reproductive toxicity published during the last 10 years. Furthermore, comments provided by interested parties during the consultation of the report on the ECHA website, have been considered in this opinion.

Key conclusions of the evaluation

- Lead and its inorganic lead compounds are easily taken up into the body via inhalation or ingestion, whilst dermal uptake is negligible. However, "hand to mouth contact" may be relevant. Lead is distributed to blood, soft tissue and bone; the half-life depends on the body compartment and in bones it can be up to several decades. The toxic species is the Pb^{2+} ion. Organic lead compounds such as tri- and tetraethyl lead are metabolised via oxidative dealkylation to triethyl lead, diethyl lead, and inorganic lead.
- Lead and its inorganic compounds are carcinogenic to experimental animals, while epidemiological data concerning carcinogenicity are inconsistent. While it is not mutagenic in most test systems, chromosomal aberrations and sister-chromatid exchanges have been observed in cell cultures, experimental animals and in exposed workers. Carcinogenicity is probably due to indirect mechanisms, such as inhibition of DNA repair.
- Whilst acute toxicity of lead and its inorganic compounds in humans is rare in industry at present exposure levels, chronic toxicity is more relevant.
- Specific target organ toxicity of lead and its inorganic compounds after repeated exposure comprises neurotoxicity, renal toxicity, cardiovascular effects, haematological effects as well as reproductive toxicity; observations are based on exposure in humans, supported by experimental animal studies. Most sensitive indicators appear to be subtle signs of neurotoxicity as well as reproductive toxicity for women of child bearing age.
- A Biological Limit Value (BLV) is to be preferred over an air limit value since internal lead levels are predictive for the chronic toxicity of lead and its inorganic compounds. Nevertheless, an air limit value complementary to the BLV is also proposed. However, due to the potential additional exposure resulting from ingestion due to hand-mouth behaviour, which could significantly affect internal

exposure, the air limit value may not sufficiently protect from exceedance of the BLV.

- Occupational exposure of women of child-bearing age should be avoided or minimized since the BLV is not protective with respect to reproductive toxicity; the blood lead level should not be higher than the reference value of the respective population not occupationally exposed to lead.
- The most sensitive adverse health effects towards organic lead compounds is neurotoxicity; here, biomonitoring via urinary lead levels as well as setting an air lead level appears to be most appropriate.

Mode of action considerations (see section(s) 7.9 of Annex 1 for full discussion)

With respect to lead and its inorganic compounds, lead ions (Pb^{2+}) are the critical species for toxic effects. Key modes of action appear to be the disruption of calcium (Ca^{2+}) homeostasis, oxidative stress and inflammatory reactions. Carcinogenicity is probably due to indirect interactions such as interactions with DNA repair systems and tumor suppressor functions.

Chronic toxicity and cancer risk assessment (see sections 7.3, 7.6 and 7.7. of Annex 1 for full discussion)

Extensive evidence shows that high doses of various water-soluble and water-insoluble lead compounds including lead acetate are carcinogenic in rodents, inducing kidney tumors in rats and mice as well as brain gliomas in rats. In contrast to experimental animals, evidence for carcinogenicity in humans is limited for inorganic lead compounds and inadequate in case of organic lead compounds. Nevertheless, more recently, Steenland et al. (2017) analysed mortality by pooling data from three cohorts from three different countries consisting of lead-exposed workers with blood lead data from health surveillance schemes (USA, Finland, UK). The three studies together included over 88 000 workers and this population experienced over 14 000 deaths. An updated analysis of the UK and Finnish cohorts has been published in Steenland et al. (2019). Both the comparison by groups and the trend analyses indicated some increase of risk by exposure for brain and lung cancer. However, associations were not consistent across the two countries and the increased risks were observed only in the Finnish cohort even though blood lead levels were higher in the UK. The number of cases was low, especially in the comparison group with a blood lead level below 200 $\mu\text{g/L}$. In an analysis in which the cohorts were compared to the general population and restricted to the highest blood lead group ($> 400 \mu\text{g/L}$), an increased incidence (SIR) was observed in the Finnish population, but not when combining the two cohorts. Therefore, even though considering these results, the evidence for carcinogenicity in humans remains limited (for more details, see Annex 1).

Concerning genotoxicity, lead compounds are not directly mutagenic, but show clastogenic effects such as DNA damage, increased micronuclei (MN) frequency as well as chromosomal aberrations (CA) also in exposed workers. Carcinogenicity is proposed to be due to indirect mechanisms, such as DNA repair inhibition, which may explain the clastogenicity. Even though some uncertainties exist, for clastogenicity in humans a LOAEL of 300 $\mu\text{g/L}$ blood can be anticipated.

Specific target organ toxicity of lead and its inorganic compounds after repeated exposure comprises neurotoxicity, renal toxicity, cardiovascular effects, haematological effects as well as reproductive toxicity; observations are based on exposed humans, supported by

experimental animal studies. Most sensitive indicators appear to be subtle deviations in neuropsychological performance as early indicators of neurotoxicity as well as reproductive toxicity for women of childbearing age.

As summarised in the Table below, data derived from occupationally exposed humans provide NOAELs or LOAELS for different endpoints of chronic lead toxicity. Thus, subtle neurotoxic effects start at blood lead levels above about 180 µg/L (Schwartz et al., 2001; Schwartz et al., 2005), while other effects start at somewhat higher concentrations. Considering all evidence, including the available meta-analyses (e.g. by Krieg et al. 2008; Seeber et al., 2002 as well as Meyer-Baron and Seeber, 2000), 180 µg/L can be anticipated as NOAEL for neurotoxicity. Elevated levels of chromosomal effects were observed at levels around and above 300 µg/L, implying that protecting from neurotoxicity would also protect from clastogenicity and thus carcinogenicity, and assuming that the NOAEL for clastogenicity is rather close to the LOAEL. It does not, however, protect from developmental neurotoxicity, and thus from potential reproductive toxicity in women of childbearing age.

Table 1: Blood-lead (PbB) levels and effects

PbB (µg/L)	Effects
>400	Adverse effects on sperm quality (Bonde et al., 2002; Kasperczyk et al., 2008)
Ca. 300	Small (0.5-2 mmHg) increases in systolic or diastolic blood pressure (Glenn et al., 2006; Weaver et al 2008) ¹⁾
≥300	LOAEL for clastogenic effects in workers (e.g., Vaglenov et al., 2001, Olevinska et al., 2010, Garcia-Leston et al. 2012, Chinde et al., 2014, and Januzzi and Alpertunga 2015)
253	Calculated BMDL ₁₀ ('NOAEL') (Lin and Tai-Yi, 2007) for sub-clinical non-adverse changes of renal parameter (NAG)
200 - 400	Increased cardiovascular mortality (Steenland et al., 2017); however, the studies did not adjust for potential confounding effects of non-occupational risk factors
195	Calculated BMDL ₅ ('NOAEL') based on an increased probability of abnormal haemoglobin (Karita et al., 2005)
180	NOAEL for subtle neurobehavioral effects in workers e.g., (Schwartz et al., 2001; Schwartz et al., 2005); LOAEL for slight neurological effects >300 µg/L (e.g., Krieg et al., 2008; Seeber et al., 2002; Meyer-Baron and Seeber, 2000)

Occupational Exposure Limits (see section 8 of Annex 1 for full discussion)

The carcinogenicity of lead compounds has been observed after high exposure in rodents, mainly in kidney, but also in the brain. Based on mechanistic findings, it seems plausible that carcinogenicity is due to indirect genotoxicity, such as oxidative stress and interactions with DNA repair systems; this is supported by the absence of mutagenicity but occurrence of clastogenicity. As indicators of the latter, elevated levels of CA and MN have been observed also in occupationally exposed humans, however at higher blood lead levels as compared to other parameters of chronic toxicity, especially subtle indicators of neurotoxicity and cardiovascular effects. Therefore, setting an OEL to avoid neurotoxicity as most sensitive endpoint of chronic toxicity is expected to also protect from carcinogenicity. It has to be emphasised, however, that special considerations are to be taken for women of childbearing age (see below). The most suitable value to protect from adverse health effects is setting a biological limit value (BLV), measuring blood lead levels. To achieve these levels, a limit value for workplace air is also proposed, based on PBPK modelling.

(Bio) monitoring of exposure (see section 6 of Annex 1 for full discussion)

- Air monitoring methods as well as biomonitoring methods are described within the Annex 1 and stated with LOQ. They are well suited for surveillance of the proposed air and biological limit values.

Technical aspects of the (bio)monitoring methods and related health surveillance are discussed in Chapters 6.3. and 8.4, respectively, of the Annex of this opinion.

Biological limit value (see sections 7.1, 7.3 and 8.2.3 of Annex 1 for full discussion)

Internal lead levels are decisive for adverse systemic effects evoked by occupational exposure towards lead and its inorganic compounds. Upon inhalation, lead deposited in the alveolar region is almost completely absorbed. Gastrointestinal absorption is comparatively poor, but depends, for example, on the actual compounds and particle size. Dermal uptake is considered negligible, but lead can become systemically available via hand-to-mouth contact. Once inside the body, lead is distributed to soft tissues (e.g., blood, liver, kidney) as well as mineralising systems (bones, teeth). In adults, more than 90 % of lead is finally stored in the bones, with estimated half-lives of 6 to 37 years. Thus, lead in bone would be the most suitable marker for cumulative lead exposure, but can not be measured routinely. Usually blood lead levels which have a broad data base, are measured as a highly sensitive indicator for current and/or recent exposure. Despite limitations, correlations with lead levels in bone (tibia) could be established (AGS, 2017), suggesting its (sufficient) suitability also for long-term occupational exposure. Given that lead is stored in the bones for decades, however, measurement of current blood lead levels of adult workers does not reflect only current occupational exposure but also bone release of past occupational or environmental exposures. This needs to be taken into account when interpreting blood lead values.

As described above and summarised in the Table above, few parameters of subtle neurotoxic effects were observed at blood lead levels of about 180 µg/L, while other effects started at somewhat higher concentrations. According to the current weight of evidence, including meta-analyses of respective data (e.g., Krieg et al., 2008), a blood lead level of 150 µg/L is proposed. This value is about two-fold lower than the LOAEL of 300 µg/L for chromosomal aberrations observed in some studies. While usually a factor

of three in LOAEL/NOAEL extrapolations is considered as precautionary approach in risk assessment under REACH, in this case a factor of two is considered sufficiently protective since the NOAEL is expected to be close to the LOAEL. Furthermore, the slope of the regression line is less steep for blood lead levels as compared to lead air levels; thus, the difference between blood lead levels of 150 µg/L (the proposed BLV) and 300 µg/L as LOAEL for clastogenicity, would resemble a factor of 2.7 in the air value, according to the modeling approach by CalEPA (Cal/EPA, October 2013). Therefore, the proposed value is assumed to protect from clastogenicity and thus from carcinogenicity. It does not, however, protect from developmental neurotoxicity, and thus from potential reproductive toxicity in women of childbearing age.

In case of organic lead compounds, blood lead levels may not show very clear increases in case of exposure; here, urinary lead excretion may be a better indicator of exposure (see below).

Biological guidance value

The biological guidance value (BGV) relates to background exposure of the general population of the same age group not occupationally exposed to lead. This exposure has dropped considerably during the last decades, mostly due to the use of unleaded gasoline; therefore, due to the long half-life, an age-dependent decline is observed. Blood lead levels vary throughout Europe, with mean values around 30 to 35 µg/L. BGVs usually relate to the 95th percentile of background exposure; therefore a value of 45 µg/L can be established. Due to a continuous decline in environmental lead exposure levels, this value should be revisited about every five to ten years. Blood lead levels above this value would indicate occupational exposure.

Air limit value

As indicated above, internal exposure levels are decisive for chronic toxicity of inorganic lead compounds and are usually assessed by measuring blood lead levels. Also, in most studies, these internal exposure levels have been related to health endpoints in epidemiological studies among occupationally exposed populations. In practice, exposure occurs through multiple routes and even if the OEL for lead in air is not exceeded, internal levels may still exceed the BLV. On the other hand, in most cases, air levels in particular are regularly monitored to prevent adverse health effects of chemicals at the workplace. In the case of lead and its compounds, however, there is usually a poor correlation between concurrent external and internal blood lead levels which can be explained by several specific factors. The most important aspects are:

- It is generally accepted that internal lead levels are critical for the occurrence of adverse health effects.
- Lead accumulates in the body, which contributes to the poor correlation between blood lead levels and air lead levels.
- Background (non-occupational) exposure has dropped considerably over the last years and as a consequence, results from older studies on the correlation between air levels to blood lead levels are not representative for the current situation anymore.
- Personal hygiene in the work environment greatly affects lead uptake and thus internal exposure may be driven considerably by uptake from surfaces and not

only through inhalation (e.g., hand to mouth contact, smoking, etc.), complicating generalisation regarding the contribution of air exposure. The respective contributions of air exposure and hand-mouth uptake are likely to differ in different industries and/or workplaces.

- Exposure towards different lead compounds may lead to different internal lead levels.

RAC understands that for practical reasons of continuity with current limits an air limit value is required, but it should be ensured that the BLV of 150 µg/L should not be exceeded in the majority of workers; i.e. at least at the 95th percentile level. Recognizing that the internal burden is predictive of adverse health effects and that correlations between air and blood lead levels are poor for the above-listed reasons, different authorities have provided indications of potential lead air levels offering various degrees of protection and containing considerable uncertainties. For example, Safe Work Australia established so-called "air slope factors" (ASF) based on published measurement data for six industrial settings between 50 and 150 µg/m³, observing steeper slopes at lower exposure levels. While 50% of the workers would be protected at an air level of about 30 µg/m³, a value of 15 µg/m³ would protect approximately 97.5 % of the workers, based on a blood lead level of 150 µg/L. However, Safe Work Australia itself acknowledged that in addition to the generally poor correlation described above and presented in more detail in Annex 1, air slope factors for air lead levels lower than 50 µg/m³ could not be estimated with confidence. Such concentrations were frequently beyond the range of the experimental data and the study authors warned against extrapolating to lower air concentrations, since the relationship becomes much more curvilinear and the air slope factor may underestimate the blood lead levels arising from low exposure (Safe Work Australia, 2014).

Alternatively, the California Environmental Protection Agency (Cal/EPA) has undertaken an extensive modelling exercise using an updated Physiologically-based Pharmacokinetic (PBPK) model to estimate various concentrations of lead in workplace air inhaled by workers without respiratory protection that could result in specific lead concentrations in workers' blood. They simultaneously adjusted blood, bone, and urine clearance parameters in the core model to fit blood, bone, and urine data collected from workers chronically exposed to lead, as well as the general population environmentally exposed to lead. Based on these calculations, a workplace air lead concentration of 3.9 µg/m³ was derived that is associated with a blood lead level at or below of 150 µg/L, at a 95th percentile level (Cal/EPA, October 2013). Critical comments were received⁴ on the accuracy of the modeling approach. Specific comments relate to the input data and particle deposition estimates as well as the fraction absorbed by the gastrointestinal tract. Nevertheless, the results of the model are considered as accurate by RAC because the model has been validated by comparison of model outcomes with data from two published studies in which individual air and blood lead concentrations were reported (see detailed description in Annex 1, 8.1.6.).

Therefore, taking into account that the majority of workers (at least 95%) needs to be protected from exceeding the proposed internal Pb level of 150 µg/m³ and considering the fact that extrapolating Pb air levels to Pb blood levels in the low dose range are beyond

⁴Gradient Corporation (2018). Review of CalEPA/OEHHA Worker Air/Blood Lead Modeling Approach. Gradient Report prepared for Wiley Rein LLP - <https://www.ila-lead.org/UserFiles/File/CalEPA%20Doc.pdf>

the experimental study data included by Safe Work Australia and might underestimate the increase in internal Pb levels, the PBPK modelling approach by Cal/EPA appears to be more appropriate. Thus, in addition to the BLV stated above, an OEL of lead and its inorganic compounds (including lead acetate) of 4 µg lead/m³ in workplace air is proposed.

Short term limit value (STEL)

Short-term increases in inorganic lead air levels would not be expected to drastically increase blood lead due to the long half-life. Therefore no short term limit value for lead and its inorganic compounds is proposed, since acute toxicity is observed only at considerably higher blood lead levels, starting above 400 µg/L, and representing very high air levels.

Groups at extra risk: Women of childbearing age

Neither the proposed BLV of 150 µg/L blood and the proposed air limit value of 4 µg/m³ for lead and its inorganic compounds protect from developmental toxicity. Therefore, RAC recommends to state in the Chemical Agents Directive:

Exposure of fertile women to lead should be avoided or minimised in the workplace because the BLV for lead does not protect offspring of women of childbearing age. The blood lead level in women of childbearing age should not exceed the (95 percentile) reference values of the general population not occupationally exposed to lead in the respective EU country. Higher blood lead levels are an indicator of potentially exceeded occupational exposure and should be followed up by an occupational hygiene expert. When national reference levels are not available, blood lead levels in women of childbearing age should not exceed the Biological Guidance Value (BGV) of 45 µg/L, the maximal European reference value.

All reference values should be re-assessed on a regular basis, as environmental lead exposure is expected to drop further in the near future.

Assessment factors:

All proposed limit values are derived from mostly human data, so there is no need for interspecies extrapolation. In the case of inorganic lead compounds, there is an extremely large data base, including meta-analyses of subtle neurotoxic effects, adequate to address the variability among workers, and also including long-term exposure. Finally, as described above, effects may have been the outcome of past, higher exposure; therefore, the current approach where lower lead levels than in the past are encountered is rather conservative.

Notations

No notation for 'Skin' or 'Sensitisation' is required for lead ions and thus for lead and its inorganic compounds, as there is no evidence to support such a notation.

Organic Lead compounds

As for lead and its inorganic compounds, neurotoxicity is the critical endpoint for organic lead compounds. Even though organic lead compounds have a higher neurotoxic potency as compared to inorganic lead compounds, they are metabolised more rapidly, showing a much faster excretion. As detailed in Annex 1, based on different meta-analyses, most countries proposed 50 to 150 µg/m³ (except for Latvia, 5 µg/m³).

However, due to limited old data and a lack of new data, in the view of RAC, no quantitative scientific evaluation is possible and thus no limit values for organic lead compounds are proposed. Nevertheless, as an indication for potential air limit values, BLV and notations, reference is made to the evaluation of the German MAK commission, who have derived the following limit values for tetraethyl lead:

- an air limit value of 50 $\mu\text{g}/\text{m}^3$ (based on lead) and a STEL of 100 $\mu\text{g}/\text{m}^3$
- a BLV of 50 μg total lead or 25 μg diethyl lead/L urine, correlating to 50 $\mu\text{g}/\text{m}^3$ lead in air, and
- a skin notation

According to the German MAK commission (2001) it should be noted, however, that also in case of organic lead compounds adverse health effects during pregnancy cannot be excluded. Since organic lead compounds have a stronger neurotoxic effects when compared to inorganic lead compounds and are also metabolised to inorganic lead, developmental neurotoxic effects may occur, even if the above mentioned air limit values are complied with.

ANNEXES:

Annex 1 gives the scientific background for the opinion.

Annex 2 Comments received on the scientific report, responses to comments provided by ECHA and RAC (excluding confidential information).