ECHA Scientific report

for evaluation of limit values for lead and its compounds at the workplace

Prepared by the European Chemicals Agency

17 October2019

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Preamble

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 (SLA) (Ares(2019)18725), to evaluate, in accordance with the Directive (98/24/EC), the following chemical agent: lead and its compounds.

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

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In the preparatory phase of making this report, a call for evidence was started on **17/04/2019** to invite interested parties to submit comments and evidence on the subject by **30/06/2019**. The scientific report was made publicly available at ECHA's website on **17/10/2019** and interested parties were invited to submit comments by **16/12/2019**.

The Committee for Risk Assessment (RAC) will develop its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion on occupational limit values for lead and its compounds, the scientific report will be further developed as the Background Document (Annex I).

Following adoption of an opinion on **[date]**, recommending an Occupational Exposure Limit for lead and its compounds by RAC, the Background Document will be amended to align it appropriately with the view of RAC. It supports the opinion of the RAC and gives the detailed grounds for the opinion[2].

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

[2] https://echa.europa.eu/documents/10162/13579/interim_wponevaluation_oel_agreed_rac_42_en.pdf/021bc290-e26c-532f-eb3f-52527700e375

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LITERATURE

This report is based on the SCOEL recommendation (2002) and international evaluations such as: German Ausschuss für Gefahrstoffe (AGS, 2017), ATSDR (2007), (ATSDR, 2019), (ANSES, 2017a), (ACGIH, 2017),(Safe Work Australia, 2014), CLH report for Lead (ECHA, 2012), Background document for the restriction on lead in PVC (ECHA, 2018a), EFSA (2010, updated 2013), IARC (2006), the Lead Risk Assessment Working Group (LDAI, 2008), NTP (2012), US EPA (2013a). This has been complemented by a review of the REACH registrations and a literature search of published papers from the last ten years.

ECHA RECOMMENDATION

A Biological Limit Value (BLV).of 150 µg Pb/L in blood is proposed for inorganic and for organic lead compounds (see section 8.2.3).

In order to help to achieve a blood-lead level below 150 µg /L, ECHA proposes to establish an Occupational Exposure Limit (OEL) (8 hour TWA) of 30 µg/m3 for inorganic compounds and organic compounds (alkyl lead compounds) (see section 8.2.1.).

ECHA considers that it does not seem possible to directly identify a maternal blood-lead level that would exclude the possibility of any effect on cognitive function development of the newborn. Therefore ECHA recommends to RAC to consider the following three options in their opinion development to address this effect:

- Option 1: A BLV of < 50 µg/L is proposed for women of childbearing age;
- Option 2: The blood-lead level for women of childbearing age should not be higher than the reference values of the respective general populations not occupationally exposed to lead;
- Option 3: It is recommended to make qualitative statement in the Chemical Agents Directive that the exposure of fertile women to lead should be minimised or avoided in the workplace because the BLV for lead is not protective of the offspring of women of childbearing age.

ECHA concludes that no 15 min Short term Exposure Limit (STEL) can be derived (see section 8.2.2.).

ECHA concludes that no Biological Guidance Value (BGV) can be established (see section 8.2.4)

ECHA does not propose any notations (see section 8.3).

1. Chemical Agent Identification and Physico-Chemical Properties

1.1 Lead

Lead is reported in the ATSDR review (2019) as an environmental contaminant that occurs naturally and, to a greater extent, from anthropogenic activities such as mining and smelting and battery manufacturing. Lead is a metal that occurs in organic and inorganic forms; the latter predominates in the environment. Lead is rarely found in its metallic form in nature and commonly occurs as a mineral with sulphur or oxygen. The most important lead mineral is galena (PbS). Other common lead-containing minerals include anglesite (PbSO4), cerussite (PbCO3), and minium (Pb3O4) (Carr et al. 2004; Davidson et al. 2014; Haynes 2014).

Lead can exist in the 0 oxidation state as metallic lead and in compounds as the +2 or +4 oxidation states. In the environment, lead is primarily found in the +2 state in inorganic compounds. The chemistry of **inorganic lead compounds** is generally similar to that of the Group 2(II) or alkaline earth metals. There are three common oxides of lead: lead(II) oxide (PbO); lead(II,IV) oxide or lead tetroxide (Pb3O4); and lead(IV) oxide or lead dioxide (PbO2). The +4 state is only formed under strongly oxidizing conditions. Inorganic Pb(+4) compounds are relatively unstable and would not be expected to be found under ordinary environmental conditions. Lead is amphoteric, meaning that it can react with acids and bases. In acid, lead forms Pb(+2) (plumbous) and Pb(+4) (plumbic) salts and in basic solution, it forms plumbites (PbO_2^{2-}) and plumbates ($Pb(OH)_6^{2-}$) (Carr et al. 2004). In **organolead compounds**, lead is typically tetravalent (Carr et al. 2004; Haynes 2014).

Lead's identification and physico-chemical properties are described in Table 1 and Table 2:

Table 1: Substance identification

Substance name	CAS No	EINECS/EC -list No	Description	Molecular formula
Lead	7439-92-1	231-100-4		Pb

Table 2: Physico-chemical properties [3]

Substance name	EC/list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility
Lead	231-100-4	Solid	11.45	326	3.2 mg/L (pH 6, 24 h) 185 mg/L (pH 11)

1.2 Lead compounds

The lead compounds considered in this report are generally those for which data are available and for which use at higher tonnages is known and which data could be extracted from the REACH registration dossiers. Inorganic lead compounds are used in greater quantities (> 99%) then organic compounds. As organic compounds fall within the scope of this report, the most commonly used organic compounds are also considered.

[3] Values retrieved from registration data published on echa.europa.eu unless indicated otherwise.

1.2.1 Inorganic compounds

In total there are 65 inorganic lead compounds registered under REACH and/or have a harmonised classification. Of these substances 33 are only used during the manufacture and recycling of lead and its compounds. These substances are all of complex and variable composition, and contain other constituents than only lead compounds. They are therefore not very useful in terms of evaluating the specific properties of lead and its compounds, and are not considered in the following evaluation (See Appendix 1, Appendix 2 and Appendix 3). Lead and four out of 32 remaining lead compounds, which are registered according to the REACH legislation, cover the use of more than 97 % in total volume of the inorganic lead compounds at the time of writing. These four lead compounds are lead monoxide, tetralead trioxide sulphate, pentalead tetraoxide sulphate and orange lead. Only these four inorganic lead compounds are considered in the report.

The substance identification and physico-chemical properties of the four inorganic lead compounds are described in Table 3 and Table 4.

Table 3: Substance identification of the four inorganic lead compounds

Substance name	CAS No	EINECS/EC -list No	Description	Molecular formula
Lead monoxide	1317-36-8	215-267-0		PbO
Tetralead trioxide sulphate	12202-17-4	235-380-9		$Pb_4O_3(SO_4)$
Pentalead tetraoxide sulphate	12065-90-6	235-067-7		$Pb_5O_4(SO_4)$
Orange lead	1314-41-6	215-235-6		Pb_3O_4

Table 4: physico-chemical properties of the four inorganic lead compounds[3]

Substance name	EC/list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility
Lead monoxide	215-267-0	Solid	9.96	888[4]	70 mg/L (pH 11) 0.1 mg/L (pH 8.4)
Tetralead trioxide sulphate	235-380-9	Solid	6.84	>500	102 mg/L (pH 8
Pentalead tetraoxide sulphate	235-067-7	Solid	7.15	>600	32.7 mg/L (pH 8.7)
Orange lead	215-235-6	Solid	8.93	>550	67.3 mg/L (pH 10.8)

1.2.2 Organic compounds

In total there are nine organic lead compounds registered under REACH and/or having a harmonised classification. Of these three substances account for more than 96 % of the

[4] Value retrieved from SCiFinder (scifinder.cas.org)

whole tonnage of organic lead compounds used (see Table 5). Tetra ethyl lead was the most commonly used alkyl-lead compounds and is therefore considered in this report. The other two are ionic lead compounds, whose hazard properties are determined by the presence of Pb^{2+} ions in the same way as for inorganic lead compounds.

The substance identification and physico-chemical properties of the organic lead compounds are described in Table 5 and Table 6.

Table 5: Substance identification of organic lead compounds

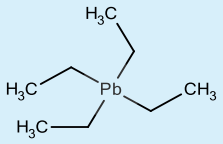
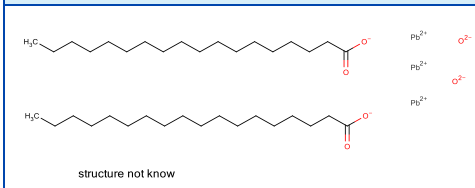
Structure	EC/list number	CAS number	Name
	292-966-7	91031-62-8	Fatty acids, C16-18, lead salts
	201-075-4	78-00-2	Tetraethyllead
	235-702-8	12578-12-0	Dioxobis(stearato)trilead

Table 6: Physico-chemical properties of organic lead compounds[3]

Substance name	EC/list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility
Fatty acids, C16-18, lead salts	292-966-7	solid	1.46	101-105	10.4 mg/L (pH 7.8)
Tetraethyllead	201-075-4	liquid	1.7	-134	< 2.35 mg/L
Dioxobis(stearato)trilead	235-702-8	solid	1.95	290 (decomp)	1.76 mg/L (pH 9.3)

2. EU Harmonised Classification and Labelling – CLP: Regulation (EC) 1272/2008

There are 20 entires of harmonised classification of lead and its compounds in Annex VI of the CLP Regulation 1272/2008.

There are harmonised classifications for lead powder (particle diameter < 1mm) and lead massive (particle diameter ≥ 1 mm) according to Annex VI of the CLP Regulation (9th ATP)[5].

Table 7: EU CLP regulation classification of lead powder and lead massive

Index No	International chemical ID	EC No	CAS No	Annex VI of CLP hazard class and category	Hazard statement code
082-013-00-1	Lead powder [particle diameter < 1 mm]	231-100-4	7439-92-1	Repr. 1A Lact	H360FD: C ≥ 0,03% H362
082-014-00-7	Lead massive [particle diameter ≥ 1 mm]	231-100-4	7439-92-1	Repr. 1A Lact.	H360FD H362

2.1 Inorganic compounds

There are harmonised classifications for lead compounds according to Annex VI of the CLP Regulation, under the entry "lead compounds with the exception of those specified elsewhere in this Annex (Index No 082-001-00-6)". The four lead compounds considered in this report (lead monoxide, tetralead trioxide sulphate, pentalead tetraoxide sulphate and orange lead) are not specified in the Annex and therefore fall under entry No 082-001-00-6 (Table 8).

Table 8: EU classification of lead compounds with the exception of those specified elsewhere in Annex VI

Index No	International chemical ID	EC/ CAS No	Annex VI of CLP hazard class and category	Hazard statement code	Specific concentration limits, M-factors
082-001-00-6	lead compounds with the exception of those specified elsewhere in Annex VI	-	Repr. 1A Acute Tox. 4* Acute Tox. 4* STOT RE 2* Aquatic Acute 1 Aquatic Chronic 1	H360-Df H332 H302 H373** H400 H410	Repr. 1A; H360D: C ≥ 0,1 % * STOT RE 2; H373: C ≥ 0,05 %

2.2 Organic compounds

The organic lead compounds considered in this report are classified by the entry for "lead compounds with the exception of those specified elsewhere in Annex VI" (see Table 8), except for tetraalkyllead, which falls in the category of "lead alkys" showing much higher acute toxicity (see Table 9).

[5] A further RAC opinion was adopted in November 2018, concluding that both the lead powder and lead massive should be classified as Aquatic Acute 1 and Aquatic Chronic 1, with M factors of 1 and 10, respectively. This latest opinion (which, along with other substances included in the 15th ATP) is currently in the COM decision making process.

Table 9: EU CLP Regulation classification of organic lead compounds

Index No	International chemical ID	EC/ CAS No	Annex VI of CLP hazard class and category	Hazard statement code	Specific concentration limits, M-factors
082-002-00-1	lead alkyls	-	Repr. 1A Acute Tox. 2* Acute Tox. 1 Acute Tox 2* STOT RE 2* Aquatic Acute 1 Aquatic Chronic 1	H360-Df H330 H310 H300 H373** H400 H410	Repr. 1A; H360D: C ≥ 0,1 % * STOT RE 2; H373: C ≥ 0,05 %

3. Chemical Agents and Scope of Legislation - Regulated uses of Lead and its compounds in the EU

Lead has been a substance of concern for many years. Due to the well-documented adverse effects of the metallic lead and lead compounds, these have been extensively regulated at national, Union and global level. This is reflected in the large number of sector specific Union legislative acts which restrict the use of lead and or its compounds in mixtures, articles and consumer products with regard to their risks to human health (incl. occupational) and the environment. An inventory of existing Union legal requirements related to lead (but non-exhaustive), is listed in the following sections 3.1-3.13 (ECHA, 2018b).

3.1 Directive 98/24/EC and Directive 2004/37/EC

Lead and its compounds are hazardous chemical agents in accordance with Article 2 (b) of Directive 98/24/EC and falls within the scope of this legislation.

Annex I of the Directive 98/24/EC specifies a binding occupational limit value for inorganic lead and its compounds of 0.15 mg/m^3.

Annex II of this Directive specifies a binding biological limit value and a health surveillance for lead and its ionic compounds:

- Biological monitoring must include measuring of the blood-lead-level (PbB) using absorption spectrometry or a method giving equivalent results. The binding biological limit value is 70 µg Pb/100 ml blood.
- Medical surveillance is carried out if:
  - exposure to a concentration of lead in air is greater than 0.075 mg/m^3, calculated as a time-weighted average over 40 hours per week, or
  - a blood-lead level greater than 40 µg Pb/100 ml blood is measured in individual workers.
- Practical guidelines for biological monitoring and medical surveillance must be developed in accordance with Article 12(2) (of the Directive 98/24/EC). These must include recommendations of biological indicators (e.g. ALAU, ZPP, ALAD) and biological monitoring strategies.

Some lead compounds, are classified as carcinogens in humans (see Appendix 2) in accordance with Article 2(a) and (b) of Directive 2004/37/EC and fall within the scope of this legislation.

3.2 REACH Registrations

3.2.1 Inorganic compound

Table 10: REACH Registrations and tonnage for inorganic lead compounds

EC/list number	Name	Intermediate registration [t/a] (# of registrations)	full registration [t/a] (# of registrations]
231-100-4	Lead	10 000-100 000 (<5 reg)	>100 000 (131 reg)
215-267-0	lead monoxide	10 000-100 000 (5 reg)	>100 000 (60 reg)
235-380-9	tetralead trioxide sulphate	10 000-100 000 (<5 reg)	>100 000 (44 reg)
235-067-7	pentalead tetraoxide sulphate	10 000-100 000 (<5 reg)	10 000-100 000 (33 reg)
215-235-6	orange lead		10 000-100 000 (11 reg)

3.2.2 Organic compounds

Table 11: REACH Registrations and tonnage for organic lead compounds

EC/list number	Name	Intermediate registration [t/a] (# of registrations)	full registration [t/a] (# of registrations]
292-966-7	Fatty acids, C16-18, lead salts		1000-10 000 (9 reg)
201-075-4	tetraethyllead		1000-10 000 (<5 reg)
235-702-8	dioxobis(stearato)trilead		1000-10 000 (6 reg)

3.3 Authorised uses under Annex XIV of REACH

Lead and 31 lead compounds are listed on the 'candidate list' of substances of very high concern for authorisation and are published in accordance with Article 59(10) of the REACH Regulation. Three lead compounds, lead chromate, lead sulfochromate yellow and lead chromate molybdate sulfate red are included in the 'Authorisation List' (Annex XIV of REACH and require authorisation before they are used.

Commission Implementing Decision C(2016) 5644 (final)[6] grants an authorisation for some uses of lead sulfochromate yellow and of lead chromate molybdate sulfate red under REACH.

[6] https://publications.europa.eu/en/publication-detail/-/publication/75e50379-7a3f-11e6-b076-01aa75ed71a1/language-en

Commission Implementing Decision C(2017) 5012 (final)[7] grants an authorisation for a use of lead chromate under REACH.

3.4 Restricted uses under Annex XVII of REACH

Annex XVII of REACH entry 16[8] restricts the placing on the market and use of lead carbonates, as substances or mixtures, where the substance of mixture is intended for use as paint.

Annex XVII of REACH entry 63[9] restricts the placing on the market and use in any individual part of jewellery articles (including jewellery, imitation jewellery articles and hair accessories) if the concentration of lead (expressed as metal) in such a part is equal to or greater than 0,05% by weight.

Annex XVII of REACH entry 28-30 restricts the use of substances classified as carcinogenic, mutagenic and reproduction (CMR) (see Appendix 2 for Tables on harmonised classification and labelling).

ECHA's Committees RAC and SEAC adopted its opinions on an Annex XV dossier proposing restrictions on lead stabilisers in PVC (see section 5.2.2.2) (ECHA, 2018b) and on an Annex XV dossier proposing restrictions on the use of lead in gunshot in wetlands (see section 5.2.2.6) (ECHA, 2018c).

ECHA will propose a restriction on Lead Chromates in January 2020 and has been requested by the European Commission to investigate the need for a restriction to address the risk to wildlife and humans (via the consumption of game meat) from Lead in gunshot, lead in ammunition (bullets) and lead in fishing sinkers.

3.5 Regulation (EC) 98/70 on petrol

Regulation (EC) 98/70 prohibits leaded petrol in EU Member States. In Annex I of regulation (EC) 98/70 it is stated that the lead content in petrol is limited to 0.005 g/l.

3.6 Plant Protection Products Regulation (EC) 1107/2009

There are no plant protection products authorised under Regulation (EC) No 1107/2009 which are based on lead. Lead and its compounds are not listed as an active substance in Annex I to Directive 91/414/EC.

3.7 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

Lead and its compounds are not used in human or veterinary medicines.

3.8 Biocidal Products Regulation (EU) 528/2012

There have been no biocidal products authorised under Regulation (EU) No 528/2012 which are based on lead and its compounds, nor has there been an active substance evaluation on Lead and its compounds. Lead and its compounds are not listed as active substances in Annex I of Regulation (EU) No 528/2012.

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[7] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52017XC0811(01)&from=EN

[8] https://echa.europa.eu/documents/10162/22dd9386-7fac-4e8d-953a-ef3c71025ad4

[9] https://echa.europa.eu/documents/10162/3f17befa-d554-4825-b9d5-abe853c2fda2

3.9 Cosmetics products Regulation (EC) 1123/2009

Lead and its compounds are listed as substances on the list of substances prohibited in cosmetic products (Annex II of the Cosmetics Regulation 1123/2009).

3.10 Drinking water Directive 98/83/EC

Harmonised levels for lead in drinking water are set by Council Directive 98/83/EC on the quality intended for human consumption. The Directive stipulates that Member States shall set limit values of 10 µg/L for lead in water intended for human consumption.

3.11 Ceramics Directive 84/500/EEC

The Directive sets migration limits for lead and cadmium, which might be released from decoration or glazing. In addition, it prescribes and analytical method for the determination of the migration of these two elements.

3.12 Safety of toys Directive 2009/49/EC

The Directive sets migration limits, from toys or components of toys that shall not be exceeded. For lead the migration limits range from 3.4 mg/kg in liquid or sticky toy material to 160 mg/kg in scraped-off toy material.

3.13 Food contaminants Regulation Lead (EC) 1881/2006/EC

Commission Regulation 1881/2006/EC sets maximum levels for certain contaminants in foodstuffs. The current maximum levels (ML) for lead are laid down in Section 3.1 of the Annex)[10].

3.14 Directive 2008/50/EC on ambient air quality and cleaner air for Europe

Directive 2008/50/EC of the European Parliament and of the Council sets a regulatory limit value for lead in air as 0.5 µg/m^3 per calendar year.

3.15 Directive 86/278/EEC on the protection of the environment, and in particular of the soil, when sewage sludge is used in agriculture

Directive 86/278/EEC set rules on how farmers can use sewage sludge as a fertiliser, to prevent it harming the environment and the human health, by compromising the quality of soil or surface and ground water. To this end, it sets limits on the concentrations allowed in soil of 7 heavy metals, including lead that may be toxic to plants and humans. It bans the use of sewage sludge that leave concentrations over these limits.

3.16 Directive 2003/40/EC on natural mineral waters

Directive 2003/40/EC establishes the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters, also sets a maximum limit for lead in natural mineral water of 10 ug/L.

[10] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1881-20150521&from=EN

4. Existing Occupational Exposure Limits

4.1 Inorganic compounds

Annexes I and II of Directive 98/24/EC specify a limit value for a binding occupational exposure to inorganic lead and its compounds (0.15 mg/m^3) and a binding biological limit value of 70 µg Pb/100 ml blood for lead and its ionic compounds.

In various EU Member States lower OEL values and additional short-term exposure limits (STEL) are established. These are presented in Table 12 but the list should not be considered as exhaustive.

The table below covers limit values for lead inorganic compounds. Please note that some Member States also have published OELs for individual lead compounds such as lead chromate. Values for these lead compounds can be found at: GESTIS.

Table 12: Existing Occupational Exposure Limits (OELs) for lead and inorganic compounds

Country/ Organisation	Lead and inorganic compounds TWA -8 hrs mg/m^3	Lead and inorganic Compounds Short term mg/m^3	Comments
Austria	0.1 (I)	0.4 (I)	Same value for lead compounds except alkyl lead compounds
Belgium	0.15		
Denmark	0.05 (I)	0.10 (I)	
Finland	0.1		
France	0.1 (I)		Restrictive statutory limit values
Hungary	0.15 (I) 0.05 (R)	0.6 (I) 0.2 (R)	
Ireland	0.15		
Italy	0.15		
Latvia	0.005	0.01	
Poland	0.05		
Romania	0.15		
Spain	0.15 (I)		
Sweden	0.1 (I) 0.05 (R)		
Switzerland	0.1 (I)	0.8 (I)	

Country/ Organisation	Lead and inorganic compounds TWA -8 hrs mg/m³	Lead and inorganic Compounds Short term mg/m³	Comments
United kingdom	0.15	1	
USA-NIOSH	0.05 (total dust)		
USA-OSHA	0.05 (total dust)		

Notes: Inhalable fractions; (R): respirable fraction;

Some Member States have also published biological limit values for lead.

Table 13 (non-exhaustive) table below shows the list of biological limit values. SCOEL (2002) recommended a BLV for lead in blood of 30 µg of lead /100 ml. (SCOEL, 2002)(SCOEL, 2002)(SCOEL, 2002)(SCOEL, 2002b)

Table 13: Biological values for lead in blood

Country/ Organisation	Lead in blood	Comments
France (ANSES, 2017b)	180 µg/L	
ACGIH (USA)	200 µg/L	
Finland	1.4 µmol/L (290 µg/L)	
Germany (TRGS 903, 28.03.2019)	400 µg lead/l blood (for women older than 45 years and for men) 100 µg lead/l blood (for women younger than 45 years)	update in preparation
AGS, 2017	150 µg/L blood (not valid for women in childbearing age)	Proposal; not yet implemented

4.2 Organic compounds

Regarding organic lead compounds, several EU Member States have established limit values for tetraethyl lead and tetramethyl lead. These are presented in

Table 14 and Table 15, respectively, but the list should not be considered as exhaustive. Some Member States also have published OELs for other lead organic compounds such as triethyl lead. Values for these lead compounds can be found at: GESTIS.

Table 14: Existing Occupational Exposure Limits (OELs) for tetraethyl lead

Country/ Organisation	Tetraethyl lead TWA -8 hrs		Tretraethyl lead Short term		Comments
	ppm	mg/m³	Ppm	mg/m³	
Austria		0.05		0.2	
Belgium		0.1			Additional indication "D" means that the absorption of the agent through the skin, mucous membranes or eyes is an important part of the total exposure. It can be the result of both direct contact and its presence in the air.
Denmark	0.007	0.05	0.014	0.10	
Finland		0.075		0.23 (1)	
France		0.1			
Germany (AGS)		0.05		0.1 (1)	
Germany (DFG)		0.05		0.1 (1)	Inhalable fraction and vapour
Hungary		0.05		0.2	
Ireland		0.1			
Latvia		0.005			
Poland		0.05		0.1	
Romania		0.01		0.03 (1)	
Spain		0.1			Skin notation
Sweden		0.05		0.2 (1)	
Switzerland		0.05		0.1	

Country/ Organisation	Tetraethyl lead TWA -8 hrs		Tretraethyl lead Short term		Comments
	ppm	mg/m³	Ppm	mg/m³	
United Kingdom		0.1			Control of Lead at Work Regulations (2002) apply Limit Value applies to total alkyl lead
USA - NIOSH		0.075			
USA - OSHA		0.075			

(1) 15 minutes average value

Table 15: Existing Occupational Exposure Limits (OELs) for tetramethyl lead

Country/ Organisation	Tetramethyl lead TWA -8 hrs		Tretramethyl lead Short term		Comments
	ppm	mg/m³	ppm	mg/m³	
Austria		0.05		0.2	
Belgium		0.15			Additional indication "D" means that the absorption of the agent through the skin, mucous membranes or eyes is an important part of the total exposure. It can be the result of both direct contact and its presence in the air.
Denmark	0.007	0.05	0.014	0.10	
Finland		0.075		0.23 (1)	
France		0.15			
Germany (AGS)		0.05		0.1 (1)	
Germany (DFG)		0.05		0.1 (1)	
Hungary		0.05		0.2	
Ireland		0.15			
Spain		0.15			Skin notation
Sweden		0.05		0.2 (1)	
Switzerland		0.05		0.1	
United Kingdom		0.1			Control of Lead at Work Regulations (2002) apply

Country/ Organisation	Tetramethyl lead TWA -8 hrs		Tretramethyl lead Short term		Comments
	ppm	mg/m³	ppm	mg/m³	
					Limit Value applies to total alkyl lead
USA - NIOSH		0.075			
USA - OSHA		0.075			

(1) 15 minutes average value

Some Member States have also published biological limit values for organic lead compounds. Table 16 (non-exhaustive) table below shows the list of biological limit values.

Table 16: Biological limit values for tetraethyl lead and tetramethyl lead

Lead compound	Country/ Organisation	Lead in blood	Comments
Tetraethyl lead	Germany (TRGS 903, 28.03.2019; DFG 2012)	25 µg diethyl lead/L urine (calculated as Pb) 50 µg total Pb/L urine (also valid for mixtures with tetramethyl lead)	
	Finland (FIOH 2019[11]	20.7 µg/L urine (action limit)	
Tetramethyl lead	Germany (TRGS 903, 28.03.2019; DFG 2012)	50 µg total Pb/L urine	
	Finland FIOH 2019[12]	20.7 µg/L urine (action limit)	

5. Occurrence, Use and Occupational Exposure

5.1 Occurrence

Lead (Pb) is an element that is found in concentrated and easily accessible lead ore deposits that are widely distributed throughout the world. Lead's high density, low melting point, ductility and relative inertness to oxidation made it useful historically. These properties, combined with its relative abundance and low cost, resulted in its extensive use in construction, plumbing, batteries, bullets and shot, weights, solders, pewters, fusible alloys, white paints, leaded gasoline, and radiation shielding. In the second half of the 20th century lead's toxicity became recognised, and its use has since been phased out of many applications, for example tetraethyllead as an antiknock agent in petrol was phased out in the EU in the year 2000.

[11] https://www.ttl.fi/wp-content/uploads/2017/11/Biomonitoring-of-exposure-to-chemicals-Guideline-for-specimen-collection.pdf

[12] https://www.ttl.fi/wp-content/uploads/2017/11/Biomonitoring-of-exposure-to-chemicals-Guideline-for-specimen-collection.pdf

5.2 Production and Use Information

Lead metal can be classified as either primary or secondary. Primary lead is produced directly from mined lead ore whereas secondary lead is produced from scrap lead products (such as automobile batteries) which have been recycled. It is rare to find pure deposits of lead in nature. The majority of the deposits are mixtures of minerals, hence lead ore is usually obtained as a byproduct of other metal mining such as zinc, silver or copper. In fact, lead ore is a main source of silver and contributes substantially towards the world's total output. The most common lead ore is galena (PbS), which contains 86.6% lead. Other common varieties include cerussite (PbCO3) and angelsite (PbSO4).

5.2.1 Production

5.2.1.1 Primary Lead - Mining

In 2012 lead mining in Europe (including Serbia, Macedonia and Turkey) accounted for 6.1% of the total worldwide production of primary lead from mining, with Poland and Sweden being the most active countries[13]. At the same time Europe accounted for 15.6% of the world's refined lead (both primary and secondary lead), with Germany being the biggest contributor.

Sweden[14]:

There are 7 active lead mines in Sweden, 5 of them operated by Boliden Mineral AB: Garpenberg, Kankbergsgruvan, Kristineberg, Maurliden, Renström. The other 2 being: Lovisagruvan (operated by Lovisagruvan AB) and Zinkgruvan (operated by Zinkgruvan Mining AB).

Poland[15]:

Four areas of Zn-Pb ore deposits are recognized in the Silesian-Cracow region: Chrzanów, Olkusz, Bytom and Zawiercie regions. Exploitation is currently carried out from Klucze I, Olkusz and Pomorzany deposits in the Olkusz region. In 2018, Polish mines extracted 1.594 million tonnes of ores yielding 43,000 tonnes of zinc and 13,000 tonnes of lead. The production of lead in Poland has been decreasing.

Apart from Sweden and Poland, other EU countries are also involved to a lesser degree in lead mining[16]:

Table 17: Lead mining in the EU

Country	2012 (t)	2013 (t)	2014 (t)	2015 (t)	2016 (t)
Bulgaria	14764	16940	17020	18370	22040
Greece	15313	14211	13016	9175	11283
Ireland	47400	42950	40500	31300	19600
Italy	3000	3000	3000	3000	3000
Poland	47100	78980	83150	49000	43060
Portugal	87	1496	3191	3077	4246

[13] https://www.ila-lead.org/lead-facts/lead-production--statistics

[14] https://www.sgu.se/en/mining-inspectorate/mines/mines-in-sweden/

[15] http://geoportal.pgi.gov.pl/surowce/metaliczne/rudy_zn-pb/2018

[16] http://www.euromines.org/mining-europe/production-mineral#Lead

Country	2012 (t)	2013 (t)	2014 (t)	2015 (t)	2016 (t)
Romania	5500	800	570	570	120
Slovakia	1800	235	162	160	200
Spain	3763	2160	1223	1598	4900
Sweden	63551	59556	70848	79354	75830
United Kingdom	100	100	100	100	100
*Macedonia**	*41300*	*42820*	*43810*	*37920*	*31030*

** Not in the EU but indicated as a relatively large lead producer in Europe (potentially exports the ore to EU countries for refining)*

5.2.1.2 Secondary lead – recycling/recovery from lead containing (used) material

The following substances account for 97.5% of REACH registered tonnage used in the secondary manufacture of lead.

Table 18: Substances used in the secondary manufacture of lead

EC_NUMBER	NAME
266-970-4	Slags, copper refining
266-967-8	Matte, copper
273-760-6	Flue dust, zinc-refining
273-825-9	Slags, lead smelting
293-314-4	Leach residues, zinc ore, lead-contg.
308-011-5	Lead, bullion
305-445-7	Wastes, lead battery reprocessing
273-809-1	Flue dust, lead-refining
305-411-1	Calcines, lead-zinc ore conc.
273-800-2	Slags, lead reverbatory smelting
282-356-9	Matte, lead
273-796-2	Lead, dross

Though not involved in mining lead, Germany is the biggest lead metal producing country in the EU (both from primary and secondary production). It is the base for some of the biggest lead smelters in Europe, and some of the biggest lead-acid battery recyclers.

Lead processing

Lead processing and smelting plants work with both primary and secondary lead. Smelting is a key process in lead product production, and involves heating lead ore or recovered lead with chemical reducing agents.

Sintering

Once the lead ore is mined, it must undergo several different processes in order to be turned into usable or metallurgical lead material. The first step is sintering which involves removing sulphur from the lead ore using a hot air combustion process.

Smelting

Once the sulphur is removed, the lead is sent into a smelter where it is heated at extremely high temperatures in order to isolate the pure lead from other metals and materials in the ore. Any remaining metals or other materials left after the smelting are removed during the refining process.

Secondary smelting of lead is similar to primary smelting, but does not require the initial sintering process. Once lead is recovered from used materials – with the majority coming form used lead-acid batteries – it is placed into a furnace where it is heated with coke or charcoal in order to isolate the lead from other compounds.

The molten lead is transferred from the blast furnace into holding pots. Lead may be mixed with alloys, including antimony, tin, arsenic, copper and nickel. It is then cast into ingots.

5.2.2 Uses

97% of the REACH registered tonnage for lead and lead compounds is accounted for by the following five substances, and along with their main uses, they are indicated in Table 19.

Table 19: Lead and lead compounds by highest registered tonnage, with their main uses

EC NUMBER	NAME	Battery production	Manufacture/ Use of Stabilisers (PVC)	Manufacture of lead monoxide	Other uses
231-100-4	Lead	x	x	X	Lead powder production, lead sheet production, lead articles, ammunition lead solder
215-267-0	Lead monoxide	x	x		Explosive manufacture , Catalyst Production, Manufacture of rubber protection, Adsorbents
235-380-9	Tetralead trioxide sulphate	x	x		Coatings and inks
235-067-7	Pentalead tetraoxide sulphate	x	x	X	
215-235-6	Lead tetroxide (Orange lead)	x	x		Ceramic/Glass production, Paints and Pigments, Adsorbents

5.2.2.1 Lead-acid battery production

Key countries for lead-based battery manufacture in Europe include the Czech Republic, France, Germany, Italy, Spain, Poland and the United Kingdom.

About 99% of lead monoxide tonnage used in the EU (500,000 tonnes) and about 80% of lead tetroxide tonnage (36,000 tonnes) is used in battery manufacture. They are transformed in the course of the battery manufacturing process into pentalead tetraoxide sulphate and tetralead trioxide sulphate, which are themselves ultimately transformed within the battery into lead metal and lead dioxide.

A lead-acid battery is commonly used in automobile applications and uninterruptible power source (UPS) systems. These batteries provide sufficient energy to start engines or provide near-instantaneous protection from input power interruptions, and are maintenance free, and durable. The difference between automobile and UPS batteries is in the way that the batteries optimize their design: a car's battery is designed to provide a very large amount of current for a short period of time, whereas the UPS uses a deep cycle battery designed to provide a steady amount of current over a long period of time: both use exactly the same chemistry for their operation. The lead battery is manufactured by using lead alloy ingots and lead monoxide. It comprises two chemically dissimilar lead-based plates immersed in sulphuric acid solution. The positive plate is made up of lead dioxide and the

negative plate with pure lead. The main parts of the battery are plates, i.e., anode and cathode plates, separators, electrolyte or sulphuric acid, case, cell connectors and terminals.

Batteries are manufactured in an automated controlled environment with careful maintenance procedures. The manufacturing processes can be divided into several stages like oxide and grid production process, pasting and curing, assembly process, formation, filling, charge-discharge process, final assembly, inspection and dispatch. These manufacturing steps are briefly explained below[17]. According to REACH registration information, the grid production and pasting activities have the highest potential for worker exposure.

1. Oxide and Grid Production Process

Lead oxide is obtained either by milling[18] or Barton Pot[19] process methods. In the milling process, the tumbling action generated by the rotating mill on solid lead generates heat and then the surface of the lead gets oxidised. The surface layers of the oxide are removed while the lead particles roll in the drum. In the Barton Pot process a fine stream of lead droplets is produced by blowing air on molten lead. These droplets are reacted with oxygen and produce lead oxide.

Casting and stamping methods are generally used for making battery grids. In the casting method, the lead alloy slabs are melted in a melting pot and this molten lead is poured into the patterns of battery grids whereas stamping operation produces on battery grids based on stamping on lead sheets. When these grids are cooled after casting operation, these are passed to trimming machine where rough edges and casting gates are trimmed.

2. Pasting and Curing

Pastes (made with oxide of lead, red lead, litharge, water and dilute sulphuric acid) are used to fill both positive and negative grids; some expander materials are added for making the negative paste. The paste is then forced or pressed on the interstices of the grids by a machine or by hand, and then these are turned into plates. These pasted plates are cured in ovens.

3. Assembling the Elements

All the parts are assembled into a battery case and covered with the plastic moulds. This step involves the formation of positive and negative plate stacks, insertion of separators, inter-cell connector and plate burning. The separator is made up of non-conductive material such as paper, plastic or a glass fibre.

During the burning operation each positive and negative plate tab is welded to lead to produce an element and these are then welded to respective positive and negative posts on the battery's case top. After keeping this element in the jar or case, sealing compound is applied to make the space leak proof between the battery jar and cover.

4. Filling and Formation

After the assembling, battery jar is filled with required amount of electrolyte through a filling or vent tube. Then, it is ready for initial charging, which may require several hours of charging depending on the battery size. This charge formation may either be dry or wet.

[17] https://www.watelectrical.com/know-about-the-steps-of-battery-manufacturing-process/

[18] https://acsengineering.in/ball-mill-oxide-system.php

[19] https://acsengineering.in/barton-oxide-system.php

5. Charging and Discharging

After the formation, batteries are subjected to high-rate discharge test for short duration to rule out any defects before sending them out to the final charge. The batteries are then recharged for certain backup hours and sent to the next level where additional connections, labelling and caps are inserted with sealed-cotton packing, before dispatching the order.

Lead–acid batteries are monometallic. All active materials, plate grids, straps, and connectors are made mostly of lead. Hence, recycling of lead from batteries is an easy process (also lead has a relatively low melting point of 327.4C). In the EU, 97% of the lead in batteries is recycled.

5.2.2.2 Lead Stabilisers in PVC

According to REACH registration information, lead stabilisers/polymer processing is the second most common "identified use", while at the same time there has been a voluntary activity to phase out this use for its use in PVC in the EU. The European Stabiliser Producers Association (ESPA) representing more than 95% of PVC stabiliser industry across Europe, have reported that from 1 January 2016 there is no more consumption of lead-based stabilisers among their members in the EU-28[20]. However the lead and lead compounds REACH registrations maintains this identified use, and there is no information about the non-members of ESPA. According to the Annex to the Restriction on the use of lead compounds to stabilise PVC (ECHA, 2018b), ESPA indicated that in 2016 that there was only one European company producing lead stabilisers for export to non-EU countries. The Annex also notes that approximately 30% of EU produced lead stabilisers are exported outside the EU, which means that 70% remains within the EU.

Lead-based stabilisers have been widely used in PVC products over many years. Due to the long life time of most PVC products (e.g. typically 40 years for window profiles, more than 50 years for pipes), lead is expected to be present in PVC waste for many years to come.

Historically lead compounds were the most cost-effective and common form of stabiliser used for PVC. Their stabilising effects are excellent and used for PVC products with long service life and required to endure longer fabrication (heating) hours[21].

The major properties of PVC compounds incorporating lead stabilisers include:

- Excellent heat and light stability.
- Good electrical properties.
- Excellent short and long-term mechanical properties.
- Low water absorption.
- Wide processing range.
- Good cost/performance ratio.

Concerns about possible adverse effects of lead on health and the environment prompted the ESPA together with the VinylPlus Voluntary Commitment and EuPC (European Plastics Converters) to commit to replacing lead-based stabilisers by the end of 2015 in the EU-28.

[20] https://www.stabilisers.eu/lead-replacement

[21] http://www.seepvcforum.com/en/content/18-lead-stabilisers

Import data from Eurostat (2016) indicate that imports from outside the EU of relevant PVC articles have progressively increased (resulting in a 140% volume increase between 2010 and 2015). Total lead emissions from PVC articles placed on the EU market in 2016 were modelled and around 90% of the estimated lead emissions are attributable to PVC articles imported into the EU during 2016. The result is the introduction of a REACH restriction[22], to strengthen the ESPCA voluntary action and further reduce human exposure to lead from PVC articles that are imported from non-EU countries[23].

5.2.2.3 Use of lead oxides in speciality and crystal glass production

Key countries for lead crystal glass manufacture are Belgium, Czech Republic, France, Germany, Italy, Hungary, Ireland, Slovenia, Poland, UK and Portugal. It is noted that crystal glass is exempted from the restriction on lead in consumer articles and in jewellery (entry 63 of Annex XVII).

Lead glass contains typically 18–40% (by weight) lead(II) oxide (PbO), while modern lead crystal, historically also known as flint glass due to the original silica source, contains a minimum of 24% lead(II) oxide. In the EU only glass products containing at least 24% of lead oxide may be referred to as "lead crystal". Products with less lead oxide, or glass products with other metal oxides used in place of lead oxide, must be labelled "crystalline" or "crystal glass".

The high density of lead (11.35 g/cm^3, at room temperature) makes it very effective for shielding against x-rays and gamma radiation. Therefore it is used in glasses used in radiation shielding (nuclear industry and medical applications), and specific optical applications/medical devices, microscopes, etc. required for precision manufacturing in other sectors.

The raw material ingredients (including lead oxides) are melted and react together to be transformed into a new substance[24]: a molten glass at high temperature (ca 1350-1550°C) in furnaces. The melting process can be obtained in pot furnaces, for small discontinuous scale manufacture, or in big continuous melting tank furnaces for continuous industrial manufacture. The obtained lead glass melt is then cooled down and delivered in ribbons, droplets or gobs. In a further step, the lead glass is shaped by different forming techniques, for instance pressing or blowing. The pressing process is relatively simple, it involves pressing a hot glass gob between a mould and a plunger. For handmade articles by blowing, lead crystal glass melt is gathered by a person with a hollow pipe, either directly from the furnace or from a feeder. A small hollow body of glass (the parison) is made by giving a short puff into the pipe, and the shape is then formed by turning in a wet wooden or metal mould. After forming, the items are carried to an annealing lehr to eliminate any internal tensions and are fire finished, polished and reheated. In semi-automatic production, most of these steps of the process (gathering, forming, and handling) are carried out with machines or robots.

5.2.2.4 Lead Alloys

Because lead is very soft and ductile, it is normally used commercially as lead alloys. Antimony, tin, arsenic, and calcium are the most common alloying elements. Lead-calcium alloys have replaced lead-antimony alloys in a number of applications, in particular,

[22] https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e180a40af7

[23] https://echa.europa.eu/documents/10162/539caf1a-68c8-1b51-1026-58d15209a2fc

[24] http://ec.europa.eu/DocsRoom/documents/13862/attachments/7/translations/en/renditions/pdf

storage battery grids and casting applications. Adding tin to lead or lead alloys increases hardness and strength, but lead-tin alloys are more commonly used for their good melting, casting, and wetting properties (ability of a liquid to maintain contact with a solid surface), as in type metals and solders. Tin gives the alloy the ability to wet and bond with metals such as steel and copper; unalloyed lead has poor wetting characteristics. Tin combined with lead and bismuth or cadmium forms the principal ingredient of many low-melting alloys[25].

The mechanical or structural properties of lead and lead alloys are relatively poor compared to other metals, but lead offers useful properties such as good corrosion resistance, malleability, energy absorption and electrical conductivity. Therefore it is often used in conjunction with other, structurally superior, materials to produce an effect that neither could achieve separately[26]. For example, sheet lead is bonded to steel for chemical tank linings, noise and radiation shielding, or as a lining for chemical or nuclear facility piping. Lead alloy solder applied to copper or steel is used in roofing applications.

Lead does not dissolve in dilute acids except in the presence of an ample supply of oxygen, owing in part to the fact that hydrogen is evolved on lead only at a considerable overvoltage. Lead is usually protected from solution by the formation of an insoluble coating on the surface, which protects the underlying metal. The stability of lead in sulfuric acid concentrations from 10% to better than 95%, at temperature ranges from room to 150 °C, is critical for its use in storage batteries and for numerous chemical manufacturing applications. Lead is practically inert to most commercial acids except nitric, which, because it is a strong oxidizer, rapidly attacks lead, especially at concentrations below 50%; above that level, to 95%, the effect is minimal.

Solders in the tin-lead system are the most widely used of all joining materials. The low melting range of tin-lead solders makes them ideal for joining most metals by convenient heating methods with little or no damage to heat-sensitive parts. Tin-lead solder alloys can be obtained with melting temperatures as low as 182 °C and as high as 315 °C. Except for the pure metals and the eutectic solder with 63% Sn and 37% Pb, all tin-lead solder alloys melt within a temperature range that varies according to the alloy composition.

5.2.2.5 Lead sheet

Lead sheet is a construction material of major importance in chemical and related industries because lead resists attack by a wide range of chemicals[27]. Lead sheet is also used in building construction for roofing and flashing, shower pans, flooring, x-ray and gamma-ray protection, and vibration damping and soundproofing. Lead sheet for use in chemical industries and building construction is made from either pure lead or 6% antimonial lead. Calcium-lead and calcium-lead-tin alloys are also suitable for many of these applications. Lead sheets are rolled and the rolling process involves passing slabs of lead back and forth between high pressured rollers. The process is computer controlled to consistently obtain an exact predetermined thickness and knitted grain structure, allowing the performance of the product to be accurately predicted whilst in situ[28].

[25] http://www.totalmateria.com/Article10.htm

[26] https://www.sciencedirect.com/topics/engineering/lead-alloys

[27] http://www.totalmateria.com/Article10.htm

[28] https://www.britishlead.co.uk/rolled-lead-sheet

5.2.2.6 Ammunition

Lead has been used in ammunition and fishing tackle for centuries. It is widely used because it is very dense, thereby providing a high amount of mass—and thus, kinetic energy—for a given volume. Lead is also cheap, easy to obtain, easy to work, and melts at a low temperature, which results in comparatively easy fabrication of bullets. The available information suggests that the use of lead gunshot, lead in civil ammunition, and lead in fishing tackle poses a risk to both human health and the environment the most significant being lead shot (estimated that in the EU around 14 000 tons of lead shot per year is dispersed into the terrestrial areas)[29]. On 17 August 2018, ECHA sent the opinion of its scientific committees supporting a restriction on the use of lead for shooting in terrestrial areas, ammunition and fishing tackle, in addition to action on lead shot in wetlands.

5.2.2.7 Fuel additives

Tetraethyllead, used as an antiknock agent in petrol, has historically contributed significantly to the background exposure of the general population. This use was phased out in the EU in the year 2000. According to REACH Registration data around 2,000 tonnes/year are still manufactured in the EU, which is comparatively small when considering more than 3.5 million tonnes/year can be attributed to lead and the main lead compounds (by quantity). All the tetraethyllead tonnage is blended into an additive formulation at the production facility. Most of the formulated fuel additive is then immediately exported outside the EU to industrial fuel blenders and refineries for blending into fuels. A very limited volume is supplied to four fuel blenders and refineries within the EU to further formulate into aviation fuel (at less than 0.1% wt), within dedicated blending equipment (closed systems). All four EU customers receive extensive ongoing storage, blending and handling advice, a 24 hour emergency response service in case of spillage or accident, and are subject to audits every three years.

5.3 Occupational exposure

Primary lead manufacture (mining, sintering, smelting): some parts of the process are contained or enclosed, but there are a number of activities that require manual intervention and this is where the occupational exposure is highest. According to REACH Registration data, during all activities local exhaust ventilation and personal protective equipment (respiratory protective equipment (RPE) and gloves) are specified. According to measured data on which the REACH registrations are based from 2013 to 2016 the blood lead levels for workers in this industry range from 220 - 350 µg/L (against a DNEL of 400 µg/L for adults in the workplace derived by the registrant[30]). The workers involved in sintering (feeding/unloading, sinter plant operation) exhibited the highest levels of lead in their blood. Those involved in raw materials handling, and refining and casting, also have comparatively high blood lead levels.

Secondary lead manufacture (recycling, smelting): since there are many aspects of secondary manufacture common with primary manufacture so there are similar levels of exposure. According to the REACH Registration data, although some parts of the process are closed, there are activities that require manual intervention which is where occupational exposure is highest. During all activities local exhaust ventilation and personal protective equipment (respiratory protective equipment (RPE) and gloves) are specified. According to measured data on which the REACH registrations are based from

[29] https://echa.europa.eu/documents/10162/13641/lead_ammunition_investigation_report_en.pdf

[30] In the proposed restriction on lead in shot, RAC has derived a DNEL of 200 µg/L for the general population (based on a NOAEL of 400 µg/L for effects on adult neurological function and using an assessment factor of 2).

2013 to 2016 the blood lead levels for workers in this industry range from 230 - 300 µg/L (against a DNEL of 400 µg/L for adults in the workplace derived by the registrant). The workers involved in melting and smelting, and refining and casting, exhibited the highest levels of lead in their blood.

According to REACH Registration data, although some parts of the lead-acid battery production is contained or enclosed, there are a number of activities that require manual intervention and this is where the occupational exposure is highest. During those activities, local exhaust ventilation and personal protective equipment (respiratory protective equipment (RPE) and gloves) are specified. According to measured data on which the REACH registrations are based from 2013 to 2016 the blood lead levels for workers in battery production ranged from 220 - 330 µg/L. The workers involved in the preparation of the grids (cutting etc.) and the mixing and pasting activities exhibited the highest levels of lead in their blood. Cleaning and maintenance activities are also notable for comparatively high blood lead levels.

For stabiliser production the majority of the process is closed, where manual intervention is only required during preparation/discharge activities (carried out under local exhaust ventilation and using personal protective equipment). Again according to measured data from 2013 to 2016, the blood lead levels for workers in this industry ranged from 250 - 330 µg/L, with the highest level recorded for workers involved in loading/unloading activities (bagging/drumming operations).

The speciality glass industry mainly involves manual activities. In this case there is complete reliance on local exhaust ventilation and personal protective equipment. Again according to measured data from 2013 to 2016, the blood lead levels for workers in this industry ranged from 100 - 300 µg/L, with the highest levels recorded for workers involved in the raw materials (lead monoxide) handling. Once the lead is incorporated into the glass then the exposure to lead is significantly reduced for subsequent tasks.

Some parts of the alloy production can be closed but there remains reliance on local exhaust ventilation and personal protective equipment. Workers do not work in specific tasks but across all tasks. Therefore it is not possible to identify specific tasks that may lead to higher exposures. Measured data from 2014 to 2016 for leaded steels, and from 205 to 2017 for leaded copper alloys indicate blood lead levels of about 250 µg/L. For activities involving the use of lead in the manufacture of articles, workers also do not work on specific tasks but across a range of tasks, relying on local exhaust ventilation and personal protective equipment. For activities like ammunition manufacturing measured data from 2010 indicates an overall blood lead level of about 340 µg/L for workers. For lead sheet manufacture the measured data from 2014 to 2016 indicates an overall blood lead level of about 250 µg/L. In both cases the highest exposures are likely to be associated with cutting and finishing operations.

All of the current monitoring of lead exposure is based on blood levels, however there are some historical studies according to IARC (2006), where the following lead concentrations in air were reported in Europe across different activities:

Table 20 Measured occupational lead concentrations in air in Europe (IARC, 2006)

Source	PbA (µg/m^3)	Reference
Primary smelter, Italy, 1977-1978	47.8 (mean), 1-1650 (range)	Cocco et al. (1997)
Cadmium plant, UK, 1970-1979	>2000 µg/m^3 (mean; 50%)	Ades and Kazantzis (1988)
Indoor range, powder gun, Sweden	660 (mean), 112-2238 (range)	Svensson et al. (1992)
Indoor range, air gun, Sweden	4.6 (mean), 1.8-7.2 (range)	Svensson et al. (1992)
Indoor range for police officers, UK	30-160 (mean)	Smith (1976)
Indoor range for soldiers, UK	190 (TWA)	Brown (1983)

5.4 Routes of exposure and uptake

5.4.1 Worker exposure

The primary routes of exposure for worker population is by inhalation and by ingestion (by hand to mouth exposure in case of insufficient personal hygiene and housekeeping). Dermal absorption of inorganic lead through unabraded human skin is considered to be minimal.

5.4.2 General population

Human exposure to lead is universal, and all humans carry a body burden of lead (IARC, 2006). Blood lead levels are generally reflective of lead exposure from multiple environmental media. From a practical perspective, exposure to airborne lead will only be a major contributor to blood lead in areas of high air lead levels. Long-term measurements of background lead concentrations have demonstrated significant reduction in lead levels in the environment after the phase-out of leaded petrol in many countries (EFSA, 2010, updated 2013).

Since the phase-out of leaded gasoline, lead levels in all environmental media (except soil) have declined, and the predominant route of lead intake for the general adult population is currently oral exposure from food and drinking water (ATSDR 2007, 2010; EFSA 2010, updated 2013).

Air

Before the phase-out of lead in gasoline, inhalation was the predominant route of exposure to lead for the general public.

Lead enters into the atmosphere mainly from anthropogenic sources, such as metal production, manufacturing industries, electricity and heat production (European Monitoring Environmental Pollution ((EMEP/CCC, 2006).

Background lead levels in ambient air range from 7.6 x 10^{-5} µg/m^3 in remote areas such as Antarctica, to >10 µg/m^3 near stationary sources such as smelters (US ATSDR, 2007).

EFSA (2010, updated 2013) summarised according to EMEP (European Monitoring and Evaluation Programme) data (which should be considered as background values for Europe), lead concentrations in air, averaged over a number of EMEP monitoring stations during the period 1990-2003, decreased from about 0.020 to about 0.005 µg/m^3 (EMEP/CCC, 2005).

According to the latest EMEP/CCC (2018) report, the lowest concentrations of lead in air (below 1 ng/m^3) can be seen in Scandinavia, and a site in Spain and in Cyprus while the highest level is in Hungary with 7 ng/m^3 followed by sites in Estonia, Belgium and in the Netherland with concentrations above 5 ng/m^3.

Food

In average adult consumers, lead dietary exposure ranges from 0.36 to 1.24, up to 2.43 µg/kg bw/day in high consumers in Europe. Exposure of infants ranges from 0.21 to 0.94 µg/kg bw/day and in children from 0.80 to 3.10 (average consumers), up to 5.51 (high consumers) µg/kg bw/day (EFSA, 2010, updated 2013).

Water

Drinking water delivered through lead pipes or pipes joined with lead solder may contain lead. Removing lead from water distribution systems is a complex problem, because even certain alloys that have been used to replace lead pipes contain small amounts of lead. In addition PVC pipes, where lead had been used as a stabiliser, are often installed in existing water distribution networks. Such pipes were installed from early 1990 to 2005. PVC pipes

installed after 2005 also contain small amounts of lead because of material recycling. Complete exclusion of lead is only possible with new products without recycled material.

According to the ”Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the quality of water intended for human consumption” the Commission proposes lowering the value to 5 µg/l 10 years after the entry into force of the Directive. During this transitional 10-year period, the current value of 10 µg/l will be maintained (EU, 2017) ((HBM4EU, 2019).

Soil

The concentration of lead in the top layer of soils varies considerably because of the deposition and accumulation of atmospheric particulates from anthropogenic sources (US ATSDR, 2007). In Europe, lead concentrations in top soils are geographically heterogeneous and vary from below 10 mg/kg up to >70 mg/kg. The median value was estimated by (WHO, 2007) to be 23 mg/kg. The lead content in uncontaminated top soils of remote areas is generally within the range of 10 to 30 mg Pb/kg.

Once absorbed, lead circulates in the bloodstream and either accumulates in tissues or is excreted as waste. Some of it is absorbed into soft tissue such as the liver, kidneys, pancreas and lungs. A very high proportion of absorbed lead is transferred to bone (hard tissue), where it accumulates over time and remains for long periods. Lead concentrations can stay in the body for many years after exposure to lead has stopped.

6. Monitoring Exposure

6.1 External exposure

6.1.1 Airmonitoring methods

The principle of most of the methods is trapping the sample on a suitable filter by using a particle sampler (for inhalable fraction). The lead compounds are then extracted with a solutions and further analysed using a suitable technique (e.g. atomic absorption). Only exception is the method based on X-ray fluorescence where there is no extraction step before the analysis. The LOQ is given as mass of lead.

The table states whether the method specifies sampling method and the relevant fraction (i.e., inhalable for lead). When a specific particulate sampler (and its associated flow rate) has been recommended the calculations of the sampling time have used the maximum flowrate recommended by the method. However, the latter does not exclude that the methods have the potential to use other sampler at different flowrates that may allow to achieve lower LOQ or to collect a different aerosol fraction.

Table 21: Methods for lead and lead compounds in air

METHOD/ Fraction	Analytical technique	LOQ and sampling volume and time	Reference
BGI 505-73-01 (inhalable)	GF-AAS Graphite furnace atomic absorption spectroscopy	0.13 µg/m^3 for a 1200 l sample (2 hours) Flow rate: 10 l/min	(DFG, 2012)
ISO 15202	ICP-AES (Inductively coupled plasma atomic emission spectroscopy)	17 µg/m^3 for a 480 l sample (less than 1 hour)[1]	(ISO, 2012)
MDHS 91-2 (inhalable)	XRFS (X-ray fluorescence spectrometry)	2 µg/m^3 for a 480 l sample (4 hours) Flow rate: 2 l/min	(HSE)

(1) Sampling time calculated for the maximum flow of 10 l/min (maximum flow rate for common inhalable fraction samplers)

6.2 Biomonitoring of exposure (internal exposure)

6.2.1 Biomarkers

6.2.1.1 Biomarkers of exposure

Lead in blood (PbB) is the most prominent and best validated biomarker for lead exposure. The parameter provides a high sensitivity for current lead exposure and depicts an intermediate observation time featured by an elimination half-time of about one month. Moreover, the parameter is positively and clearly associated with the external exposure. The crucial advantage of this parameter is its frequent implementation in studies on lead toxicity and thereby high availability of valid exposure limits and assessment values (Klotz and Goen, 2017).

Lead in bones such as tibia, patella or calcaneus, is another biomarker for lead exposure; the skeleton contains approximately 80–90% of the total body lead burden in the steady state. It represents the cumulative exposure to lead (Klotz and Goen, 2017).

Further considerations of the biomonitoring parameters 'lead in blood' and 'lead in bones' with regards to their toxicological role can be found in section 7.1.5 of this report.

Lead in urine is another probable biomarker. This approach is supported by the fact that urinary excretion is the major elimination route of lead. Moreover, a significant correlation was found between urine lead and blood lead in both, occupationally exposed employees and individuals of the general population without occupational exposure. However, the comparison of both parameters by a linear correlation model showed high variance and uncertainty in general, which may be explained by different kinetic behavior of both parameters. The correlation between urine lead and plasma lead was found to be comparable or slightly stronger than between urine lead and blood lead. Presently, scientific knowledge on the association between urinary lead levels and toxic effects is poor, which contradicts the evaluation of health-based exposure limits for this parameter. Consequently, the use of the parameter for risk assessment of lead exposure is limited. (Klotz and Goen, 2017).

6.2.1.2 Biomarkers of effect

Klotz and Goen (2017) reviewed "biomarkers of effect" which include δ-aminolevulinic acid dehydratase (ALAD) and erythrocyte porphyrins (EPs) in blood as well as δ-aminolevulinic acid (ALA) in urine and plasma and coproporphyrin in urine. The author concludes that biomarkers of effect alone are not sufficiently sensitive for an early detection of a health impairment caused by lead.

6.2.2 Background levels

Blood lead concentration is the most commonly used estimate of exposure to lead in the general population. Numerous reports show blood lead concentrations declining over time in many parts of the world, thereby validating global efforts to reduce lead exposures.

There has been a clear decline in environmental exposure to lead over the past decades. This is due to elimination of lead for example in petrol or paint and other control measures. In Sweden, the geometric mean PbB concentration in schoolchildren decreased from about 60 µg/L in 1978 to about 25 µg/L over a 15 year period (Gerhardsson et al., 1996). In Germany the geometric mean PbB in students decreased from 80 to 10 µg/L over a 28 year period in 1981 to 2009 (Becker et al., 2013).

In the US average PbB levels in children 1-5 years of age have decreased 10-fold over the last 30 years, from 151 µg/L in 1960-1980 to 15.1 µg/L in 2007-2008 (geometric means; CDC 2007, 2011). The percentage of children with PbB levels higher than 100 µg/L decreased from 88.2 % to 4.4 % in less than two decades (ATSDR, 2007).

IARC (2006) lists PbB levels measured in the US general population which are summarised in Table 22.

Table 22: Measured blood lead concentrations in the general population with specific lead exposure (IARC, 2006)

Source	PbB (µg/L)	Reference (IARC, 2006)
Air dust		
air dust sources such as burning of newspaper in fireplaces	350 (individual value)	(Perkins and Oski, 1976)
dust at home from occupational exposure	420-733 (mean) 310-360 (range)	(Baker et al., 1977) (Gerson et al., 1996)
dust from removal of lead-based paints	200->800 (range)	(CDC, 1997)
tile-glazing activities	600 (median), 120-1006 (range)	(Vahter et al., 1997)
Food/food containers		
lead-bearing cocktail glasses	1310-1560 (range)	(Dickinson et al., 1972)
water heated in lead-soldered electric kettels	350-1450 (range) 1470-1540 (range)	(Ng and Martin, 1977) (Lockitch et al., 1991)
Ceramics from southern Italy	740-1440 (range)	(Wallace et al., 1985)
contaminated flour	800-1220 (mean)	(Hershko et al., 1989)
contaminated paprika	188-2130 (range)	(Kakosy et al., 1996)
apple cider prepared in lead-soldered evaporator	330-400 (range)	(Carney and Garbarino, 1997)
food colouring	250-840 (range)	(CDC, 1998)
Others		
traditional remedies such as Ayurvedic metal-mineral tonics	26-921 (range)	(Prpic-Majic et al., 1996)
cosmetics such as traditional surma	342 (mean) 129 (mean)	(Ali et al., 1978) (Sprinkle, 1995)

Current data from the German Environmental Specimen Bank, the following statistically derived *reference levels* were identified: 40 µg/L for adult men, 30 µg/L for adult women and 35 µg/L for children (HBM4EU, 2019).

Table 23 lists PbB levels in the general population of Europe reported for the past 10 years (HBM4EU, 2019).

Table 23: Summary of European blood lead survey reported in the past 10 years (HBM4EU, 2019)

Country	N	Years of sampl.	PbB (µg/L)			Reference
			Males	Females	Children	
Armenia	159	2013			60±30 (GM±SD; 4-6 years old)	(Grigoryan et al., 2016)
Belgium	52, 54, 98	2009	31.7 (27.9-36.1) [GM (95% CI)]	21.4 (18.1-25.3) [GM,(95% CI)]	16.6 (14.8-18.2) [GM,(95% CI)]; 2.5-6 years old]	(Fierens et al., 2016)
Croatia	46	2007-2008			17.9 (10.0-42.0) [GM (range); 7-14 years old)	(Hrubá et al., 2012)

Country	N	Years of sampl.	PbB (µg/L)			Reference
			Males	Females	Children	
Czech Republic	8	2007-2008			GM:15.5;Range: 12.0- 22.0; 7-14 years old	(Hrubá et al., 2012)
	5667, 3798	1994-2003 and 2005-2009		GM: 14.0 (breastfeeding primipare)	GM boys: 22.0, GM girls: 19.0 (8-10 years old)	(Černá et al., 2012)
	4472		GM: 23.0			
Denmark	73	2011-2014		GM: 8.1 (95th% 15.8)		(Rosofsky et al., 2017)
Finland	126, 123	1997	GM: 17.06 S.D.:± 1.84	GM: 9.06; S.D.: ± 2.2		(Abass et al., 2017)
France	1949	2006 -2007	GM: 26; 95% C.I.: 68-77 (18-75 years old)			(Falq, 2008)
	579		GM: 19; 95%C.I.: 44-62 (18-39 years old)			
	947		GM: 29; 95%C.I.: 66 -85 (40-59 years old)			
	423		GM: 39; 95%C.I.: 86 -115 (60-75 years old)			
	3831	2008-2009			GM: 14.9 (95% C.I.:14.5 -15.4) (1-6 years old)	(Etchevers et al., 2014)
Germany	2731	1985 - 1986	GM: 61			(Schulz et al., 2017)
	4287	1990-1992	GM: 45			
	812	1990-1992			GM: 32	
	4822	1997 -1999	GM: 32			
	1790		2003-2006		GM: 17 (3-14 years old)	
Hungary	253	2006			GM: 30 (4 – 15 years old)	(Rudnai et al., 2009)
Italy	1423	2008-2011	GM: 19.9 (95% C.I.:19.2-20.5) (18-65 years)			(Bocca et al., 2013)
Kosovo	1423	2008-2011	GM: 19.9 (95% C.I.:19.2-20.5) (18-65 years old)			(Bocca et al., 2013)
	166	? 2012-2014			AM: 24 ±19 (Range: 5-163) (5-11 years old)	(Kutllovci-Zogaj et al., 2014)
	53				AM: 23 ±7 (Range: 12-52) (6-12 years old)	
	31				AM: 38 ±13 (Range: 22-77)	

Country	N	Years of sampl.	PbB (µg/L)			Reference
			Males	Females	Children	
					(Kindergarten)	
Poland	594	2007-2018		GM: 11.0; Range: 3.0-57.0 GM: 11.0; (pregnant women)		(Polanska et al., 2014)
	78	? 2010-2011			AM: 19.7 ± 13.59 (2-18 years old)	(Szkup-Jabłońska et al., 2012)
	678	2013			GM: 24.7 ± 17.5	(Kowalska et al., 2018)
Slovakia	57	2007-2008			19.4 (8.0-47.0) [GM (range); (7-14 years old)	(Hrubá et al., 2012)
Slovenia	42	2007-2008			GM: 13.4; Range: 6.9-24.0 (7-14 years old))	(Hrubá et al., 2012)
	147, 127,66, 174	2011-2014	GM: 19.6 (20-35 years old)	GM: 17.3 (20-35 years old) GM: 26.7 (50-60 years old)	GM: 16.1 6-11 years	(Tratnik et al., 2013)
Spain	1,880	2007-2010	24 (23.0-25.1) [GM,(95% CI)]			(Cañas et al., 2014)
Sweden	619, 926, 41	2004-2014, 2007-2008	11.1 [25-35 years old] 15.1 [50-60 years old]	9.69 [25-35 years old] 13.1 [50-60 years old]	14.0 (6.0-25.0) [GM (range); 7-14 years old]	(Hrubá et al., 2012) (Wennberg et al., 2017)

6.2.3 Biological monitoring and occupational exposure

An overview of PbB levels of occupationally exposed workers worldwide is presented in IARC 2006. In Table 24, data from EU countries are summarised:

Table 24: Measured blood lead concentrations in European workers (IARC, 2006)

Source	PbB (µg/L)	Reference
Lead acid battery factory, Finland	300 (mean)	(Erkkila et al., 1992)
Primary smelters, Sweden, 1950-1987	621-331 (mean; decreased over study period)	(Lundstrom et al., 1997)
Primary smelters, Sweden, 1987	320 (median), 50-474 (range)	(Gerhardsson et al., 1993)
Cadmium plant, UK, 1970-1979 Furnace area, UK, 1970-1979 Sinter area, UK, 1970-1979	280 (mean) 590 (mean) 560 (mean)	Ades and Kazantzis (1988)
Secondary smelters, Sweden, 1969-1985	621-331 (mean; decreased over study period)	(Gerhardsson et al., 1995)
Indoor range, powder gun, Sweden Indoor range, air gun, Sweden	138 (median), 69-228 (range) 84 (median), 20-222 (range)	Svensson et al., 1992
Indoor range for police officers, UK	300-590 (mean)	Smith 1976
Indoor range for soldiers, UK	193 (mean), 96-301 (range)	Brown (1983)
Automobile mechanics, Denmark 1976	400-448 (mean)	(Clausen and Rastogi, 1977)
Lead-exposed industry workers, Finland, 1973-1982	290-145 (median; decrease over study period)	(Antilla et al., 1995)
Electrician, Italy	660 (mean)	(Franco et al., 1994)

6.2.4 Biomonitoring analytical methods

There are analytical methods available to measure lead in blood that are able to reach concentrations well below the proposed BLV. Some examples of methods and techniques can be found in Table 25.

Further information on analytical methods for blood in lead including sampling preparations and typical LOQs for the different techniques can be found in several publications, see for example (Klotz and Goen, 2017).

Table 25: Example of analytical methods for lead in blood

Reference /METHOD	Analytical technique	LOQ
(Schaller, 2012)	flame atomic absorption spectrometry (FAAS)	15 µg lead/L in blood
(Schutz et al., 1996)	ICP –MS Inductively coupled plasma - mass spectroscopy	0.015 µg lead/L in blood
(Trzcinka-Ochocka et al., 2016)	ICP-MS GF-AAS	0.16 µg/L 1.0 µg/L and

7. Health Effects

The literature on health effects of lead in humans is extensive with very many epidemiological studies in workers and the general population, in particular among children. Due to the extensiveness of the lead database in humans, it is not possible to cite or review all the literature, thus this report does not provide a comprehensive review of all literature but summarises the key studies and focuses on the key endpoints and key epidemiological evidence for establishing occupational exposure limit values.

The toxicity of lead compounds is thought to be due to the lead cation, irrespective of whether the source is metallic lead or an inorganic lead compound and whether the source is occupational or via the environment. The human studies have almost exclusively used blood lead (PbB) as a measure of exposure or body burden and thus to relate health effects observed to measured PbB levels. However, one must note that environmental exposure to lead has declined up to 10-fold in a few decades (see section 6.2.2). Given that lead is stored in the bones for decades (half-life in bones 6 to 37 years), measurement of current PbB levels of adult workers does not reflect only current occupational exposure but also bone release of past occupational or environmental exposures. This complicates interpretation of studies on health effects linked to low lead exposures in adults today (see section 7.1.5). Individual studies have been published that measured lead in bones which provides information on the whole lead body burden at the time that the investigation was conducted and gives indications of the amount of lead exposure in the past (taking into account the half-life of the substance in bones). Blood lead and bone lead as exposure metrics are further discussed in section 7.1.5 in order to facilitate interpretation of the studies reported in section 7.

Another important consideration in human studies is that in epidemiological studies exposure groups are heterogeneous as regards individual exposures and there is variation between the studies in how this heterogeneity was considered and reported. For example when studying low exposures, some studies examined and reported groups where all subjects had exposures below a given PbB while other studies reported groups with mean exposures below such levels. In the latter case, using the group mean as exposure metric, it remains possible that individuals significantly above the mean PbB are driving the effect observed in that group.

Lead and its inorganic compounds have been shown to have diverse biological effects in humans. This document has focussed on neurological, renal, cardiovascular, haemopoietic, reproductive, genotoxic and carcinogenic effects observed in humans, with the focus on workers. Studies in the general population were also reviewed and some selected ones are briefly summarised in the Appendixes of this report.

Organic and inorganic lead compounds differ in terms of both toxicokinetics and toxicodynamics. Organo-lead compounds, such as tri-alkyl-lead and tetraalkyl-lead compounds, are more toxic than inorganic forms of lead (ATSDR, 2007), (UNEP, 2008). To some extent, organic lead compounds are metabolised to inorganic lead both in humans and in animals ((IARC, 2006)).

The literature database on adverse effects of lead in laboratory animals is similarly extensive, and considering the available human data, the animal data is only briefly addressed to reflect the full picture.

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

7.1.1 Human data

7.1.1.1 Inorganic compounds

Absorption

The oral and the inhalation routes are the most significant routes of exposure to lead.

When inhaled, in most inorganic forms lead deposited in the alveolar regions appears to be almost completely absorbed although it is possible that lead compounds of low solubility, such as lead sulphide, may accumulate to some extent in the lung (SCOEL, 2002).

Gastrointestinal absorption of lead is relatively poor in adults, but little is known about comparative rates of gastrointestinal absorption of different forms of lead (SCOEL, 2002). The efficiency of oral uptake of lead can vary depending on, for example particle size and shape (surface area), amount of time spent in the GI tract, concurrent food intake and the iron- and calcium status of the individual. A number of case reports prove that even one larger piece of lead ingested orally can create sufficient systemic exposure to produce clinical lead intoxication or even death. As a worst-case assumption, one can assume that the bioavailability of metallic lead is equivalent to that of soluble lead compounds such as for example lead acetate (LDAI, 2008).

Even though absorption directly through the skin is considered negligible, lead can become systemically available through hand-to-mouth behaviour. This route of exposure is possible for both children and adults that come in contact with lead containing articles, both at home and occupationally (LDAI, 2008).

Representative uptake values for lead in adults and children via different exposure routes are presented in the following Table 26. These representative uptake rates can be applied to calculate the uptake of lead oxide from individual exposure sources, but are put forward with the caveat that the kinetics of lead uptake can be curvilinear in nature and subject to modification by a number of variables. The uptake estimates given are thus representative values that are only applicable to relatively low exposure levels yielding blood lead levels <10 – 150 µg/L (ECHA, 2018a).

Table 26: Representative lead uptake rates (ECHA, 2018a)

Intake route	Adults	Children
Oral (food)	10%	50%
Oral (soil)	6%	30%
Dermal	<0.01%	<0.01%
Air (deep lung disposition)	100%	100%
Air (upper airway desposition)	Variable	NA

Distribution

EFSA (2010, updated 2013) summarised the information on the distribution of lead as follows. Under steady-state conditions, lead in blood is found primarily in the red blood cells (96 to 99 %). At PbB levels < 400 µg/L, whole PbB levels increase linearly with serum levels. At higher PbB levels a non-linear relationship is apparent, and the serum to blood ratio increases dramatically as levels increase, due to saturation of binding in erythrocytes.

Most of the lead found in erythrocytes is bound to proteins, the primary binding ligand being deltaaminolevulinic acid dehydratase (ALAD). Lead binding capacity of ALAD is approximately 8500 µg/L red blood cells (or approximately 400 µg/L whole blood) and the apparent dissociation constant is approximately 1.5 µg/L.

Once it is absorbed, inorganic lead appears to be distributed to both soft tissues (blood, liver, kidney, etc.) and mineralising systems (bones, teeth) in a similar manner regardless of the route of absorption. The distribution of lead seems to be similar in children and adults, but in adults a larger fraction of lead is stored in skeletal tissue. More than 90% of the total amount of accumulated lead ends up in bone and teeth in adults, while in children, 75% is accumulated in bones (ATSDR, 2007). The large pool of lead in adult bone maintains elevated PbB levels long after exogenous exposure has ended. Lead accumulation occurs predominantly in trabecular bone in children and both in trabecular and cortical bone in adults. About 8% of total body burden of lead is in soft tissues and 2% chelatable (EFSA, 2010, updated 2013). Red blood cells (0.4%), plasma (0.02%) and brain (0.1%) account for a minor part of the total body burden.

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

Lead may be mobilised from the bones to form a major source of blood lead in persons with previous exposures (SCOEL, 2002).

Lead concentration is also related to calcium status; stored lead can therefore be released from bone tissue into the blood stream under the condition of calcium deficiency or osteoporosis (LDAI, 2008).

It should be noted that lead is easily transferred to the foetus via the placenta during pregnancy. The foetal/maternal blood lead concentration ratio is approximately 0.9 (Carbone et al., 1998). As explained by Bradbury and Deane (1993) the blood-cerebral barrier is permeable to lead ions and the most sensitive end-point is connected to neurotoxicity and developmental effects (ECHA, 2018a).

Metabolism

The lead ion is not metabolised in the body.

Excretion

Klotz and Goen (2017) summarised that the main elimination route of lead is via the urine, which accounts for 75 to 80% of the total excretion. The secondary route is the gastrointestinal elimination pathway. Other elimination routes, for example, hair, nails and sweat, cover altogether less than 8% of the total excretion. Additional elimination takes place within the lactation period by breast milk. In general, the rate of elimination is very slow. As the various tissues and compartments provide different characteristics of lead storage and exchange, the lead blood level displays multiphasic elimination kinetics. After cessation of lead exposure the blood concentration decreases in the first phase with a half-life of 29 to 36 days. Due to counterbalancing from soft tissues and the different bone compartments, further compartment elimination processes have to be considered with half-life values of 1.2 years for a second compartment and 13 years for a third compartment. *In vivo* studies on the decrease of the lead concentration in bone demonstrated half-lifes of 6 to 37 years.

The half-life is longer in cortical bone than in trabecular bone. In young children, continuous growth results in constant bone remodeling, and bone Pb is exchanged with PbB much more frequently than in adults (reviewed in Barbosa et al. (2005) and Hu et al. (2007). Due to this long half-life, lead can lead to an internal exposure long after the external exposure has ended, by redistribution between different tissue pools (LDAI, 2008).

The mobilisation of lead from bone increases during pregnancy when the maternal bone is catabolised to produce the fetal skeleton. Lead content in bone decreases also with aging. This decrease is most pronounced in females and may be due to osteoporosis and consequent release of lead from bone to blood. Lead levels also rapidly equilibrate between blood and other soft tissues, however, data on turnover in other organs is limited (NTP, 2012).

7.1.1.2 Organic compounds

In an inhalation study on volunteers with radioactively labelled tetraethyl lead (TEL) and tetramethyl lead (TML) (^{203}Pb; concentration 1 mg/m^3, 10 – 40 breaths), 37% of the inhaled TEL and 51 % of the TML was retained. Within 48 hours 20% TEL and 40% TML were exhaled again. The study is only available in the form of an abstract from which the details of the study are not apparent (DFG, 1995).

According to early data, under conditions similar to those found in practice, 6 % of the absorbed dose of lead alkyls was taken up through the skin (DFG, 1995).

Ingested lead alkyls are absorbed via the gastro-intestinal tract. According to (Grandjean and Nielsen, 1979), both tetraalkyl lead compounds (TEL, TML) are transformed in part to the corresponding trialkyllead soon after oral uptake by the hydrochloric acid in the stomach (DFG, 1995).

Tetraethyl lead (TEL) is metabolised via oxidative dealkylation to triethyl lead, diethyl lead, and inorganic lead. Oxidative dealkylation is catalysed in the endoplasmatic reticulum of the liver cells by cytochrome P450. The urine metabolites triethyl and diethyl lead have, in contrast to TEL, ionic character and therefore their distributional behaviour in the organism is different from that of tetraethyl lead. Similar metabolism of TEL and TML is assumed (Klotz and Goen, 2017).

In an investigation on the excretion of alkyllead species, excretion products in the urine were determined in a patient intoxicated with TEL on the 21st day after exposure: 50% of the total amount of lead excreted was in the form of diethyl lead and only 2 % was triethyl lead, which corresponds in principle with later findings on the excretion of triethyl lead and diethyl lead in persons occupationally exposed to TEL. The highest concentrations of lead in persons intoxicated with TEL were found in the liver, followed by the kidneys and brain (DFG, 1995).

7.1.2 Animal data

According to EFSA (2010, updated 2013), studies in experimental animals provide additional evidence for an age-dependence of gastrointestinal absorption of lead. Absorption of lead, administered by oral gavage as lead acetate (6.37 mg lead/kg), was 38 % in juvenile Rhesus monkeys compared to 26 % in adult female monkeys (Pounds et al., 1978). Rat pups absorb approximately 40 to 50 times more lead via the diet than adult rats do (Kostial et al., 1978, Aungst et al., 1981, Forbes and Reina, 1972).

7.1.3 In vitro data

No relevant in vitro information that would contribute to the evaluation of toxicokinetics has been identified.

7.1.4 Toxicokinetic modelling

ATSDR (2007) reports that several models of the toxicokinetics of lead in humans have been developed such as Bert et al. (1989), US EPA (1994a), US EPA (1994b), Leggett (1993), Marcus (1985b), Marcus (1985c), Marcus (1985a), O'Flaherty (1993), Rabinowitz et al. (1976). ATSDR noted major uncertainties in these models which include: (1) absence of calibration data for the kinetics of lead in blood and bone in children in association with exposures that have been quantified with high certainty; (2) absence of calibration data

on bone lead concentrations in adolescents and adults in association with exposures that have been quantified with high certainty; (3) absence of data on the absolute bioavailability of ingested lead in older children and adolescents; (4) incomplete understanding of lead kinetics during periods of changing bone metabolism, including adolescence, pregnancy, and menopause; and (5) incomplete understanding of inter- and intra-individual variability in model parameters values in humans. In addition, there is a need for models that predict concentrations of lead in tissues other than blood.

According to ATSDR (2007) "Pharmacokinetic models have been developed that attempt to relate environmental levels to PbBs (Leggett 1993; O'Flaherty 1995). The Integrated Exposure Uptake Biokinetic Model (IEUBK) developed by EPA is one of the most extensive efforts to date to make population-based predictions of PbBs based upon environmental data. The model incorporates both exposure/uptake parameters and a biokinetic component to estimate the PbB distribution in the exposed population (EPA 1994)". EFSA (2010, updated 2013) noted that the IEUBK is the most widely validated exposure assessment model and is a classic multicompartmental model linked to an exposure and probabilistic model of PbB distributions in populations of children 0 to 7 years. The main limitation of the IEUBK model is that its applicability is restricted to children.

According to EFSA (2010, updated 2013) "The Carlisle and Wade model, used by the California EPA, considers lead from dietary, drinking water, soil and dust and an empirically determined pathway-specific factor that reflects the ratio between lead intake and B-Pb. The model estimates B-Pb using exposure from dietary and non-dietary sources, their corresponding medium-specific contact rates and an empirically determined ratio between intake and blood level (Carlisle and Wade, 1992). The Carlisle and Wade model has successfully been applied to adults but is less suitable for children (Lakind, 1998)."

7.1.5 Biological monitoring

Lead in blood

Most of the information on human exposure to lead and the consequent health effects is based on measurements of lead in blood (PbB). Relevant studies mainly in workers correlating effects with PbB measurements are summarised in sections 7.2 to 7.8.

As explained above under distribution, PbB has two main pools. The short-half-life pool is in the blood and soft tissues and the long-half-life pool is mainly in the skeleton. Thus, the PbB reflects a combination of recent exposure and that which occurred several years previously (EFSA, 2010, updated 2013).

Lead in blood does not necessarily correlate with the total body burden of lead (Lauwerys and Hoet, 2001). A major advantage of this measure is the wealth of information that can be linked to PbB particularly the effects of low environmental exposure on central nervous system functions in children (EFSA, 2010, updated 2013).

PbB is usually determined from an analysis of venous blood. Most of the lead in blood is present in the cells. The relationship between lead uptake and PbB is curvilinear. At low lead uptake there is a steady linear increase in PbB with increasing uptake, while at high lead uptakes, the curve flattens out as binding sites in erythrocytes become saturated (EFSA, 2010, updated 2013).

In this regard, it is noteworthy that there has been a clear decline in environmental exposure to lead during the past decades. This is due to elimination of lead for example in petrol or paint and other control measures. This complicates studying health effects from low lead exposures in adults today. Notably using concurrent PbB level as exposure metric in adults today reflects not only their current exposure but may have a significant contribution from the bone-release of their past environmental burden in earlier life. In those subjects without excessive exposure to Pb, 45–75% of the Pb in blood may have come from bone (NTP, 2012).

Lead in bones

Bone lead levels represent the cumulative dose of lead over several decades. Lead concentration in bone can be determined *in vivo* by non-invasive methods based on K-x-ray fluorescence (KXRF) (Barbosa et al., 2005, Hu et al., 2007). Bone lead measurements are, however, technically challenging and limited to few research institutions. They are also subject to substantial measurement error due to uncertainties in bone mass, thickness of the soft tissue covering the bone, variations in the placement of the instrument in relation to target bone, subject movements during the measurement period, variability in measurement time and calibration issues, among other factors. They are not used routinely to monitor lead exposure for example among workers. However, such measurements from tibia (shinbone), patella (kneecap) or calcaneus (heel bone) have been used in some epidemiologic studies as a metric of cumulative dose. The most commonly used KXRF devices have a relatively high detection limit (~10 µg/g bone mineral) and a wide error of measurement, so studies that use this method may underestimate the effect on health (NTP, 2012).

7.1.6 Summary

Lead is most easily taken up into the body through inhalation or ingestion, dermal uptake makes a negligible contribution to systemic lead levels. Tetraethyl lead is metabolised via oxidative dealkylation to triethyl lead, diethyl lead, and inorganic lead. Once taken up into the body, lead is not further metabolised. However, it will distribute to various tissue compartments such as blood, soft tissue and bone. The half-life of lead in the body varies depending on the body compartment; lead is retained far longer in bones, up to several decades. Lead in blood (PbB) is the most prominent and best validated biomarker for current lead exposure. Lead in bones such as tibia, patella or calcaneus, is another biomarker for lead exposure which represents the cumulative exposure to lead but is not measured routinely.

7.2 Acute toxicity

7.2.1 Human data

7.2.1.1 Inorganic compounds

Very limited data are available describing the acute toxicity of lead. According to KEMI (2012) human data for acute toxicity actually describe effects after exposure to lead over a period of weeks or years (sub-acute or chronic duration). The US National Institute of Occupational Safety and Health (NIOSH) estimated the acute lethal dose for an adult to be approximately 21 grams (equivalent to 450 mg/kg bw) by the oral route, and 21 000 mg/m^3 for 30 minutes via inhalation (ECHA, 2018b).

Acute lead intoxication in children has been reported following the ingestion of lead paint chips containing 1% or higher of lead (Lin-Fu, 1992). Acute lead intoxication is serious and can be fatal, especially in children. In 2006, a four year old boy in the USA died after swallowing a bracelet charm containing 99% lead. The boy's blood lead level was 1800 µg/L at the time of death CDC (2006). It should be noted that during acute lead poisoning (e.g. after oral ingestion of an object composed of lead), the lead blood level reaches a peak, but it does not reflect the total amount present in the body (ECHA, 2018c).

Symptoms of acute lead poisoning include but are not limited to: dullness, restlessness, irritation, poor concentration, muscle "vibration" and weakness, headaches, abdominal discomfort and cramping, diarrhoea, memory loss and an altered mental state including hallucinations. These effects can occur at PbB levels of 800 to 1000 µg/L in children (TNO, 2005). Furthermore, the US EPA (2013a) has identified a LOAEL value of 600 to 1000 µg/L related to colic in children as a result of lead poisoning. Then a LOAEL of 800 µg/L (ATSDR, 2007) and a NOAEL of 400 µg/L (TNO, 2005) could be identified for acute effects in

children. Due to the long elimination half-life of lead in the body, chronic toxicity should generally be considered a greater risk than acute toxicity (ECHA, 2018b).

7.2.1.2 Organic compounds

The acute lethal dose of organolead compounds for humans is not known exactly but can be estimated. A minimum lethal oral dose of 15 ml tetraethyl lead (TEL; approx. 0.35 g/kg bw) was estimated based on 16 accidental or suicidal cases of intoxication (11 men and 5 women from 16 to 71 years old; observed in Poland 1979 to 1983). The first symptoms of intoxication are known to occur after ingestion of 6 ml TEL (approx. 0.14 g/kg bw). A LD_{50} value of 0.25 g TEL/kg body weight for humans was estimated (DFG, 1995).

The first intoxications with TEL were reported only a few months after the start of commercial production in October 1924. By 1984 150 cases of intoxication with TEL with a lethal outcome were known. Cases of intoxication during cleaning of petrol tanks have also been described (DFG, 1995)

The latency period between TEL exposure and the occurrence of first symptoms ranges from a few hours in severe cases to approx. 10 days. Signs of intoxication described include loss of appetite, nausea and vomiting, sleeplessness, weakness, headache, aggression, depression, irritability, diffuse pains, tremor, hyperactivity, increased proprioceptive muscle reflexes, muscle weakness, concentration and memory difficulties, confusion and unusual sensory sensations such as for example metallic taste in the mouth (DFG, 1995).

If large amounts of TEL are taken in orally gastro-intestinal symptoms are predominant (vomiting, abdominal pains, diarrhoea). From the occurrence of the first symptoms it can take hours or even days until the condition of the patient becomes critical. Acute psychosis, convulsions, delirium, fever and coma then develop. Further symptoms accompanying organolead intoxication include hypotonia and bradycardia. The longer the symptom free phase after acute intoxication lasts, the better the prognosis. Even after very severe clinical symptoms practically complete recovery is supposed to have taken place within two to six months (DFG, 1995).

Autopsy of intoxicated persons revealed degenerative changes of nerve cells of Auerbach's plexus and Meissner's plexus and in the CNS reduction of the neurons in the cortex, coagulation necrosis of the ganglions and myelinoclastic changes in the medulla oblongata and spongial transformation of the white matter (DFG, 1995).

7.2.2 Animal data

As reported by EFSA (2010, updated 2013), lead has been described as a classic chronic poison. Health effects are generally not observed after a single exposure, and oral LD_{50} values for lead salts have been reported to be greater than 2000 mg/kg bw. The lowest observed lethal doses in animals after multiple short-term oral exposure to lead acetate, lead chlorate, lead nitrate, lead oleate, lead oxide or lead sulphate range from 300 to 4,000 mg/kg bw (JECFA, 2000).

7.2.3 *In vitro* data

No relevant *in vitro* information for the evaluation of acute toxicity has been identified.

7.2.4 Summary

Acute lead intoxication is serious and can be fatal, especially in children. Symptoms of acute lead poisoning include but are not limited to: dullness, restlessness, irritation, poor concentration, muscle "vibration" and weakness, headaches, abdominal discomfort and cramping, diarrhoea, memory loss and an altered mental state including hallucinations. These effects can occur at PbB levels of 800 to 1000 µg/L in children (TNO, 2005). The US National Institute of Occupational Safety and Health (NIOSH) estimated the acute lethal

dose for an adult to be approximately 21 grams (equivalent to 450 mg/kg bw) by the oral route, and 21 000 mg/m^3 for 30 minutes via inhalation (LDAI, 2008). Due to the long elimination half-life of lead in the body, chronic toxicity should generally be considered a greater risk than acute toxicity.

The acute minimum lethal dose of organolead compounds for humans was estimated with 15 mL tetraethyl lead, approximately 350 mg/kg bw. The first symptoms of intoxication are known to occur after ingestion of 6 mL TEL (approx. 140 mg/kg bw). An LD_{50} value of 250 mg tetraethyllead/kg bw was estimated for humans (DFG, 1995).

7.3 Specific target organ toxicity/Repeated dose toxicity

According to the group entry in Annex IV of CLP, all lead compounds are classified as STOT RE 1;H372 or STOT RE 2;H373 (causes or may cause damage to organs through prolonged or repeated exposure). Affected organs and route of exposure have not been indicated in these entries.

Adverse health effects of Pb have been observed in every organ system. This is because the mechanisms that induce toxicity (mimicking calcium action and/or disruption of calcium homeostasis) are common to all cell types and Pb is widely distributed throughout the body (ATSDR 2019).

7.3.1 Human data

The literature evaluating the health effects of Pb is enormous and includes an extensive database in humans. Information on health effects reviewed below is taken from epidemiological studies in lead-exposed workers that have investigated neurological, renal, cardiovascular, haematological and immunological effects that were published since the year 2000 and for which PbB levels have been reported in the range of 400 µg/L and below. To evaluate a biological limit value (BLV) for women of childbearing age, the higher sensitivity of the developing nervous system of children exposed in utero has to be considered. The conclusions of the latest reviews are summarised under "Neurological effects".

Studies in workers with measured low lead exposure (<100 µg/L) but assumed exposure to other relevant hazardous substances are not included. These include studies in painters for which with potential co-exposure to cadmium and/or solvents such as benzene is not excluded (Conterato et al., 2013, Mohammad et al., 2008), car repair workers, taxi drivers, or workers working in a polluted environment (Ukaejiofo et al., 2009).

7.3.1.1 Neurological effects

Studies investigating workers

Nerve conducting velocity

SCOEL (2002) summarised that studies of peripheral nerve toxicity, based upon measurement of nerve conduction velocity (NCV) provide evidence of a causal relationship between a reduction in NCV and PbB greater than 700 µg/L, with effects possible at PbB levels as low as 300 µg/L.

Krieg et al. (2008) performed a meta-analysis of 49 studies investigating the effects of lead exposure on nerve conduction in adults, mainly with occupational exposure to lead. 1629 subjects were included in the control groups (849 males, 230 females) and 2825 subjects in the exposed groups (1717 males, 255 females). Gender of the subjects was not always reported. Differences between the control and exposed groups, and the slopes between nerve conduction measurements and $\log_{10}$ blood lead concentrations were estimated using mixed models. Conduction velocity was reduced in the median, ulnar, and radial nerves in the arm, and in the deep peroneal nerve in the leg. Distal latencies of the median, ulnar, and deep peroneal nerves were longer. No changes in the amplitudes of

compound muscle or nerve action potentials were detected. The lowest concentration at which a relationship with blood lead could be detected was 330 µg/L for the nerve conduction velocity of the median sensory nerve.

Yu et al. (2019) investigated peripheral nerve conduction velocity in 328 newly hired men (mean age 28.3 years; participation rate 82.7%). Mean blood lead levels were 45.4 µg/L (IQR 26.0–89.0 µg/L). Subgroups with different ranges of mean blood lead levels (18, 46, 110 µg/L) were analysed. There was no association between blood lead levels and autonomic nervous activity or nerve conduction velocity.

Neurobehavioral effects

SCOEL (2002)(2002) concluded that consistent neurobehavioral effects which are to be considered as "adverse" appear in a multiplicity of studies at PbB levels of 400 µg/L and above.

Seeber et al. (2002) summarised two different meta-analytical analyses consisting of the publication by Seeber et al. (2002) and an expert opinion elaborated for the German Battery Association (Exponent 2000) on neurobehavioural effects in order to show the main tendencies of 24 selected publications on the matter. Calculations of effect sizes are compiled for 12 tests analysed in two meta-analyses and of ten tests analysed in one meta-analysis. The survey of six tests of learning and memory indicates effects in two tests, covering Logical Memory and Visual Reproduction. Impairments in attention and visuospatial information processing were described in four tests, namely Simple Reaction, Attention Test d2, Block Design, and Picture Completion. The survey of four tests for psychomotor functions shows impairments for three tests, namely Santa Ana, Grooved Pegboard, and Eye-hand Coordination. These test results provide evidence for subtle deficits being associated with average blood lead levels between 370 and 520 µg/L.

Krieg et al. (2005) performed a survey to (1) assess the relationship between blood lead levels and neurobehavioral test performance in a nationally representative sample of adults from the third National Health and Nutrition Evaluation Survey (see below) and (2) analysed the results from previously published studies of occupational lead exposure that used the same neurobehavioral tests (performance on a simple reaction time, a symbol-digit substitution, and a serial digit learning test) as those included in the survey. 26 occupational studies were identified. The average blood lead levels of the control groups ranged from 36.7 to 204 µg/L, with an average blood lead level in the control groups of 114 µg/L. The average PbB levels of the exposed groups ranged from 240 to 720 µg/L, with the average PbB levels of 411 µg/L. The groups exposed to lead (411 µg/L) consistently performed worse than control groups on the simple reaction time and digit-symbol substitution tests.

Murata et al. (2009) reviewed adverse effects of lead. Based on data from previous reports using a BMD approach (Araki et al., 1992, Araki and Honma, 1976, Iwata et al., 2005, Murata et al., 1995, Mutti and Smargiassi, 1998), the critical organ system for lead toxicity in workers was thought to be the nervous system and the BPb level (number-weighted mean) of reversible neurological effects was between 107 and 175 µg/L.

Vlasak et al. (2019) performed a meta-analysis aimed to investigate associations between neurocognitive performance and lead exposure in adults and further assessed potential effect thresholds. Articles indexed in Medline published until January 2017 reporting associations between lead exposure, blood lead, cognitive abilities and sensomotoric performance were included. The unbiased, standardized mean differences between lead exposure and control groups extracted from the primary studies were pooled using a three-level, random-effects meta-analytic model with a restricted maximum likelihood estimator. Moderator analyses were conducted using weighted, mixed effects regression analyses. The authors identified 22 articles (n=3,849 participants, mean age 39.94±7.87 years) published between 1976 and 2014 reporting lead exposure effects on cognitive and sensomotoric parameters (verbal abilities, visuospatial abilities, memory, attention,

psychomotor function). The mean blood lead level in the exposed group was 340.8 ± 136.3 µg/L, and for the control group 121.8 ± 71.9 µg/L. On average, blood lead concentrations were 210.9 ± 64.4 µg/L higher in exposed than in control subjects. After exclusion of outliers, the random-effects three-level meta-analysis identified a significant ($p < 0.001$) pooled mean difference between exposure and control groups. Except for a smaller effect in the digit symbol test ($p < 0.05$), lead exposure did not result in different outcomes across the examined cognitive measures. Due to methodological limitations of the studies (low number of eligible samples), no threshold for cognitive impairment could be derived. Furthermore, the effect sizes were limited. Based on a marginally significant ($p = 0.06$) effect of difference in exposure levels, a blood lead increase of 100 µg/L translated into a decline in cognitive abilities of Hedges $g = 0.09$. As a rule of thumb, Cohen[31] considered Hedges g effects of 0.2 "small effects", 0.5 as "medium effects" and 0.8 as "large effects". Using this scale, a Hedges g of 0.09 could be interpreted as a small effect.

Relevant studies investigating neurological effects in lead-exposed workers with PbB-levels of 400 µg/L or below published since the year 2000 are summarised in Table 27. The studies are sorted by decreasing PbB levels.

Table 27: Selected individual studies on neurological effects in lead-exposed workers

Blood lead (µg/L)[1)]	Bone lead (µg/g)[2)]	Cohorts[3)]	Reported effects	Reference
434±90 (<400 - >700)		72 male workers, mean age 39.4±10.4, 13.0±8.7 years employed, grouped according to PbB levels ranging from <400 µg/L to >700 µg/L No controls	**Cognitive tests** No evidence of severe cognitive impairment. Mean values of MMSE (Mini-Mental State Exam), IST (Information Sampling Task), DRT (Digit Repetition Test) and CDT (Clock Drawing Test) scores showed a statistically significant tendency for a decrease with increase of PbB levels. The greater part of positively screened workers had blood lead concentrations between 400 µg/L and 500 µg/L.	(Nestorova et al., 2018)
>400 (before and after 1980) >400 (before 1980) <400 (after 1980)		40 workers with continuing high exposure (H-H) 40 workers with previous high but since 1980 lower exposure (H-L); age, education, and years of employment similar for both groups; no controls	**Neuropsychological performance** 5 neuropsychological measures; verbal memory performance sign. better in H-L workers (after adjustment for the covariates) suggests that reversibility of function may occur when proximate PbB levels are maintained below 400 µg/L.	(Lindgren et al., 2003) not yet ordered

[31] Cohen, J. (1977). Statistical power analysis for the behavioural sciences. Routledge.

Blood lead (µg/L)[1)]	Bone lead (µg/g)[2)]	Cohorts[3)]	Reported effects	Reference
400±150 (60-890) *Not reported*		121 workers, 66% smokers, battery recycling, Japan, 60 controls, matched for age, height, body mass index, alcohol consumption, 35% smokers	**Postural balance** affected: $BMD_{95\%}$ 144 (121-173) µg/L	(Iwata et al., 2005)
320±150 53±18		938 workers, 6 industries, mean age 40, South Korea 135 controls, mean age 35, higher education status than workers	**Neurobehavioral and peripheral nervous system** Blood lead negatively associated with 8 tests (psychomotor speed, executive abilities, verbal memory and learning, visual memory, nonverbal intelligence, manual dexterity, neuropsychiatric status, peripheral nervous system sensory-vibration threshold, peripheral nervous system motor strength); **suggested threshold 180 µg/L**	(Schwartz et al., 2001)
314±142 (40-760)	38.4±43 (-7-338)^{T}	Longitudinal study, 1997 to 2001, 3 examinations, 576 current and former workers, South Korea (follow up of Schwartz et al., 2001)	**Neurobehavioral test scores** Consistent associations of blood lead with test scores at baseline and of tibia lead with declines in test scores over the next year, mainly in executive abilities, manual dexterity, and peripheral vibration threshold. Lead likely has an acute effect on neurobehavioral test scores as a function of recent dose and a longer-term (possibly progressive) effect on cognitive decline as a function of cumulative dose.	(Schwartz et al., 2005)
309±167	33.5±43.4^{T} 75.1±101^{P}	652 lead workers	**Neurobehavioral Test Scores** Patella lead associated with worse performance on 7/19 tests (manual dexterity, sensory vibration threshold, and depressive symptoms). Associations of patella lead with cognitive function similar to those with blood lead or tibia lead but of lower magnitude	(Dorsey et al., 2006)
308±112 55±27		47 currently exposed workers 48 formerly exposed workers matched for age and verbal intelligence	**Cognitive tests** Currently exposed workers performed worse than formerly exposed in the Modified Wisconsin Card Sorting Test and Block Design Test. No effects on Visual Recognition Test, Simple Reaction Time, Choice Reaction and Digit Symbol Substitution	(Winker et al., 2006)
306±102 430±61 253±63 *Not reported*		70 male workers, copper works facilities, Germany 21/70 high PbB 49 /70 low PbB 27 male controls	**Psychometric/psychophysio-logical performance** Only main motor performance parameters (slowed poststrain resetting behaviour of the vegetative nervous system) correlated with PbB levels	(Böckelmann et al., 2011)

Blood lead (µg/L)[1)]	Bone lead (µg/g)[2)]	Cohorts[3)]	Reported effects	Reference
290 (160-420)	39 (-12-90)^{T}	61 lead smelter workers, Canada, mean age 40 years, 19 years employed; no controls	**Cerebral white matter** Changes correlated with working lifetime weighted integrated blood lead (8260 (650-14515) µg year/L)	(Bleecker et al., 2007b)
263±74.4 (60-480) LoCR 259±107 (60-620) HiCR		112 lead smelter workers, Canada, 56 pairs of workers of low (LoCR) and high (HiCR) cognitive reserve, CR groups of comparable mean (38 years), years employed (14), alcohol use, PbB levels	**Cognitive reserve protective for lead effects (neurobehavioral performance)** Cognitive reserve: maintenance of cognitive performance in spite of ongoing underlying brain pathology	(Bleecker et al., 2007a)
260±71 (130-430)	40±23.8^{T}	74 lead smelter workers, Canada, mean age 44, 20 years employed no controls	**Peripheral nerve function** Chronic blood lead associated with impairment of large and small myelinated sensory nerve fibers	(Bleecker et al., 2005)
286±146 124±47		16 female workers, printing, China, mean age 35±5, 13±5 years employed 36 controls	**Neurobehavioral Core Test Battery** Simple reaction time, Digit Symbol, Pursuit Aiming (PA) II and correct PA significantly lower in the Pb exposed group. All negative Profile Mood States scores slightly higher in workers (some with a significant difference)	(Qiao et al., 2001)
263±120 (1994) 83±69 (1997) 69±42		27 workers, lead glaze factory, Taiwan, mean age 39.7±9.6 Controls mean age 39.6±8.5	**Neurobehavioral Performance** 263 µg/L: sign. difference in 1/8 tests (finger tapping) Reduction from 263 µg/L to 83 µg/L: improvements in 3 subtests: finger tapping, pattern comparison, pattern memory	(Chuang et al., 2005)
170±104 34±11	61.6±30.2^{T} 66.3±19.5^{P} 18.5±22.4^{T} 7.14±9.81^{P}	22 workers, lead paint factory, mean age 46, Taiwan 18 controls matched for age, BMI, sex, smoking, alcohol drinking	**Brain metabolism** Blood and bone Pb levels significantly associated with altered brain metabolism especially in the occipital lobe suggesting that lead induces neuronal and axonal damage or loss. *Not controlled for exposure to other hazardous substances*	(Hsieh et al., 2009a)
115±12 32±12	51.7±1.79^{T} 61.2±1.35^{P} 20.8±2.88^{T} 14.2±1.76^{P}	Prospective cohort study, Taiwan 19 male and female workers, lead paint factory, mean age 44.2±6.9, 11.8±8.4 years exposed 18 controls, 46.9±10.0 years old	**Microstructure of white matter** Subclinical microstructural (early) changes in the white matter of workers *Not controlled for exposure to other hazardous substances such as cadmium*	(Hsieh et al., 2009b)

Blood lead (µg/L)[1)]	Bone lead (µg/g)[2)]	Cohorts[3)]	Reported effects	Reference
120 median (80-120), 30 (30-40)	57 (20-86)[T] 12 (8-19)[T]	89 former lead battery workers, USA; mean age 54, 25±8 years exposed, 6 years since last exposure 52 controls, 55 years old	**Cognitive function** Reduced cognitive function following chronic exposure; higher bone Pb levels in workers older than 55 years; cumulative body burden most likely responsible for the progressive cognitive decrement because of aging	(Khalil et al., 2009a)
Not measured	23.99±18.46[T]	513 former male organolead manufacturing workers, mean age 60±7.9, 8.6 years exposure, 18 years since last exposure	**Cognitive function** Cumulative tibia Pb dose sign. associated with adverse function in the visuo-construction, executive function, and eye-hand coordination domains	(Caffo et al., 2008)
54±27 47±25		48 former workers, males, mean age 40, 10 years exposed, 5 years since last exposure 48 matched controls	**Cognitive function** No effects on modified Wisconsin card sorting test, block design test, visual recognition test, simple reaction time, choice reaction and digit symbol substitution. Lead exposure was assessed using both current and cumulative measurements.	(Winker et al., 2005)
45 (13-122)		328 newly hired lead workers, mean age 28±10	**Nerve conduction velocity** No sign. trend in workers with low, medium and high PbB levels (18, 46, 110 µg/L, respectively)	(Yu et al., 2019)
41 GM (9-135) 20 (12-65)		31 formerly exposed workers, mean age 60, 9 years exposed, 12 years since last exposure, Brazil 34 controls, mean age 59, higher education level than workers	**Neural activation and cognitive performance/working memory** Formerly lead-exposed workers showed poorer working memory performance during high memory loading task than the healthy subjects and reduced activation in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, pre supplementary motor areas, and inferior parietal cortex.	(Seo et al., 2014)

[1)] mean values ± SD (range) if not stated otherwise; GM meometric mean
[2)] cross-sectional studies if not state otherwise

In the following, the result of the studies presented in Table 27 are summarised.

In a meta-analysis, the LOAEL derived for nerve conducting velocity in workers was 330 µg/L (Krieg et al., 2008). In another meta-analysis (Seeber et al., 2002) evidence for subtle neurobehavioral deficits were reported between 370 and 520 µg/L. A third meta-analysis reported changes in cognitive and sensory motor parameters (verbal abilities, visuospatial abilities, memory, attention, psychomotor function) in lead exposed workers with mean blood lead concentrations of 340.8±136.3 µg/L (Vlasak et al., 2019). At mean PbB levels between 310 and 200 µg/L, several further studies indicated effects observed in neurobehavioral tests (Böckelmann et al., 2011; Dorsey et al., 2006; Qiao et al., 2001; Chuang et al., 2005; Winker et al., 2006). Based on a cross-sectional study in 938 workers, **Schwartz et al. (2001) suggested a threshold for neurobehavioral effects of 180 µg/L**. In lead paint factory workers changes in brain metabolism were reported at mean PbB levels of 170 µg/L (Hsieh et al., 2009a) and early changes in the white matter at 115 µg/L (Hsieh et al., 2009b); however, no adjustment was made for exposure to

other potentially hazardous substances (such as cadmium or solvents). Based on data from previous reports using a BMD approach, the critical blood lead level for effects on the nervous system was calculated to be between 107 and 175 µg/L (Murata et al., 2009). Iwata et al. (2005) calculated a $BMD_{95\%}$ of 144 (121-173) µg/L for an effect on postural balance.

In older workers with past lead exposure, reduced cognitive function at current median PbB levels of 120 µg/L were reported (Khalil et al., 2009a) as well as adverse functional impairments that were associated with cumulative Pb exposure in bone (tibia) (Caffo et al., 2008). Also observed were poorer working memory performance during a high memory loading task and reduced activation in the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, pre supplementary motor areas, and inferior parietal cortex (Seo et al., 2014).

In newly hired lead workers with mean PbB levels of 45 µg/L (range 13-122 µg/L) no changes in nerve conducting velocity could be observed (Yu et al., 2019).

Tetraethyl lead

Intoxication in "petrol sniffers" has been repeatedly reported in the international literature. As a result of such chronic exposure excitability, depression, headache, low blood pressure, neurasthenia, tremor, ataxia, chorea and hallucinations occur. Patients, who often sniffed petrol for many years from an early age, were often mentally greatly retarded. With increased blood lead values abnormal EEG findings were recorded. Autopsy of petrol sniffers who had died showed brain oedema, necrosis of nerve cells in the hippocampus, loss of Purkinje's cells in the cerebellum and demyelination of the pons , as well as atrophy of the cerebellum and altogether a reduced brain weight (DFG, 1995) (DFG, 1995).

Robinson carried out investigations on the mortality and the general state of health of TEL workers who had handled TEL for at least 20 years. In a mortality study 592 workers exposed to TEL (51 deaths) were compared with 660 non-exposed workers (68 deaths) (Robinson, 1974). In a further cohort study on the state of health 153 workers exposed to TEL and 153 non-exposed workers were investigated (Robinson, 1976). Examinations were carried out and data collected on height and weight, systolic and diastolic bloodpressure, haemoglobin content of the blood, electrocardiogram, number of children and days sick off work. With regard to the state of health and mortality, between the workers exposed to TEL and the non-exposed control groups in these studies no significant differences were found. The meaningfulness of these studies were, however, called into question later by Grandjean and Nielsen (Grandjean and Nielsen, 1979). Their criticism was that at the beginning of the mortality study 89 % of the TEL workers were still under the age of 40. Furthermore, the medical examination did not determine any specific long-term effects such as cerebral functions; moreover, no worker was investigated who had in the meantime left the firm (DFG, 1995).

In 1595 male workers who were employed in a refinery between 1949 and 1982 increased mortality due to lung, kidney and brain tumours as well as leukaemia was determined (Bertazzi et al., 1989). To what extent TEL was involved in the induction of tumours could not be deduced from these data as exposures to mixtures of hydrocarbons, hydrogen sulphide and other substances were involved (DFG, 1995).

Further, investigations on 38 employees in a German factory producing lead alkyls have been described (Seeber et al., 1990). The exposure to tetraethyllead was considerably greater than to tetramethyllead. The average tetraethyllead exposure varied individually between 0.6 and 43.1 µg/m^3 (calculated as Pb). In this study extensive neuropsychological investigations were carried out in which individual correlations between exposure indicators and behavioural parameters were apparent. In the course of the investigation these proved, however, to be inconstant and thus could not be validated. Therefore, the

range of exposure described in this study can be considered as being below a no effect level with regard to the occurrence of CNS effects (DFG, 1995).

(Zhang et al., 1994) reported on changes in some clinical parameters in a study in the province Hubei/China in which 277 petrol depot workers exposed to tetraethyllead, 36 municipal traffic police and 342 public office clerks were investigated. The average tetraethyllead exposures (± sx) in these groups were 1.1 ± 0.4 (office employees), 5.2 ± 2.4 (traffic police) and 84.8 ± 34.3 µg/m^3 tetraethyllead (calculated as lead). No conspicuous changes were found in the traffic police. There was a significantly increased occurrence of tremor (hands, tongue, eye-lids) in the employees at the petrol depot, which was recognisable above exposure levels of 50 µg/m^3 (as lead) and intensified with greater exposures in a dose-dependent manner. Furthermore, sinus bradycardia was seen more often in the petrol depot employees than in the office workers. As differences in the physical activity and fitness between these two groups must be taken into consideration, this finding is difficult to interpret. Within the group of petrol depot workers a clear tendency towards a dose-dependent increase in such changes with the level of tetraethyllead exposure was, however, once again conspicuous (DFG, 1995).

7.3.1.2 Renal effects

Exposure to high level of lead (>600 µg/L) may cause renal dysfunction (Assi et al., 2016).

ATSDR (2019) noted that numerous epidemiologic studies in adults show that exposure to Pb can cause altered kidney function and contribute to the development of chronic kidney disease (CKD). Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis (Diamond 2005; Goyer 1989; Loghman-Adham 1997). Functional deficits in humans that have been associated with excessive Pb exposure include enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed GFR. A few studies have revealed histopathological features of renal injury in humans, including intranuclear inclusion bodies and cellular necrosis in the proximal tubule and interstitial fibrosis (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979). Studies show consistent evidence of renal damage and reduced renal function associated over a wide range of PbB (≤100 – >500 µg/L), with the overall dose-effect pattern suggesting an increasing severity of nephrotoxicity associated with increasing PbB.

Studies investigating workers

SCOEL (2002) concluded that there is no evidence of nephrotoxic effects at PbB levels of 400 µg/L and below.

Ekong et al. (2006)reviewed the epidemiological evidence on lead-related nephrotoxicity. The studies in general, occupational and patient populations were assessed separately. The authors reviewed 40 studies conducted in occupationally exposed populations. The PbB levels were typically 200 – 500 µg/L. Compared to general population studies the results were less consistent. Eleven studies identified a positive association, i.e. the higher lead dose was associated with worse clinical renal function. Nine studies identified some degree of association between lead dose and renal biomarkers, but did not assess clinical outcomes. Twelve studies identified significant associations between lead dose and renal biomarkers, but these were not associated with clinical outcomes. Five studies identified paradoxical associations, with higher creatinine clearance in lead exposed and/or an association between increasing lead dose and higher clinical renal function. Four studies did not find any significant associations. This inconsistency in the data base was considered puzzling. A number of possible reasons, both those inherent to occupational studies and those specific to nephrotoxicity, were discussed:

- Occupational studies often have smaller sample sizes than general population studies.

- Most were cross-sectional studies among currently employed and healthy worker effect is of particular concern for two reasons: (1) due to workers being in general healthier than the overall population and (2) because lead workers follow a medical surveillance programme and would have been removed from exposure if indication of renal function decline was observed.
- Many studies also used exclusion criteria for diseases like hypertension or diabetes, but did not report the number of such excluded cases. The comparison was often made to populations with lead exposure levels in the range where general population studies already found associations with early renal function biomarkers.
- Few studies assessed cumulative exposure and individual PbB was anticipated to vary more in the occupational setting than in environmental settings.
- Confounding by cadmium was possible in some studies.

In general, these limitations would result in bias towards the null, meaning that actual associations are obscured.

Evans and Elinder (2011) reviewed studies reporting findings in occupational setting in 1985 to 2010. The majority of the studies (19) were cross-sectional and only 3 were longitudinal. The authors also discussed aspects related to mechanisms, as well as differences in outcome measurement historically (classical lead nephropathy) and more recently (early biological effect markers). The authors concluded that among the 19 cross-sectional studies, only 2 found a significantly reduced glomerular filtration rate (GFR) (i.e. lower than 60 ml/min which is the clinical benchmark for CKD if observed at least over 3 months). Those studies reported mean PbB of 640 and 530 µg/L. Furthermore, the 3 longitudinal studies did not provide further evidence of lead-related chronic renal failure at the PbB experienced in those occupationally exposed populations (mean PbB levels during follow-up visits 310-330 µg/L and 300-600 µg/L in two of the studies, third study did not use PbB as exposure metric). The authors commented that in the occupational studies, in which individuals had been exposed to lead at high levels for many years giving rise to PbB >600 µg/L, there is possibly a risk of developing acute lead nephropathy with typical morphological findings in the kidney, hypertension, and often elevated plasma uric acid. In workers with PbB levels >400 µg/L, alterations in the secretions of early markers like eicosanoid 6-keto-prostaglandin-$F_{1\alpha}$, thromboxane B_2, and fibronectin have been observed together with the increased urinary secretion of brush border antigen, intestinal alkaline phosphatase, prostaglandin-$F_{2\alpha}$, and prostaglandin-E_2. In a descriptive analysis they calculated that the prevalence of CKD in the reviewed studies among lead exposed was comparable to the prevalence of CKD overall in Europe among those aged 40-59 years. The authors concluded that kidney is not the most sensitive endpoint for lead toxicity.

Studies investigating parameters for kidney effects

Relevant studies investigating renal parameters in lead-exposed workers with PbB-levels preferably below 400 µg/L and published since the year 2000 are summarised in Table 28. The studies are sorted with decreasing PbB.

Table 28: Selected studies on parameters for kidney effects in lead-exposed workers

Blood lead (µg/L)[1)]	Population[2)]	Reported effects	Reference
697±132 185±36	53 miscellaneous lead workers, mean age 31 years, Nigeria 42 control subjects, mean age 30 years	**Creatinine** and **urea** sign.* higher than controls Creatine: 97.4 µmol/L* versus 84.9 µmol/L Urea: 5.7 µmol/L* versus 4.7 µmol/L	(Onuegbu et al., 2011)

Blood lead (µg/L)[1)]	Population[2)]	Reported effects	Reference
625±15 410±19	135 storage battery plant workers, males and females, mean age 29 years, China 9 workers ALAD1-2 126 workers ALAD1-1	**uNAG** and PbB levels higher in ALAD1-2 workers compared to ALAD1-1 workers	(Gao et al., 2010)
422±18.6 GM±GSD 119±19.6	135 storage battery workers, mean age 29 years, China 143 mechanics without occupational lead exposure, mean age 27 years	**uNAG** most sensitive parameter with $BMDL_{10}$ of 253 µg/L **urinary total protein** $BMDL_{10}$ of 402 µg/L Note: no adjustment for other risk factors	(Lin and Tai-Yi, 2007)
466±141 422±133 435±145	Adults (occupational or environmental Pb exposure), mean age 37 years, Mexico 156 male workers 257 female workers 413 general population	≥400 µg Pb/L compared to <400 µg/L; sign effects on: **serum creatinine** increased (>1.5 mg/dL), **hyperuricemia** (serum uric acid >7mg/dL) **uremia** (blood urea >50 mg/dL)	(Hernandez-Serrato et al., 2006)
387±99 56±35	57 non-ferrous smelter workers, mean age 44, France 57 matched controls (by age, gender, smoking, drug use and socioeconomic status)	**NAG** or **retinol-binding protein** not associated with PbB No adjustment for other risk factors	(Garcon et al., 2007)
390±40 170±40	25 paint factory workers, Nigeria 25 controls (students, staff members)	**Serum creatinine** or **serum urea** not different between exposed and controls Creatinine: 80.5 µmol/L versus 80.4 µmol/L Urea: 3.15 versus 3.44 µmol/L	(Orisakwe et al., 2007)
362±177	108 lead workers, mean age 37 years, mean exposure 9.8 years, Iran	**GFR no correlation with PbB** Note: only 30 workers had a correctly collected 24-hour urine volume	(Karimooy et al., 2010)
313 326 314 (3 evaluations)	Two-year prospective cohort study, South Korea, 537 current and former lead workers combined (298 males, 139 females), mean age 42±9.3 years, 8.8±6.3 years exposed, 3 evaluations October 1997 to June 2001	**No indication of nephropathy** **Renal function changes within normal range but associated with PbB and bone Pb.** In males, serum creatinine declined and calculated creatinine clearance increased over the course of the study; both in those with increasing and declining PbB and those with high or low tibia lead. In females, decreasing serum creatinine was associated with declining PbB (as in males); however, increasing PbB was associated with a concurrent increase in serum creatinine.	(Weaver et al., 2009)
ca. 600 (1989) ca. 300 (1999)	Longitudinal study 1989-1999 30 lead workers (17 males, 13 females), 1992: mean age 38.3 years, 13.1 years exposed	Effect on **creatinine** unclear Red blood cell production stimulated	(Hsiao et al., 2001)

Blood lead (µg/L)[1)]	Population[2)]	Reported effects	Reference
190 (GM) >300 (22%) <300 (78%)	459 lead battery and lead lead stabiliser factory workers, mean age 39±11 years, 13±10 years exposed, Vietnam, Singapore	**uNAG** associated with PbB levels ALAD2 genotype workers more susceptible especially at higher exposures (above 400 µg/L) Adjustment for age, sex, race, exposure duration, ALAD polymorphism	(Chia et al., 2006)
291 median (90-611) 83 median (10-217)	87 lead smelter workers, mean age 40 61 age and gender matched office workers of the same plant, mean age 38	Effects in workers compared to controls: **GFR** sign. lower (86.05 vs 94.81 mL/min) **urea** sign. higher (5.09 vs 4.25 µmol/L) **Creatinine** not sign. higher (81.83 vs. 79.72 µmol/L) **uric acid** not sign. higher (357 vs 332 µmol/L). No adjustment for other risk factors No sub-categorisation	(Khan et al., 2008)
200 GM (67-658) 90 GM (36-219)	155 storage battery factory workers mean age 44, China 36 male office workers of the same plant, 45 years old	**uNAG** most sensitive parameter $BMDL_{05}$ of 101 µg/L	(Sun et al., 2008)
25 (0-340) median of maximum current PbB 290 (40-950) median of maximum previous PbB	211 current and former lead exposed workers, surveillance programme, USA, median age 62 years, median exposure duration 20 years	**GFR** showed a positive sign. trend only for bone lead levels, driven by Pb bone levels ≥13.8 µg/g bone, not for current PbB levels	(Barry et al., 2019)

[1)] mean values ± SD (range) if not stated otherwise
[2)] cross-sectional studies if not stated otherwise

Abbreviations: GFR: glomerular filtration rate; GM: meometric mean; uNAG: Urinary N-acetyl-β-D-glucosaminidase

In the following, the result of the studies presented in Table 28 are summarised. Some further studies in occupational setting and in the general population are described in Appendix 4 Table 48 and Table 49

The studies measuring GFR in lead-exposed workers showed inconsistent results. Whereas no effect on GFR was found in workers with mean PbB levels of 390 µg/L (Garcon et al., 2007) and 362±177 µg/L (Karimooy et al., 2010), a significant reduction was reported in workers with median PbB levels of 291 µg/L (range up to 611 µg/L; Khan et al., 2008). In current and former exposed workers with lower current PbB levels (median 25 µg/L; maximum 340 µg/L; Barry et al., 2019) a significant positive trend was observed for GFR an Pb bone levels, not with current PbB levels indicating an association with former Pb exposure.

In studies investigating lead-exposed workers, serum creatinine, as an indicator of the GFR, was slightly increased in cross-sectional studies at mean PbB levels of 700 µg/L (Onuegbu et al., 2011) and 400 µg/L (Hernandez-Serrato et al., 2006) but not at 390 µg/L (Orisakwe et al., 2007). In a larger longitudinal study investigating 537 workers, changes in renal function (blood urea nitr`ogen, serum creatinine, calculated creatinine clearance) were reported at mean PbB levels measured over 3 years between 313 and 326 µg/L (Weaver et al., 2009) but the findings differed between men and women. In men kidney function increased (i.e. serum creatinine decreased and GFR increased) during the course of the study also in those with increasing PbB, although not as much as among those with

decresing PbB. In the other longitudinal study that investigated only 30 workers with current PbB levels of about 300 µg/L and previous higher levels (ca. 600 µg/L), the effect on renal function (creatinine) was unclear (Hsiao et al., 2001).

Early biological effect markers asuch as N-acetyl-β-D-glucosaminidase (NAG) was increased at mean PbB levels of 625 µg/L (Gao et al., 2010) with no effects at 390 µg/L (Orisakwe et al., 2007, Garcon et al., 2007). A $BMDL_{10}$ of 253 µg/L for changes in NAG was calculated (Lin and Tai-Yi, 2007). These are sub-clinical changes and their long-term prognostic value is unclear and therefore they cannot be considered as adverse.

Studies on chronic kidney disease/end-stage renal disease

Evans et al. (2010) performed a case-control study in 926 patients with incident severe chronic kidney disease and 998 controls. Exposure to lead was defined as no exposure (< 3 µg/m^3), low (3 – 10 µg/m^3), medium (11 – 29 µg/m^3) and high (> 30 µg/m^3). PbB levels were not measured. The adjusted OR for incident severe chronic kidney disease was not increased (0.97; 95% CI 0.68-1.38) in ever lead-exposed participants compared with non-exposed participants and there was no trend by increasing average or cumulative exposure. The cases were further followed for 7-9 years and there was no statistically significant difference in change of GFR between lead exposed and unexposed patients with chronic kidney disease either when comparing ever/never exposed or most exposed/non-exposed to lead by cumulative or average exposure.

Evans et al. (2017) identified, in a cohort of 10,303 lead-workers, 30 individuals with who developed end-stage renal disease (ESRD) during the median follow-up period of 26.3 years. The ESRD incidence (obtained through register-linkage) among the lead-exposed workers was compared with the age, sex and calendar period-adjusted expected incidence based on data from the Swedish renal registry. The standardised incidence ratio (SIR) for ESRD incidence was 0.79 (95% CI 0.54 to 1.13). Among those who achieved the highest blood lead (>414 µg/L), the SIR was 1.01 (0.44 to 1.99). The authors concluded that this study shows no statistically significant association between lead exposure (following the current occupational recommendations for Sweden) and ESRD.

Studies on mortality from kidney diseases

The studies on mortality from kidney diseases are described in detail in Appendix 4, Table 47.

Bertke et al (2016) followed 1900 US lead smelter workers. Based on 17 deaths from chronic and unspecified renal disease, the SMR compared to regional rates was increased (SMR 1.83; 95% CI 1.06 – 2.93), but there was no indication of dose-response by estimated cumulative exposure (p for trend 0.27). PbB data were not available.

Steenland et al. (2017) analysed mortality pooling data from three cohorts of lead-exposed workers with PbB data from health surveillance schemes including over 88 000 workers and over 14 000 deaths (USA, Finland, UK). Both internal comparisons (those with PbB of > 400 µg/L, 300 – 390 µg/L or 200 – 290 µg/L vs less than 200 µg/L) and external comparisons to national mortality rates were performed. In the internal comparison, the risk of death from kidney disease was not statistically significantly increased in any of the exposure categories and there was no indication of a trend by exposure (p = 0.25). In the external comparison, the SMR for kidney disease was not statistically significantly increased in any of the exposed categories. This pooled analysis includes also the data published by McElvenny et al (2015) and Chowdhury et al (2014).

7.3.1.3 Cardiovascular effects

SCOEL (2002) discussed the mechanisms of Pb on blood pressure and concluded that there is a need of further research on the effects of Pb on blood pressure and whether low levels

of PbB (up to 400 µg/L blood) might cause effects which should be considered as being "adverse" is not clear at present.

Effects on blood pressure

Nawrot et al (2002) performed a meta-analysis of 31 studies investigating the association between PbB and blood pressure in adults. There were 19 general population surveys and 12 occupationally exposed surveys including altogether 58 518 subjects. Only four of the studies were prospective while most were cross-sectional. The association between blood pressure and PbB was similar in men and women. In the combined studies, a two-fold increase in PbB was associated with a 1.0 mm Hg higher systolic pressure (95% CI + 0.5 to + 1.4 mm Hg; $p < 0.001$) and with a 0.6 mm Hg higher diastolic pressure (95% CI +0.4 to +0.8 mm Hg; $p < 0.001$). The studies included had a mean PbB level ranging from 23 to 640 µg/L and 8 of them had mean PbB levels > 150 µg/L. It is to be noted that the associations were observed for a doubling of PbB without further analyses by absolute PbB level although it is stated that "there was no significant relationship between the association size and the mean blood lead concentration, the weighted correlation coefficient was 0.27 (P = 0.07) for systolic pressure and 0.17 (P = 0.23) for diastolic pressure". The study did not present a funnel plot analysis to explore publication bias.

Navas-Acien et al (2008) performed a meta-analysis of 3 prospective cohort studies and 7 cross-sectional studies investigating the association between bone lead concentration and blood pressure and hypertension in adults. A 10 µg/g increase in tibia bone lead was associated with higher systolic blood pressure (0.26 mm Hg (95% CI + 0.02 to + 0.50 mm Hg) and hypertension (OR = 1.04; 95% CI 1.01 – 1.07), but not with diastolic blood pressure (0.02 mm Hg (95% CI – 0.15 to + 0.19 mm Hg). For a 10 µg/g increase in patella lead, the summary odds ratio for hypertension was 1.04 (95% CI 0.96 to 1.12). As all the studies reported also PbB data, the meta-analysis also calculated the association by PbB level for comparison with previous meta-analyses. A 50 µg/L increase in PbB was associated with statistically non-significant higher systolic blood pressure (1.53 mm Hg; 95% CI – 0.19 to + 3.25), diastolic blood pressure (1.19 mm Hg; 95% CI – 0.69 to + 3.08) and hypertension (OR = 1.02; 95% CI 0.93 – 1.13). As the number of studies was small, the authors acknowledged that it was difficult to estimate the extent of between-study heterogeneity and the sources of heterogeneity or to assess possibility of publication bias. The studies included had a mean tibia bone lead level ranging from 4.2 to 38.4 µg/g and PbB level ranging from 23 to 320 µg/L. It is to be noted that the associations were noted for an increase of 10 µg/g in tibia bone lead or 50 µg/L in PbB without further analyses by absolute tibia bone lead or PbB level.

The individual studies included in the above meta-analyses differed as regards which potentially confounding factors were adjusted for in the analyses. Most studies considered age, while there was more variation as regards considering body mass index, smoking, alcohol consumption, intake of caffeine, milk, dietary calcium intake or serum calcium, serum zinc, exposure to cadmium, the blood haemoglobin concentration or haematocrit, physical activity or fitness, socio-economic status and menopausal status. An additional methodological aspect is that in the meta-analysis of Nawrot et al (2002) some large studies, which supported a positive relationship between blood pressure and PbB, based their conclusions on a single blood pressure reading. More reliable measurements would be based on repeated measurements or a 24 hour ambulatory blood pressure recording which is characterised by high reproducibility, and not subject to digit preference or observer bias and minimize the transient rise of a person's blood pressure in response to the observer, the so-called white-coat effect.

Relevant studies investigating blood pressure in lead exposed workers published since the year 2000 are summarised in Table 29. The studies are sorted with decreased PbB.

Table 29: Selected studies on effects on blood pressure (BP) and/or hypertension (HT) in lead-exposed workers

Blood lead (µg/L)[1)]	Population[2)]	Reported effects	Reference
714±113 380±109 129±48	529 Pb smelter workers 63 workers 374 workers 92 workers	**Systolic (p = 0.09) and diastolic (p = 0.33) BP not sign.* increased** with increasing PbB (<200, 200-600, >600 µg/L SBP (mm Hg): 115±16, 117±14, 120±15 DBP (mm Hg): 75±10, 77±10, 77±10 **ECG conduction abnormalities** (high QRS voltage) sign.* increased with increasing PbB: High QRS voltage (%): 4.3, 9.9, 23.8* Sinus arrhythmia (%): 20.7, 30.2, 39.7*	(Xie et al., 2019)
655±185 625±154 584±202 102±58	Male workers in battery manufacture, India 30 (>10 years exposure) 30 (6-10 years exposure) 30 (1-5 years exposure) 30 control	**Systolic and diastolic BP sign.* increased** with increasing exposure duration (control, 1-5, 6-10, >10 years exposure) SBP: 116, 123*, 127*, 131* mmHg DPB: 77, 81*, 87*, 90* mmHg sign decrease in serum and ionized calcium, phosphorous, vitamin D	(Dongre et al., 2013)
554±135 (225-994) 64±15.5 (38-114)	123 female crytal toy workers, meag age 27 years, China 70 female control workers, mean age 24 years	**Systolic and diastolic BP sign.* increased** with increasing PbB level (control (< 114), 114-400, **>400-600, ≥600**): SBP: 110, 115, 116*, 120* mmHg DBP: 73, 76, 77*, 79* mmHg Aging, urine protein, and plasma triglyceride also contributed to systolic/ diastolic/ pulse pressure increase	(Nomiyama et al., 2002)
484±201 137±48.1	60 male automechanics, Nigeria, age 18-55 60 age-matched controls	**Systolic and diastolic BP sign. increased** compared to controls SBP: 124* versus 119 mmHg DBP: 82* versus 78 mmHg	(Obi-Ezeani et al., 2019)
314±142 203, 208, 198 350, 365, 354	Longitudinal study, 3 examinations (1997 to 2001), 575 lead-exposed workers, mean age 41 years, 8.5 years exposed, South Korea 140 females 435 males	**Change (increase) in systolic BP** during the study associated with concurrent blood lead change, with an average annual increase of 0.9 (95% confidence interval = 0.1 to 1.6) mmHg for every 100 µg/L increase in blood lead per year Systolic BP at the 3 visits: Females: 125, 124, 124 mmHg Males: 123, 121, 120 mmHg No effects on diastolic BP	(Glenn et al., 2006)
309±167	652 current and former lead workers (77% males), mean age 43±10, 10.0±6.5 years exposed, South Korea, including workers of 3rd examination of Glenn et al., 2006	**Systolic BP** (mean 123 mmHg) associated with PbB (not with patella lead) No effects on diastolic BP or hypertension	(Weaver et al., 2008)

Blood lead (µg/L)[1)]	Population[2)]	Reported effects	Reference
254±120 65±37	144 workers, battery manufacture, China, 78% men, 94 controls	**Systolic BP and diastolic BP sign.* higher** in exposed workers compared to controls: SBP (mm Hg): 121±9.9* versus 117±10 DPB (mm Hg): 80±7.8* versus 76±7.3 Abnormal ECG (%): 30 versus 15 *Note:* controls sign. older (42 vs 38 years), fewer smokers (26.6 vs 35.4%, less alcohol drinkers (22.3 vs 27.1%))	(Qu et al., 2019)
Quartiles: <46 (Q1) 47-109 (Q2) 110–175 (Q3) >175 Q4)	21,688 workers in different size of factories, China	**Systolic BP and diastolic BP sign.* changed** in Q2, Q3, Q4 compared to Q1: SBP (mm Hg change): 1.98*, 1.81*, 1.34* DBP (mm Hg change): 0.65*, 1.26*, 0.7* **OR for hypertension sign. increased** Q2, Q3, Q4 compared to Q1 HT (OR): 1.06, 1.14*, 1.11* Adjusted for up to 8 variables, including e.g. gender, age, factory type; no adjustment for potential confounding by any known life-style risk factors of increased PB and HT	(Han et al., 2018)
79.2±34.4	182 male battery workers, Iran	**Systolic and diastolic BP** not sign. different comparing PbB >100 µg/L and <100 µg/L (multivariate model)	(Taheri et al., 2014)
46±26 (10-200)	Longitudinal study, 3 to 4 examinations (1994 to 1998), 496 current and former employees, mean age at baseline 56, 18 years (mean) since last exposure	**Change (increase) in systolic BP** associated with lead dose, with an average annual increase of 0.64 mmHg (95% CI 0.14 – 1.14), 0.73 mmHg (0.23 – 1.23), and 0.61 mmHg (0.09 – 1.13) for every standard deviation increase in blood lead at baseline, tibia lead at year three, or peak past tibia lead, respectively	(Glenn et al., 2003)
25 median of maximum current PbB(range 0-340) 290 median of maximum previous PbB (range 40-950)	211 lead exposed workers, surveillance programme, USA, median age 62 years, median exposure duration 20 years	**Systolic BP** showed a positive linear trend only for bone lead levels, driven by Pb bone levels ≥13.8 µg/g bone, not for current PbB levels	(Barry et al., 2019)
45 (GM; interquartile range 26.0 – 91.5)	236 newly hired workers, mean age 29 years, without previous Pb exposure, not treated for hypertension	No association between **systolic or diastolic blood pressure** and PbB	(Yang et al., 2018, Yang and Staessen, 2018)

[1)] mean values ± SD (range) if not stated otherwise
[2)] cross-sectional studies if not stated otherwise

In the following, the results of the studies mentioned in Table 29 are summarised. Some further studies in the occupational setting and general population are described in Appendix 5, Table 50.

In cross-sectional studies investigating lead-exposed workers with current mean PbB levels **>400 µg/L**, significant increased in systolic and diastolic blood pressure was reported (Dongre et al., 2013; Nomiyama et al., 2002; Obi-Ezeani et al., 2019). The blood pressure values were still within normal and not interpreted as hypertension. In a further study with even higher PbB levels 380±109 µg/L and 714±113 µg/L, only a light but

statistically non significant increase in systolic blood pressure was observed (Xie et al., 2019).

In a longitudinal study investigating 575 workers (Glenn et al., 2006) and in a separate cross-sectional analysis of the same occupationally-exposed group of 652 workers in the last follow-up visit (Weaver et al., 2008) increases in systolic but not in diastolic blood pressure were reported. The mean PbB levels were **314 µg/L** in the longitudinal study and **309 µg/L** in the cross-sectional study. The change in systolic blood pressure was associated with concurrent PbB change with an average annual change of 0.9 (95% CI 0.1 – 1.6) mm Hg for every 100 µg/L increase in PbB per year (Glenn et al., 2006). In the cross-sectional study (Weaver et al., 2008), PbB, either when studied alone or in the same model with patella lead, was significantly associated with higher systolic blood pressure. None of the Pb biomarkers were associated with diastolic blood pressure.

In a smaller cross-sectional study in 144 workers with mean PbB level of 254±120 µg/L (Qu et al., 2019), systolic and diastolic blood pressure were significantly increased (but within normal). However, the results were not adjusted with regard to significant differences between exposed and controls for age, smoking and alcohol drinking.

In a very large cross-sectional study (n=21,688) in workers (Han et al., 2018) PbB levels of > 175 µg/L were associated with differences in systolic blood pressure (1.34 mm Hg), differences in diastolic blood pressure (0.70 mm Hg) and in the adjusted OR for hypertension 1.11 (95%CI 1.08-1.15), adjusted for up to 8 variables, including for example gender, age, factory type. Blood pressure changes were also observed in the lower exposure groups. However, the risk estimates were not adjusted for potential confounding by any known life-style risk factors of increased blood pressure and hypertension.

A cross-sectional study in 182 workers with PbB levels > or < 100 µg/L, did not find statistically significant differences between the groups with regards to systolic or diastolic blood pressure (Taheri et al., 2014).

Based on those studies, small increases in systolic blood pressure (within normal) can be observed relatively consistent at PbB levels >300 µg/L. In larger populations, small differences in systolic blood pressure can even be observed at low PbB levels such as 46±26 µg/L (Glenn et al., 2003). In formerly lead exposed workers (mean age 62 years) a positive trend for increase in systolic blood pressure was found for lead in bone (indicative of provious higher exposure) but not for lead in blood (median PbB levels of 25 µg/L).

A small effect on blood pressure wihin the normotensive range of blood pressure is not a health outcome per se but a risk factor for cardiovascular and cerebrovascular disease. Considering increases of the order of 1 mmHg of systolic or diastolic blood pressure the risk is small for many individuals, however in a population it may be important, since it could shift a population's distribution to increase the percentage of individuals considered hypertensive. There are no studies having assessed in a working population the long-term predictive value of such small blood pressure increases for cardiovascular morbidity of mortality. In the general population it has been estimated that each 10 mmHg below-usual systolic blood pressure is associated with a lower risk of hypertensive disease and ischeamic heart disease (WHO, 2004). There is uncertainty in applying such estimates for calculating a health benefit to a healthy worker population and more minor differences in blood pressure.

Cardiovascular disease and mortality

Navas-Acien et al (2007) reported a systematic review of lead exposure and cardiovascular disease. Clinical cardiovascular endpoints covered cardiovascular disease in general, coronary heart disease, stroke and peripheral artery disease. The review also assessed intermediate cardiovascular endpoints; left ventricular mass, heart rate, heart rate variability and electrocardiographic abnormalities. There were eighteen studies in working

populations.PbB levels were mostly not reported in the review. Most studies were retrospective cohort studies and used external comparisons to the general population to derive standardized mortality ratios. Relative risk estimates across occupational studies varied widely, with positive, inverse, and null associations. The authors argued that the validity of occupational studies of lead and cardiovascular mortality was limited by several methodologic problems especially by the healthy worker effect.

In addition to the studies reviewed by Navas-Acien et al (2007) cardiovascular disease incidence and mortality by lead exposure have been reported more recently in occupational cohorts (Appendix 5, Table 51) and in the general population (Appendix 5, Table 52 Table 53).

Steenland et al. (2017) analysed mortality pooling data from three cohorts of lead-exposed workers with PbB data from health surveillance schemes (USA, Finland, UK) including over 88 000 workers and over 14 000 deaths. Both internal comparisons (> 400 µg/L , 300 – 399 µg/L and 200 – 299 µg/L vs less than 200 µg/L) and external comparisons to national mortality rates were performed. In the internal comparison, the risk of death from ischemic heart disease was statistically significantly increased in each of the exposure categories and there was a statistically significant trend by exposure (p = < 0.0001). In those with PbB > 400 µg/L the hazard ratio was 1.41 (95% CI 1.28 - 1.57). Also the risk of death from stroke was statistically significantly increased in each of the exposure categories and there was a statistically significant trend by exposure (p = 0.0002). In those with PbB > 400 µg/L the hazard ratio was 1.41 (95% CI 1.16 - 1.72). In the external comparison the SMR for ischemic heart disease or for cerebrovascular disease was not statistically significantly increased in any of the exposed categories. None of the above analyses was adjusted for smoking or other known risk factors of ischemic heart disease. Smoking habits were known in a subset of 112 study participants that were invited to bone lead analysis and there was no correlation between pack-years of smoking or frequency of never/ex-smokers and PbB thus not indicating a confounding effect in this relatively small US subpopulation of the international study. It is to be noted that internal comparisons are considered less prone to confounding by life-style factors because the comparison group, i.e. lead surveillance program workers with PbB < 200 µg/L, would presumably have quite similar lifestyles and cardiovascular risk factors as the workers from the same program but with higher PbB.

In the internal comparisons the cohort studies of McElvenny et al. (2015) and Chowdhury et al. (2014) reported also increased risks of circulatory disease mortality by increasing PbB in 9122 and 56 368 UK and US workers, respectively, identified from among subjects who had undergone past blood lead monitoring due to their occupational exposure. However, as these cohorts were included in the pooled analysis by Steenland et al (2017) they are not described here (for further details see, Appendix 5 Table 51).

Bertke et al (2016) followed 1900 US lead smelter workers. Based on 703 deaths from cardiovascular disease, the SMR compared to regional rates was increased (SMR 1.22; 95% CI 1.13 – 1.31) and there was indication of a dose-response relationship by estimated cumulative exposure (p for trend 0.04). PbB data were not available. Overall, there was also a statistically significantly increased mortality from diseases of the heart and from cerebrovascular disease, but for them the trend by cumulative exposure was only of borderline significance (p = 0.08 and 0.13, respectively). The above analyses were not adjusted for smoking or other known risk factors of cardiovascular disease.

In the Australian cohort of 4114 exposed male workers from a health surveillance scheme (Gwini et al 2012), there was no statistically significant mortality from ischemic heart disease (SMR 0.95; 95% CI 0.76 – 1.19) or stroke (SMR 1.25; 95% CI 0.84 – 1.86). The analyses were not adjusted for smoking or other known risk factors of cardiovascular disease. The geometric mean PbB was 196 µg/L, but the results on cardiovascular mortality were not reported by level of PbB.

Kim et al (2015) followed 81 067 South Korean exposed workers who had undergone PbB testing as part of their health surveillance. Comparison was made to those who had PbB levels below 100 µg/L. Among men, the risk for cardiovascular disease mortality was not increased in those with PbB level of 100-199 µg/L (RR 0.98; 95% 0.45 – 2.16) but there was some indication, although statistically not significant, of increased risk among those with > 200 µg/L (RR 1.99; 95% CI 0.95 – 4.15). For women the numbers of cases were too low for meaningful comparisons. The analyses were not adjusted for smoking or other known risk factors of cardiovascular disease.

Min and Ahn (2017) prospectively evaluated the association between PbB levels and increases in hospital admissions for treatment of cardiovascular diseases among 54,788 lead-exposed male workers in Korea. The adjusted hospital admission hazard ratio (AHR) of cardiovascular diseases for each PbB grade (100-200 and ≥200 µg/L) was compared with that of the reference grade (<100 µg/L). The adjusted variables included age and exposure to other metals. The authors were unable to control for other major risk factors such as smoking, socioeconomic status, and antihypertensive medication. There was no increase in hazard ratio of hospital admissions for hypertensive diseases, while there was some indication of a trend of increasing hazard ratio by increasing PbB for ischemic heart disease and cerebrovascular disease (Appendix 5, Table 51).

7.3.1.4 Haematological effects

Effects on enzymes involved in haem synthesis

SCOEL (2002)(2002) summarised that in the previous 10 years, growing attention has been paid to subclinical effects and indeed to early or subtle health effects, the hypothesis being that these form a physiopathogenic continuum with the clinical or generally overt effects (EPA, 1986; Goyer, 1990). Lead inhibits enzymes of haem synthesis in a dose-dependent manner (both as regards prevalence and severity) and there are a number of related parameters for which it is possible to tentatively identify PbB levels at which changes cannot be detected;

- coproporphyrin: 400 µg/L;
- urinary and blood δ-aminolevulinic acid levels: 300 to 350 µg/L;
- inhibition of iron chelation: 200-250 µg/L;
- zinc protoporphyrin: 200 µg/L;
- δ-aminolevulinic acid dehydrase (ALAD): 100 µg/L.

However, the clinical significance of these biochemical changes is uncertain. Masci *et al*. (1998) have conducted a longitudinal study on workers performing tin/lead alloy welding. Blood lead levels of these workers gradually declined with time to lower values (60-340 µg/L, accompanied by similar decreases in zinc protoporphyrin concentrations (20-470 µg/L); thereby it appeared that effects on haem synthesis (which might be regarded as non-adverse) occur even at very low levels of Pb exposure. SCOEL (2002) concluded that some subclinical changes in parameters of haem synthesis may occur even below 400 µg Pb /L blood, but these are not regarded as being "adverse".

LDAI (2008) reviewed the data and conclused:

- PbB levels already < 100 µg/L are associated with inhibition of ALAD
- PbB levels of 170 to 250 µg/L are required to produce elevation of ZPP
- PbB levels >500 µg/L decreased haemoglobin production in adults

Assi et al. (2016) reviewed the data on lead and concluded that while ALAD inhibition is known at PbB levels of 100 to 200 µg/L, biosynthesis of haeme does not reduce till the action of ALAD is restricted by 80-90% that takes place at a higher concentration of lead of about 550 µg/L in blood.

Murata et al. (2009) reviewed adverse effects of lead. Based on data from previous reports using a BMD approach (Araki et al., 1992, Araki and Honma, 1976, Iwata et al., 2005,

Murata et al., 1995, Mutti and Smargiassi, 1998) the authors concluded that BPb levels below 50 µg/L inhibited enzymes such as ALAD involved in haeme synthesis in workers. As noted by SCOEL (2002) such effects are not considered as adverse.

Effects on blood parameters

SCOEL (2002) noted that although the data-base is weak, there appears to be a risk of developing lead-induced anaemia (haemoglobin concentration < 140 g/L) at PbB in excess of about 500 µg/L (IPCS, 1995; ATSDR, 1992; Silbergeld, 1990).

Hsiao et al. (2001) assessed the relationship between PbB levels, hematological, liver and renal indicators among 30 workers in a lead battery factory in Taiwan over a 10-year period 1989 to 1999. PbB levels in 1989 were about 600 µg/L and in 1999 about 300 µg/L. The authors concluded that long-term exposure stimulates production of red blood cells and haematocrit, but the effect on liver (alanine aminotransferase) and renal function (creatinine) was unclear.

Karita et al. (2005) investigated 388 lead-exposed workers in Japan with mean PbB levels of 296 ± 207 µg/L (range 10 to 1139 µg/L). The mean haemoglobin concentrations were reported to be 150 ± 11 g/L with a range from 110 to 176 g/L. For an increased probability of abnormal blood parameters, BMDs (lower 95% confidence limits) were estimated to be 195 µg/L for an effect on haemoglobin, 194 µg/L for an effect on the level of red blood cells, and 296 µg/L for effect on haematocrit.

Khan et al. (2008) reported a slight but statistically significant reduction in the haemoglobin concentration in 87 workers compared to controls (15.12±1.24 versus 15.62±0.96 g/L). PbB levels in workers were 291µg/L (range 90-611) and 83 µg/L in controls (range 10-217 µg/L). The 10-fold lower haemoglobin concentrations than normal in workers and controls are noted.

7.3.2 Animal data

Although the literature on adverse effects of Pb in laboratory animals is extensive, due to the large number of available epidemiological studies, only individual relevant studies are cited.

Neurological effects in adult animals

EFSA (EFSA, 2010, updated 2013) summarised the neurological effects of lead on adult animals as follows:

Numerous human studies ascribe lead-related cognitive dysfunction to attention deficits. In experimental studies, discrimination reversal deficits in lead-exposed non-human primates have been interpreted as increased distractibility to irrelevant stimuli ((Rice, 1985).

Clinical diagnosis of attention deficit hyperactivity disorder (ADHD) relies on three behavioural domains: inattention, hyperactivity and impulsivity (Goldman et al., 1998). Collective findings across two recent studies support the possibility, based on the clinical diagnosis domains, that impulsivity is more strongly affected by lead than sustained attention, and that impulsivity as a behavioural dysfunction could ultimately lead to cognitive impairments (Cory-Slechta, 2003). With respect to hyperactivity, reports of hyperkinetic behaviour have been inconsistent in animal models of lead exposure, with increases, decreases and no change all reported (Bornschein et al., 1980).

Two groups of 7-week old rats were given 50 mg/L sodium acetate and 50 mg/L lead acetate, respectively, in the drinking-water for 3 months. Ocular motor function was tested by rotating the animals on a platform at an increasing angular velocity and measuring ocular nystagmus when the rotation is abruptly stopped. The lead-exposed animals showed a reduction in post-rotatory nystagmus that was statistically significantly correlated with B-Pb and brain lead concentrations, while no such alterations were

observed in animals treated with sodium acetate. The results show that low concentrations of lead may impair both sensory and motor functions, and indicate that such measurements provide a screening tool for neurotoxic effects of lead even in the absence of clinical signs of lead intoxication (Mameli et al., 2001).

Five cats at an age of 12 to 28 months were stimulated with a precisely controlled electrical current via electrodes inserted into the lateral hypothalamus. The response measure was the predatory attack threshold, i.e. the current required to elicit an attack response in 50 % of the trials. Lead was mixed (as lead acetate) into cat food at doses of 50 to 150 mg/kg b.w. lead per day for 4 to 5 weeks. B-Pb concentrations were <10, 210 to 770 and <200 µg/L before, during and after lead exposure, respectively. The predatory attack threshold decreased significantly during lead exposure in three of the five cats and increased after cessation of exposure in four of the five cats ($p < 0.01$). There was a significant ($p < 0.002$) negative association between threshold current and B-Pb concentration. These data show that lead exposure enhances predatory aggression in cats (Li et al., 2003).

Results of behavioural tests performed primarily in rats and monkeys exposed to lead have suggested that the impaired performance is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding, and perseverance of behaviours that are no longer appropriate (ATSDR, 2007).

In monkeys impairments of cognitive capabilities were found at PbB levels in the range of about 100 to 150 µg/L (the lowest doses tested), with rats comparable effects were observed at little higher PbB. In the case of higher concentrations the eyesight and hearing were impaired and alterations in behaviour were observed and also neuro-biochemical and neurophysiological changes. Like in humans, certain effects persisted which had been triggered by exposure in earlier times ((ATSDR, 2007); EPA, 2006; (LDAI, 2008).

Neurological effects in offspring

EFSA (2010 updated 2013) summarised the neurological effects of lead on the offspring of animals as follows:

Studies in rats and nonhuman primates have demonstrated deficits in learning associated with B-Pb concentrations between 100 and 150 µg/L, a range that is comparable to those reported in epidemiological studies, in which learning deficits were found in children (Cory-Slechta, 2003).

Deficits in reversal or repeated learning have been a consistent finding with lead exposure. These learning impairments appear to be generalised, having been reported across species and stimulus dimensions. Prenatal exposure of 8 pregnant (5 to 8.5 weeks of gestation) squirrel monkeys to lead, resulting in a maternal blood concentration between 210 µg/L and 790 µg/L showed that at blood concentrations above 400 µg/L, behavioural alterations, such as learning ability of the offspring, were affected at an age of 5 to 6 years. At lower maternal B-Pb concentrations there were still some effects on learning ability (Newland et al., 1994). In monkeys given lead at doses resulting in a blood concentration of 320 to 360 µg/L from birth, the spatial discrimination reversal task was impaired at age 7 to 8 years (Rice, 1990). Whether this reflects different critical exposure period(s) for different types of learning paradigms is not known. Studies on the impact of lead on various behavioural domains have not been carried out systematically across developmental periods of exposure, and thus the ability to define critical periods for any behavioural deficit is not possible (Cory-Slechta, 2003).

Rats were exposed to 775 mg lead/kg feed at different stages of development, and tested with respect to active-avoidance learning and hippocampal long-term potentiation. When exposure comprised the prenatal and the early postnatal period and was continued into adulthood, both processes were impaired. However, when exposure started 16 days after birth, neither learning nor hippocampal potentiation was affected. These results reflect the higher vulnerability of the developing hippocampus to lead-induced functional deficits compared with the mature hippocampus (Altmann et al., 1993).

Renal toxicity

EFSA (2010 updated 2013) summarised the renal effects of lead on adult animals as follows:

Chronic intoxication with lead is associated with the presence of characteristic intranuclear inclusions in proximal tubular epithelial cells of the kidney. Lead-induced formation of nuclear inclusion bodies has been observed in kidneys of rabbits, rats (Six and Goyer, 1970; Choie and Richter, 1972a, b), monkeys (Allen et al., 1974) and dogs (Stowe et al., 1973).

Experimental models of lead nephropathy were developed in male Sprague-Dawley rats fed a low calcium diet (Khalil-Manesh et al, 1992, 1993). Lead acetate was used in concentrations of 0.5 % (high dose) and 0.01 % (low dose) in drinking water for periods from 1 to 12 months and leadexposed animals were compared to pair-fed control rats. Animals treated with 0.5 % reached a maximum B-Pb of 1,254 ± 101 µg/L after 6 months, when lead acetate was reduced from 0.5 to 0.1 % (Khalil-Manesh et al, 1992). B-Pb in these animals at 12 months averaged 550 µg/L. In lead-treated rats, Glomerular Filtration Rate (GFR) was increased at 3 months (1.00 ± 0.14 vs.0.83 ± 0.26 ml/min/100 g b.w., P=0.05), then declined after 6 months (0.78 ±0.16 ml/min/100 g b.w. vs.0.96 ± 0.08). At 6 months, focal tubular atrophy and interstitial fibrosis appeared, increasing in extent up to 12 months. Glomeruli at 12 months showed focal and segmental sclerosis.

In the second study (Khalil-Manesh et al, 1993) the course of events was examined over 12 months in continuous low level lead-exposed animals. Maximum B-Pb levels in these animals were reached at three months, averaging 294 ± 41 µg/L. GFR was statistically significantly increased above that in pair-fed controls at 1 and 3 months, but was normal at other time points. There were no other pathological alterations in the kidneys up to 12 months, when mild tubular atrophy and interstitial fibrosis were seen. It should be noted that both low dose lead-treated and high dose lead-treated animals showed a —hyperfiltration‖ effect during the first 3 months of lead exposure.

Cardiovascular effects

EFSA (2010 updated 2013) summarised the renal effects of lead on adult animals as follows:

A number of animal experiments have suggested a biphasic response of blood pressure to lead exposure (Victery et al., 1982) (Victery, 1988). Evis et al. (1985) reported that prolonged (3 or 12 months) low-level exposure of spontaneously hypertensive rats to lead (25 mg/L as lead acetate in the drinking-water) enhanced the susceptibility of the heart to ischaemia-induced arrhythmias at 3 but not at 12 months, in the absence of any effect on blood pressure. In contrast, subchronic (3 months) high-level exposure of these rats to lead (250 or 1,000 mg/L in the drinking-water) resulted in only slightly enhanced susceptibility of the heart to arrhythmias induced by myocardial ischaemia. Both doses of lead accelerated the development of high blood pressure and in normotensive rats the higher dose also resulted in an elevated blood pressure ((Evis et al., 1987). A consistent and significantly higher systolic blood pressure (SBP) was seen in all dosed groups of 15 to 18 female weanling Long-Evans rats fed a diet low in lead and exposed to lead at 0.1, 1.0 or 5.0 mg/L in the drinking water for 3 months, 6 months or 1 year compared to control (Perry et al., 1988). This was confirmed in a study where groups of ten albino rats were given lead at 25, 50 or 1,000 mg/L in the drinking water. After 90 days the blood pressure was measured in five rats per group and the remaining five were terminated for histopathological and histochemical studies on heart tissue. The increase in arterial blood pressure was statistically significant only in the two highest dose groups. In this study lead increased calcium influx in atrial trabeculae and papillary muscles. It was suggested that the mechanism is related to the ability of lead to alter calcium transport processes (B et al., 1991).

Haematological effects

According to US EPA (2013) many studies are available showing consistent findings for decreased red blood cell survival and function (decreased haemoglobin, haematocrit, packed cell volume haematocrit, increased eryptosis, decreased hematopoiesis, increased oxidative stress) in rodents with relevant PbB levels of 17 to 71 µg/L (US EPA, 2013b).

7.3.3 In vitro data

No relevant *in vitro* information that would contribute to the evaluation of repeated dose toxicity of lead has been identified.

7.3.4 Summary

Neurological effects

SCOEL (2002) concluded that there is no consistent evidence of effects of Pb on the peripheral nervous system at levels up to 400 µg/L blood and that consistent neurobehavioural effects which are to be considered as "adverse" appear in a multiplicity of studies at lead blood levels of 400 µg/L and above. The reviewed meta-analyses investigating neurological effects concluded on a LOAEL for nerve conducting velocity of 330 µg/L (Krieg et al., 2008), on subtle neurobehavioral deficits between 370 and 520 µg/L (Seeber et al., 2002) and on changes in cognitive and sensomotoric parameters in lead exposed workers with mean blood lead concentrations of 340.8±136.3 µg/L (Vlasak et al., 2019). Based on a cross-sectional study in 938 workers, Schwartz et al. (2001) suggested a threshold for neurobehavioral effects of 180 µg/L. Based on data from previous reports using a BMD approach, the critical PbB level for effects on the nervous system was calculated to be between 107 and 175 µg/L (Murata et al., 2009). Iwata et al. (2005) calculated a $BMD_{95\%}$ of 144 (121 to 173) µg/L for an effect on postural balance. The threshold for neurobehavioral effects of 180 µg/L is considered the most reliable value currently available as a conclusion on a threshold for lead-induced neurological effects in adults due to the relatively large number of workers investigated.

The most reliable information is from Schwartz et al. (2001) which suggested a threshold for neurobehavioral effects of 180 µg/L based on a cross-sectional study in 938 workers. It has to be noted that such effects are subtle.

Renal effects

Based on the data available at the time, SCOEL (2002)(2002) concluded that there is no evidence of nephrotoxic and/or gastrointestinal toxicity at Pb blood levels of 400 µg/L and below.

In studies investigating workers, serum creatinine, as an indicator of the glomerular filtration rate, was slightly increased in cross-sectional studies at mean PbB levels of 700 µg/L (Onuegbu et al., 2011) and 400 µg/L (Hernandez-Serrato et al., 2006) but not at 390 µg/L (Orisakwe et al., 2007). In a larger longitudinal study investigating 537 workers, changes in renal function (blood urea nitrogen, serum creatinine, calculated creatinine clearance) were reported at mean PbB levels measured over 3 years between 313 and 326 µg/L (Weaver et al., 2009). However, in men the associations indicated lower creatinine and higher glomerular filtration rate during the course of the study regardless of whether PbB increased or decreased. In the other longitudinal study that investigated only 30 workers with current PbB levels of about 300 µg/L and previous higher levels (ca. 600 µg/L), the effect on renal function (creatinine) was unclear (Hsiao et al., 2001).

Early biological effect markers asuch as N-acetyl-β-D-glucosaminidase (NAG) was increased at mean PbB levels of 625 µg/L (Gao et al., 2010) with no effects at 390 µg/L (Orisakwe et al., 2007, Garcon et al., 2007). A $BMDL_{10}$ of 253 µg/L for changes in NAG was calculated (Lin and Tai-Yi, 2007). This is a sub-clinical effect that cannot be considered as adverse.

In a recent mortality study (Steenland et al., 2017) which included over 88 000 workers and over 14 000 deaths, the risk of death from kidney disease was not statistically significantly increased in any of the exposure categories (PbB levels > 400 µg/L, 300 – 390 µg/L and 200 – 290 µg/L vs less than 200 µg/L) and there was no indication of a trend by exposure (p = 0.25).

Cardiovascular effects / Increased blood pressure

In cross-sectional studies investigating lead-exposed workers with current mean PbB levels **>400 µg/L**, significant increased in systolic and diastolic blood pressure was reported (Dongre et al., 2013, Nomiyama et al., 2002, Obi-Ezeani et al., 2019). In a longitudinal study investigating 575 workers (Glenn et al., 2006) and in a separate cross-sectional analysis of the same occupationally-exposed group of 652 workers in the last follow-up visit (Weaver et al., 2008) increases in systolic but not in diastolic blood pressure were reported. The mean PbB levels were **314 µg/L** in the longitudinal study and **309 µg/L** in the cross-sectional study. In a very large cross-sectional study (n=21,688) in workers (Han et al., 2018) PbB levels of **>175 µg/L** were associated with differences in systolic blood pressure (1.34 mm Hg), differences in diastolic blood pressure (0.70 mm Hg) and in the adjusted OR for hypertension 1.11 (95%CI 1.08-1.15). Blood pressure changes were also observed in the lower exposure groups. However, the risk estimates were not adjusted for potential confounding by any known life-style risk factors of increased blood pressure and hypertension. A cross-sectional study in 182 workers with PbB levels **> or < 100 µg/L**, did not find statistically significant differences between the groups with regard to systolic or diastolic blood pressure (Taheri et al., 2014).

Based on those results, the LOAEL for small increases in blood pressure (order of 1 mm Hg) that have been observed in working populations is around 300 µg/L. In the general population, similar effects have been observed at even lower PbB levels. However, a small effect on blood pressure within the normotensive range of blood pressure is not a health outcome per se but a risk factor for cardiovascular and cerebrovascular disease. Considering increases of 1 to mmHg of systolic or diastolic blood pressure the risk is small at the individual level and there are no studies which have assessed in a working population the long-term predictive value of such small blood pressure increases for cardiovascular morbidity of mortality.

Cardiovascular effects / Cardiovascular mortality

Some of the recent studies, especially in their internal comparisons by exposure level (Steenland et al 2017, Bertke et al 2016, Kim et al 2015, McElvenny et al 2015, Chowdbury et al 2014), provide some indication of an association between past exposure to lead and cardiovascular mortality. In the studies reporting PbB as an exposure metric, the effect was typically seen at levels above 200 - 400 µg/L. However the studies did not adjust for potential confounding effects of non-occupational risk factors.

It is also unclear why the PbB concentrations in workers that have been associated with increases in cardiovascular disease incidence or mortality are higher when compared to the general population (50 to 100 µg/L). It is acknowledged that the healthy worker effect and potential confounding by lifestyle risk factors is a problem in interpretation of data particularly for cardiovascular morbidity and mortality in occupationally exposed populations.

Haematological effects

(SCOEL, 2002) summarised that lead inhibits enzymes of haem synthesis in a dose-dependent manner (both as regards prevalence and severity) and there are a number of related parameters for which it is possible to tentatively identify PbB levels at which changes cannot be detected (NOAELs):

- coproporphyrin: 400 µg/L;

- urinary and blood δ-aminolevulinic acid levels: 300 to 350 µg/L;
- inhibition of iron chelation: 200 to 250 µg/L;
- zinc protoporphyrin: 200 µg/L;
- vδ-aminolevulinic acid dehydrase (ALAD): 100 µg/L.

SCOEL (2002) concluded that subclinical changes in parameters of haem synthesis may occur below 400 µg Pb /L blood, but these are not regarded as being "adverse".

SCOEL (2002) also noted that although the data-base is weak, there appears to be a risk of developing lead-induced anaemia (haemoglobin concentration < 140 g/L) at PbB in excess of about 500 µg/L. Karita et al. (2005) estimated a $BMDL_5$ for an increased probability of abnormal haemoglobin with 195 µg Pb/L blood.

7.4 Irritancy and corrosivity

There is no reported evidence of lead being a skin irritant or being corrosive.

However, some substances containg lead might be irritating or corrosive due to the properties of the other constituents of the substances.

7.5 Sensitisation

There is no reported evidence of lead being a skin sensitiser or respiratory sensitiser.

However, some substances containing lead might be skin or respiratory sensitisers due to the properties of the other constituents of the substances.

7.6 Genotoxicity

SCOEL (2002) summarised that lead has been tested for genotoxic potential in a range of mutagenicity assays, with equivocal results, which may be related to poor compatibility of the materials with the test systems (Winder and Bonin, 1993). Overall, lead is mostly negative in genotoxicity assays, but there is evidence that exposures of cells in culture can induce chromosomal aberrations (Silbergeld et al., 2000). Also, cytogenetic effects (chromosome aberrations and sister chromatid exchanges) have been reported in some, but not all, studies of lead-exposed workers (IARC, 1987). The significance of these effects is not clear. The idea has been put forward that the carcinogenic activity of lead is based on an indirect role in carcinogenesis, for example, in inhibiting DNA repair, rather than being due to causing alterations in DNA directly (Silbergeld et al., 2000).

7.6.1 Human data

A large number of studies on the genotoxicity of lead are available, the majority of which report a clastogenic effect as summarised in ATSDR (2019), AGS (2017) and IARC (2006).

This section focusses on studies published in the year 2000 or later that investigated workers occupationally exposed to lead, measured as PbB levels. Such studies are summarised in Table 30.

Table 30: Studies investigating genotoxic effects in adult lead-exposed workers

PbB (µg/L)[1)]	Cohort[2)]	Result(s), comments	Reference
727±341 44±21	23 workers, battery manufacture, mean age 40±5, 57% smokers, Turkey 23 controls, matched for sex, age and smoking	**CA and DNA repair capacity positive** DNA damage sign. increased in workers compared to controls; e.g.: CA: 0.014±0.011 vs 0.007±0.010 DNA Repair: 10.6±3.4 vs 12.4±3.7 Dose-related increases in CA and reduction in DNA repair capacity	(Karakaya et al., 2005)
  762-880 218-791 10-19 6-34	113 workers, battery plant, 88% males, 35% smokers, with symptoms of lead poisoning, India 6/113 ALAD 1-2/2-2 107/113 ALAD 1-1 102 controls, 86% males, 9% smokers 2/102 ALAD 1-2/2-2 100/102 ALAD 1-1	**Comet** assay, **MN** (buccal cells), and **CA positive** DNA damage sign. increased in workers compared to controls; e.g.: CA (% aberrant cells): 13.18 vs 8.41* (1.6-fold incr.) ALAD 1-2/2-2 type subjects had higher PbB levels compared to ALAD 1-1 subjects	(Shaik and Jamil, 2009)
504±92 (282-655) 56±28 (17-180)	44 male workers battery department, mean age 39±7, 70% smokers, Poland 52 controls, 67% males, 42±7 years old, 63% smokers	**Comet, MN** (CBMN)**, SCE positive** DNA damage sign. increased in workers compared to controls; e.g.: MN (‰): 18.6±5.0 vs 6.6± 3.9 (2.8-fold incr.)	(Palus et al., 2003)
559±20 207±8.3	103 workers, battery plant, mean age 39±1, 11.1 cigarettes/day Bulgaria 78 'matched' controls, mean age 42, 11.1 cigarettes/ day 43/78 internal 35/78 external	**MN** (MN and BNMN in PBL) **positive** BNMN correlated with PbB (<250, 250-400, 400-600, >600 µg/L) MN and BNMN frequencies sign. increased in all workers compared to all controls: MN (‰): 42.7±1.9 vs 21.8±1.1 (2.0-fold incr.) BNMN (‰): 37.3±1.7 vs 20.2±1.0 (1.8-fold incr.)	(Vaglenov et al., 2001)
594±283 24.4±11.5	53 workers, automotive battery recycling, mean age 36±10, 28% smokers, Brazil 53 controls, mean age 33±12, 13% smokers	**Comet** assay and **MN** (CBMN) **postive** Comet assay and MN frequencies sign. higher in workers compared to controls: Comet assay ('damage frequency') 14.1±16.2 vs 1.76±1.84, MN: 13.9±8.46 vs 4.53±2.08 (3-fold incr.); no sign. difference in comet assay or MN between smoking and non-smoking workers	(Minozzo et al., 2010)
532±124 581±112 482±121 *not provided*	20 male workers, 60% smokers, Romania 10/20 one or more intoxications last 10 years 10/20 no intoxications 20 Controls, 55% smokers	**MN** (CBMN) **positive** MN sign. increased in all workers compared to control group: MN (‰): 6.0±2.33 vs. 2.7±0.98 (2.2-fold incr.); MN (‰) higher in intoxicated workers (7.0±2.87; 3.2-fold incr.) compared to non-intoxicated workers (5.0±1.51; 1.9-fold incr.)	(Stoia et al., 2009)
435±188 45.8±27.1	15 male workers, mean age 45, 67% smokers, battery manufacture 15 controls matched for sex, age and smoking	**MN** (CBMN) **positive** MN sign. increased in workers compared to control group: MN (‰): 21.6±14.7 vs. 9.2±5.5 (2.3-fold incr.)	(Kasuba et al., 2010)

PbB (µg/L)[1)]	Cohort[2)]	Result(s), comments	Reference
>500 350-500 200-350 <100	100 male workers 22/100 high PbB (HE) 47/100 medium PbB (ME) 31/100 low PbB (LE) zinc and lead production, 65% smokers, Poland 42 controls, 49% smokers	**Comet** assay positive DNA in the tail (%) sign. higher in the LE, ME, and HE subgroups compared to control group: 10%, 15%, and 20%, respectively	(Dobrakowski et al., 2017) working group Pawlas
432±78.9 54.1±22.7	62 workers, metal work, Poland 26 controls	**Comet** assay **negative** (for measured PbB), **positive** (duration of Pb exposure)	(Olewinska et al., 2010) working group Pawlas
400±180 120±40	31 workers metal powder-producting factory, mean age 41±8, 65% smokers, Turkey 20 controls, mean age 39±8, 50% smokers	**MN** (CBMN) **positive** MN sign. increased in workers compared to control group: MN: 0.65±0.28 vs. 0.24±0.13 (2.7-fold incr.)	(Hamurcu et al., 2001)
392±103 30.3±29.4	78 male workers lead and zinc smelter and battery recycling, mean age 37±9, 33% smokers, Poland 38 controls, mean age 35±10, 39% smokers	**Comet** assay **negative** **8-OHdG positive**	Pawlas et al. (2017)
396±76 44±17	37 battery plant workers, mean age 41±7, 27% smokers) 29 controls, mean age 38±5, 38% smokers	**Comet** assay **positive** Sign. trend with increasing PbB levels ranging from <250 to 250-350 to over 350 µg/L	(Fracasso et al., 2002)
354±148 19.5±19.7	26 workers, mean age 31±9, 38% smokers, battery recycling, Brazil 29 controls, mean age 34±11, no information on smoking	**MN positive** MN frequency in workers sign. increased compared to controls: MN (‰): 3.9±2.4 vs 1.5±1.4 (2.6-fold incr.)	(Minozzo et al., 2004)
345±15 (134-718) 104±4 (81-135)	71 battery plant workers, mean age 30±0.4, 'moderate' smokers, Turkey 20 controls, mean age 30±0.7, 'moderate' smokers	**SCE positive** SCE sign. higher in workers (7.8±0.5) compared to controls (5.4±0.1)	(Duydu and Suzen, 2003)
325±145 93±29 42±14	23 high PbB workers, mean age 47±9.9, 26% smokers 34 low PbB workers, mean age 42±9, 18% smokers Battery plant, China 30 controls, mean age 49±5, 37% smokers)	**DNA-Protein-Crosslinks (DPC)**, **SCE positive** DPC and SCE affected by smoking DPC (1.4±0.5% vs 1.0±0.3%) and SCE (5.9±0.7 vs 4.9±0.4) sign increased in high exposed non-smoking workers	(Wu et al., 2002)

PbB (µg/L)[1)]	Cohort[2)]	Result(s), comments	Reference
320±25 20±3	25 workers, 80% males, mean age 38, 40% smokers, manufactir of lead batteries, China 25 controls, matched for sex, age and smoking	**Comet** assay and **MN** (CBMN) **positive** **TCR gene mutation negative** MN and TCR mutation frequencies in workers compared to controls: Comet (% tail DNA): 13.0±2.3 vs 4.8±2.6 MN (‰): 9.0±1.5 vs 2.4±0.1 (3.8-fold incr.) TCR mutation (x10^{-4}): 1.69±0.15 vs 1.74±0.17	(Chen et al., 2006)
320 280 370	70 male workers 34/70 plant 1 (chemical production) 36/70 plant 2 (battery manufacture) 38 controls	**Comet** assay negative, **TCR mutation** frequency **positive**	(Garcia-Leston et al., 2011)
320±11 36.5±4.1	148 workers, manufacture of lead substances or lead batteries, mean age 48±9, 41% smokers, Portugal 107 controls, mean age 43±12, 17% smokers	**Comet** assay, **MN** (flow cytometry; PBL), **TCR mutation** frequency **positive** MN (flow cytometry analysis) sign. higher in workers (19.8±0.3 vs 17.8±0.3%; 1.1-fold incr.,) TCR mutations sig. higher in workers (21.1±1.9 vs 6.9±1.0)	(Garcia-Leston et al., 2012)
301±41.3 324±32 281±46 67.1±9.7 73±9 70±8	200 male workers 152/200 smokers 48/200 non-smokers lead acid storage battery recycling and industrial manufacturing, India 200 male controls matched for age and socioeconomioc status 68/200 smokers 142/200 non-smokers	**Comet** assay, **MN** (CBMN in PBL and buccal cells), **CA** (PBL) **positive** Comet, MN (PBL) and CA frequencies sign. higher in all workers compared to all controls; e.g.: Comet (% tail DNA): 13.0±2.3 vs 4.8±2.6 MN/PBL (‰): 3.8±1.0 vs 2.3±0.9 (1.6-fold incr.) CA (%/200): 2.5±0.7 vs 1.6±0.6 (1.6-fold incr.) MN and CA slightly higher in smoking compared to non-smoking workers increases statistically significant for non-smoking workers statistically non significant (possibly due to lower statistical power)	(Chinde et al., 2014)
303±20.9 32±2.6	90 male workers in secondary Pb recovery, 62% smokers, India 90 male controls matched for age and socioeconomioc status, 42% smokers	**Comet** assay, **MN** (CBMN in PBL and buccal cells), **CA** (PBL) **positive** Comet, MN (PBL) and CA frequencies sign. higher in all workers compared to all controls Comet (tail length): 17.9±0.9 vs 8.2±0.6 MN/PBL (‰): 6.5±0.9 vs 3.2±0.7 (2.9-fold incr.) CA (%): 7.2±1.0 vs 2.5±0.5 (2.9-fold incr.) MN and CA slightly higher in smoking compared to non-smoking workers; for both groups increases statistically non significant (possibly due to lower statistical power)	(Grover et al., 2010)
286±38 284±49 280±61 35.8±0.8 34.2±0.7 37.9±1.4	25 male workers 14/25 non-smokers 11/25 smokers Battery plant, Turkey 25 male controls 16/25 non-smokers 9/25 smokers	**Comet** assay (leukocytes) and **DNA repair** (challenge assay) **positive** Comet (%tail DNA): 9.95±0.93 vs 7.56±0.61 DNA repair capacity: 25.0±3.8 vs 48.2±4.4 Smokers slightly more affected (but statistically not significanty)	(Jannuzzi and Alpertunga, 2016)

PbB (µg/L)[1)]	Cohort[2)]	Result(s), comments	Reference
115 (28-433) ≥265 <265 50 (27-114)	147 workers mean age 37, 69% smokers 74/147 high Pb workers 73/147 low Pb workers 50 controls, mean age 33, 52% smokers	**MN** (CBMN in PBL) **positive** MN frequency in PBL of high Pb workers (8.1±3.1‰; 2.9-fold increase) and low Pb workers (5.7±2.3‰; 2.0-fold increase) sign. higher than controls (2.8±1.9‰) MN frequency higher in PBL of workers with methylated human tumor suppressor genes compared to PBL of workers with unmethylated tumour suppressor genes	(Yu et al., 2018)
248±147 260±147 228±147 27.5±15.2 30.7±17.7 25.2±13.1	45 male workers, 28/45 smokers 17/45 non-smokers Pb recovery, India 36 male controls 'matched' for age and socioeconomioc status 15/36 smokers 21/36 non-smokers	**Comet** assay **positive** Positive for smoking and non-smoking workers compared to their respective controls. Smoking had a significant effect on DNA damage in the control group whereas a non-statistically significant effect was noticed in the exposed workers.	(Danadevi et al., 2003)
220±18 (42-405) 30±2.4 (12-52)	30 workers, ceramic pottery, Croatia 30 controls matched for age, smoking, gender	**Comet** assay (alkaline), **MN** (cytokinesis-blocked) **positive** Comet - tail length: 16.71.2 vs 14.1±0.2 - tail intensity: 3.21±0.73 vs 1.54±0.14 Apoptosis: 19.6±3.8 vs 5.6±1.1 MN 18.2±1.6 vs 7.8±1.1 (2.3-fold increase)	(Kasuba et al., 2012)
126±122 180±133 47.7±24.7	61 male workers 35/61 smokers 26/61 non-smokers, occupational Pb exposure, Turkey No controls	**Comet** assay **positive** when comparing smoking workers (180±133 µg Pb/L) with non-smoking workers (47.7±24.7 µg Pb/L) **Comet** assay **questionable** when comparing workers >100 µg/L with workers <100 µg/L due to missing adjustment for smoking	(Kayaalti et al., 2015)
105±31 71±28	25 male painters, Mexico 25 male controls matched for age	**MN**, **CA**, **SCE positive** (according authors) **PbB levels did not correlate positively with the cytogenetic damage, neither did smoking or alcohol intake**. Chromatid and chromosome damage in lymphocytes associated with occupational exposure time (years of exposure) However, potential confounders such as solvents (e.g., benzene) not considered	(Pinto et al., 2000)
52.8±2.5 32.8±6.4	30 workers in manufacture and recycling of car batteries, 83% males; 47% smokers, 53% non-smokers, India 30 health controls (83% males; no information with regard to smoking)	**Comet** assay **questionable** (positive according to authors but questionable due to missing information on smoking status of controls; presumably not adjusted for smoking) Cigarette smoking among the workers had a synergistic effect on inducing DNA damage; no information on smoking status in controls	Manikantan et al. (2010)
44.1 (28-137) *Not provided*	78 workers, exposed to cadmium, cobalt and lead, Germany 22 controls	DNA **SSB negative** Co-exposure (e.g., cadmium and lead) may cause genotoxic effects	(Hengstler et al., 2003)

Abbreviations: BNMN: binucleated micronuclei; CA: chromosomal aberration assay; CBMN: cytokinesis-block micronucleus; MN: micronucleus assay; PBL: peripheral blood lymphocytes; SCE: sister chromatid exchange; SSB: single-strand breaks

[1)] mean values ± SD (range) if not stated otherwise; GM meometric mean
[2)] cross-sectional studies if not state otherwise

In workers exposed to mean PbB levels ≥400 µg/L increased frequencies of genotoxic effects were reported:

- DNA damage measured in the comet assay in lymphocytes (Dobrakowski et al., 2017; Minozzo et al., 2010; Olewinska et al., 2010; Palus et al., 2003; Shaik and Jamil, 2009),
- clastogenic effects measured as micronuclei (MN) (Hamurcu et al., 2001; Kasuba et al., 2010; Minozzo et al., 2010; Palus et al., 2003; Stoia et al., 2009; Vaglenov et al., 2001),
- chromosomal aberrations (CA) (Shaik and Jamil, 2009),
- sister chromatid exchange (SCE) (Palus et al., 2003),
- impaired DNA repair capacity (Karakaya et al., 2005).

Several studies are available investigating workers with mean PbB levels between 300 and 400 µg/L. All studies reported also clastogenic effects such as increases in the following parameters:

- DNA damage measured in the comet assay in lymphocytes ((Chen et al., 2006); (Chinde et al., 2014); (Danadevi et al., 2003); (Fracasso et al., 2002); (Grover et al., 2010); (Jannuzzi and Alpertunga, 2016); (Kasuba et al., 2012)),
- clastogenic effects measured as micronuclei (MN) (Chen et al., 2006b; Chinde et al., 2014; Grover et al., 2010; Kasuba et al., 2012; Minozzo et al., 2004; Yu et al., 2018),
- chromosomal aberrations (Chinde et al., 2014; Grover et al., 2010;)
- impaired DNA repair capacity (Jannuzzi and Alpertunga, 2016),
- sister chromatid exchanges (SCE) ((Duydu and Suzen, 2003); (Palus et al., 2003); (Wu et al., 2002), and
- increased DNA-protein cross-links (Wu et al., 2002).

In one study (Pawlas et al., 2017) DNA damage did not show a difference in workers compared to controls, but did show an increase in the urinary concentration of 8-OHdG indicating oxidative stress in workers.

Three studies investigated gene mutations in workers that had similar mean PbB levels of 320 µg/L. Chen et al., 2006b found no increase in TCR mutation frequency in 25 exposed workers, whereas a significant increase of TCR mutations was reported by Garcia-Leston et al. (2011, 2012).

There are fewer studies investigating smaller numbers of workers with mean PbB levels between 200 and 300 µg/L. However, in all studies genotoxic effects were reported such as increased DNA damage and DNA repair (Jannuzzi and Alpertunga, 2016), or DNA damage (Danadevi et al., 2003), or DNA damage and increased MN frequency (Kasuba et al., 2012), or increased MN frequency (Yu et al., 2018). However some of the exposed workers had PbB clearly higher than the mean (e.g. mean 220 vs highest 405 µg/L in Kasuba et al., 2012). Studies were often small (Kasuba et al., 2012) investigated only 30 lead-exposed workers) and did not adjust for other occupational exposures or did it only for a limited number of factors (e.g. Kasuba et al., 2012 adjusted only for cadmium exposure).

The available database investigating genotoxic effects in workers with mean PbB levels below 200 µg/L is insufficient. At such PbB levels, potential confounders are becoming

more relevant and require an appropriate adjustment. Smoking has been demonstrated in several publication to have an effects on DNA damage. In addition, DNA damage levels in smoking workers were found to be significantly higher than the levels observed in non-smoking workers (Kayaalti et al., 2015). This difference may be related to the direct effects of cigarette smoke or impaired lung clearance mechanisms and could be important for workers with already elevated blood lead levels (Brown et al., 1980). Smoking could also lead to higher PbB levels via hand-to-mouth behaviour in case of insufficient hygienic working environment.

Kayaalti et al. (2015) found increased DNA damage in smoking workers (PbB 180±133 µg/L) compared to non-smoking workers (PbB 47.7±24.7 µg/L); however, no non-exposed controls were investigated.

Manikantan et al. (2010) reported increased DNA damage in 30 workers (PbB 52.8±2.5 µg/L) compared to 30 controls (PbB 32.8±6.4 µg/L). 47% of the workers were smokers. However, smoking habits of the controls were not reported. The authors reported a "synergistic" effect of smoking on DNA damage among workers. Due to the uncertainty with regard to the smoking habits of the contols, the results of this study are not considered reliable.

Pinto et al. (2000) investigated 25 male painters with PbB levels of 105±31 µg/L. In comparison with 25 age-matched controls (PbB 71±28 µg/L) Mn, CA and SCE frequencies were significantly increased. However, PbB levels did not correlate positively with the cytogenetic damage, neither did smoking or alcohol intake. Chromatid and chromosome damage in lymphocytes was associated with occupational exposure time (years of exposure). It is to be noted that the difference in PbB levels is small between the painters and the controls. Furthermore, the authors reported exposure of the workers to organic solvents such as gasoline, but did not adjust for other potential confounders such as benzene. Therefore, the result of this study is not considered reliable to investigate effects of lead only.

Hengstler et al. (2003) found no increase in the frequency of DNA singles stand breaks (SSB) in 78 workers (PbB 44.1 µg/L, range 28 to 137 µg/L) compared to 22 controls. However, in the presence of constant exposures to cobalt and cadmium (8 µg/m^3 and 3.8 µg/m^3) increasing Pb air concentrations from 1.6 to 50 µg/m^3 led to an almost 5-fold increase in the odds ratio of DNA-SSB. The authors assumed that the mechanism behind these interactions might be repair inhibition of oxidative DNA damage, since a decrease in repair capacity will increase susceptibility to reactive oxygen species generated by cadmium or cobalt. In the study, the repair of 8-oxoguanine decreased with increasing exposures and inversely correlated with the level of DNA-SSB.

Epigenetic effects

Zhang et al. (2019) used the Illumina Infinium Methylation EPIC BeadChip (850K) to investigate genome-wide differences in DNA methylation between occupational workers with high PbB levels (371 to 487 µg/L; n=4) and low PbB levels (22 to 55 µg/L; n=4). The identified differences in methylation between workers with high exposure and low exposure were subtle. The authors did not observe special areas of methylation changes but instead observed subtle CpG changes distributed at specific gene loci. A potential interpretation of these small scale modifications is, according to the authors, that unlike the changes in conditions such as cancer where large differences in DNA methylation are found, the DNA methylation changes in response to environmental factors such as Pb exposure may be subtle and gene specific.

Devoz et al. (2017) investigated in 100 male workers employed in automotive battery factories global DNA methylation. The PbB levels were 200±110 µg/L (range 18-480 µg/L) and % global DNA methylation was 2.8±1.1% (ranging from 1.1 to 6.5%). A marked association was noted between PbB and DNA global methylation.

Yu et al. (2018) found that the MN frequency was higher in lymphocytes of workers with methylated human tumour suppressor genes compared to lymphocytes of workers with unmethylated tumour suppressor genes. PbB levels in workers were in average 115 µg/L (range 28-433 µg/L).

Conclusion

AGS (2017) concluded on a LOAEC of 300 µg/L, taking into account IARC (2006), Garcia-Leston et al. (2010, 2012b), Grover et al. (2010), Kasuba et al. (2012), and Khan et al. (2010). AGS also concluded that other publications indicate a lower effect concentration (Manikantan et al., 2010; Pinto et al., 2000), that require further confirmation.

Safe Work Australia (2014) concluded "*Markers of mutagenicity (e.g. sister chromatic exchange frequency, DNA protein cross-links) were elevated in workers with mean or median PbB ranging from 20 µg/dL (Kasuba et al. 2012) to 61 µg/dL (Vaglenov et al. 1998).*"

Taking into account the positive findings for DNA damage in lead-exposed workers as summarised in Table 30, a LOAEL for clastogenic effects of 300 µg/L is assumed. The uncertainty of the limited data in the exposure range below 300 µg/L is noted as discussed above.

7.6.2 Animal data (in vivo)

DNA strand breaks

The following summary of the available data from investigations conducted in rats and mice is based on the review of the data by Garcia-Leston et al. (2010). Valverde et al. (2002) used a lead inhalation model in mice in order to detect the induction of genotoxic damage as single-strand breaks and alkali–labile sites in several organs. They found induction of DNA damage after a single inhalation only in the liver and the lung. In subsequent inhalations the response was positive in all organs tested except for the testicle. These results showed that lead acetate inhalations induced systemic DNA damage but some organs are special targets for this metal, such as lung and liver, depending in part on the length of exposure. Devi et al. (2000) also found a significant increase in mean comet tail length at all time intervals tested after oral treatment of mice with lead nitrate compared to controls. Yuan and Tang (2001) studied the accumulation effect of lead on DNA damage and the protection offered by selenium in mouse blood cells in three generations. Significant induction of DNA damage was observed in both sexes of the second and third generations, suggesting that the accumulation effect of lead was very significant already from the second generation. Valverde et al. (2001) explored the capacity of lead, cadmium, or a mixture of both metals to interact with acellular DNA in cells from several organs of CD-1 mice by employing a variant of the comet assay. By means of this modified assay (described by Kasamatsu et al., 1996) which used an enriched-lysis solution with proteinase K, DNA was no longer held under the regulation of any metabolic pathway or membrane barrier. They obtained a negative response in the induction of DNA damage in cells derived from the liver, kidney and lung. However, they observed the production of lipid peroxidation and an increase in free radical levels in the different organs after inhalation of lead acetate, suggesting the induction of genotoxicity and carcinogenicity by indirect interactions, such as oxidative stress."

DFG (2009) also reviewed the studies by Devi et al. (2000) and Valverde et al. (2002) and concluded that "These studies are thus of little value due to methodological shortcomings."

Nava-Hernandez et al. (2009) reported increased DNA damage in pachytene spermatocytes of male rats exposed for 13 weeks to lead acetate.

Xu et al. (2008) exposed mice to 10-100 mg Pb acetate/kg bw/day via gavage for four weeks and observed a concentration-dependent increase in DNA single strand breaks in lymphocytes that was statistically significant at 50 and 100 mg/kg bw/day. The authors

characterized the observed DNA damage as severe. Indicators for oxidative stress (ROS, MDA) were also increased.

Narayana and Al-Bader (2011) observed no statistically significant increase in DNA damage in the livers of rats exposed to 5,000 or 10,000 ppm Pb nitrate in drinking water for 60 days. However, variability within exposure groups was high and DNA fragmentation appeared to be lower in the exposed animals.

Chromosomal aberrations

Garcia-Leston et al. (2010) reviewed the available data and summarised that "Significant increases in the CA rate were found in several mammalian studies: leukocytes from male and female mice fed with lead acetate (Muro and Goyer, 1969), in cynomolgus monkeys (Macaca irus) administered lead acetate in the diet (Jacquet and Tachon, 1981), in bone marrow cells of rats after intraperitoneal administration of lead acetate (Tachi et al., 1985), and in maternal bone marrow and fetal liver and lung cells of ICR Swiss Webster mice following maternal exposure to lead nitrate (Nayak et al., 1989). Other authors did not find any increase in the frequencies of CA in mice fed with lead acetate (Deknudt and Gerber, 1979). […] Other studies reported differential induction of several types of CA. Jacquet et al. (1977) carried out an experiment in which dietary lead at different dose levels was given to female C57B1 mice for periods up to 3 months. They found no severe chromosome or chromatid aberrations at any dose level, but the frequency of chromatid gaps increased significantly at the highest doses. Deknudt et al. (1977a) reported that the type of CA induced by lead acetate in cynomolgus monkeys (M. irus) depended on the intake of calcium in the diet. The frequency of "severe" abnormalities (dicentrics, rings, translocations and exchanges) was significantly increased only in the group on a low calcium diet, whereas "light" abnormalities (gaps and fragments) increased with time in all groups receiving lead irrespective of the diet. Aboul-Ela (2002) found only structural aberrations like chromatid gaps, deletions and fragments in bone marrow cells of male Swiss mice after oral administration of lead acetate. Nehéz et al. (2000) investigated the possible genotoxic effects exerted by the pyrethroid cypermethrin and by either of the metals cadmium and lead alone or in combination, on bone marrow cells of outbred male Wistar rats. Treatment with lead acetate only increased significantly the number of aberrant cells and numerical aberrations but did not alter the number of structural aberrations. In contrast, the combination of cypermethrin and lead caused a significant increase in aberrant cells and in structural aberrations but not in numerical aberrations. The most frequently observed structural aberrations were gaps and acentric fragments. These results agree with Lorencz et al. (1996), who found increases in numerical aberrations in Wistar rats treated with different doses of lead acetate."

Micronuclei

Garcia-Leston et al. (2010) reviewed the available data and summarised these data as follows: "Several studies that evaluated the genotoxic effects of lead acetate in rodents by means of the MN test showed an increase in the frequency of MN (Tachi et al., 1985; Robbiano et al., 1999; Çelik et al., 2005; Piao et al., 2007; Tapisso etal., 2009). Alghazal et al. (2008) analysed the MN rate in bone marrow erythrocytes of male and female Wistar rats treated with lead acetate trihydrate. They found a significant increase in the total number of MN in polychromatic erythrocytes of both male and female rats with regard to the control group. Moreover, there was a decrease in the ratio of polychromatic to normochromatic erythrocytes in male rats, indicating both genotoxic and cytotoxic effects of lead acetate in male rats. Similarly, Jagetia and Aruna (1998) observed an increase in the frequency of MN in bone marrow cells of male and female mice treated with lead nitrate. The frequency of MN did not show a dose-related increase but male mice were more sensitive to the induction of MN than female mice, evidenced by higher frequencies of micronucleated polychromatic erythrocytes. On the contrary, three studies carried out in mice (Jacquet et al., 1977), rabbits (Willems et al., 1982) and fish (Ramsdorf et al., 2008) did not find any increase in the MN frequency when compared the lead-exposed

group to the control group. However, Ramsdorf et al. (2008) related their negative results to the low number of fish analysed and to the fact that the piscine MN assay may lack sensitivity, since it does not detect the mitotic disjunctions if they do not provoke chromosomal loss in the anaphases neither chromosome aberrations caused by rearrangement, such as translocations or inversions, if these do not originate acentric fragments (Metcalfe, 1989)."

Table 31: Selected studies in experimental animals investigating clastogenic effects (MN or CA) of lead

Blood lead (µg/L)	Exposure	Reported effects	Reference
Monkeys			
Not measured	Cynomolgus monkey, lead acetate, 0, 1 or 5 mg/day, oral, 12 months	**CA**: sign. increase in frequency of chromosome and chromatid gaps	(Jacquet and Tachon, 1981)
Not measured	Cynomolgus monkey, lead acetate, oral, 1.5, 6, 16 mg/day, 6 days/week, 16 months	**CA**: frequency of severe abnormalities (dicentrics, rings, translocations and exchanges) sign. increased only in the group on a low calcium diet, whereas "light" abnormalities (gaps and fragments) increased with time in all groups receiving lead irrespective of the diet	(Deknudt et al., 1977)
Rabbits			
66, 532, 615	Rabbits (5 males per group), lead acetate, 0, 0.25, 0.50 mg/kg bw, subcutaneously, 3 days/week, 14 weeks	**MN** in bone marrow erythrocytes and **SCE** in lymphocytes **negative** Also no effects on sperm count or on morphologic abnormalities of the sperm, nor on the histopathology of the testes	(Willems et al., 1982)
Rats			
67±28 18±8	Wistar rats (7 animals per sex and group), lead acetate, 25 mg/kg bw, 7 i.p. injections once every two days	**MN** (MNPCE/7000 PCEs) sign.(*) increased compared to control: Control: 23 (0.33%) 25 mg/kg bw: 40 (0.57%)* In addition, sign. increase of abnormal sperm, reduced serum thyroid hormone concentrations and sign., increase in serum cortisol	(Piao et al., 2007)
Not measured	Wistar rats (4 females per group), lead acetate, gavage, 140, 250, 500 mg/kg bw/d, 10 weeks	**MN** (MNPCE/1000 PCEs) sign.(*) increased compared to control: Control: 0.87±0.125 140 mg/kg bw/d: 1.75±0.25* 250 mg/kg bw/d: 1.91±0.05* 500 mg/kg bw/d: 2.41±0.16*	(Celik et al., 2005)
Not measured	Wistar rats (8 females, 6 males), lead acetate 100 mg/L drinking water, 125 days, controls (8 females, 5 males)	**MN** (MNPCE/1000 PCEs) sign.(*) increased compared to control: Control: 9.6±3.2 (F), 4.0±4.5 (M) 125 mg/L: 13.4±2.7 (F), 24.2±7.9 (M)*	(Alghazal et al., 2008)
Not measured	Wistar rats (10 males per group), lead acetate, 10 mg/kg bw/d, 4 weeks, 5 d/week	**CA** number of aberrant cells (%) sign.(*) increased Control: 1.6±0.31 10 mg/kg bw/d: 3.6±0.48* Numerical aberrations (chromosome number <42) sign. (*) increased Control (n=10): 5.0% 10 mg/kg bw/d (n=30): 15%*	(Nehez et al., 2000)

Blood lead (µg/L)	Exposure	Reported effects	Reference
Not measured	Algerian mice (6 males per group), lead acetate, 0.46 mg/kg bw, 5 or 10 i.p. ingections	**MN** (MNPCE%) sign. (*) increased in Pb groups following 5 or 10 injections: Control 10 injections: 2.83±1.47 0.46 mg/kg 10 injections:8.50±2.43* **Abnormal sperm** (%) sign.(*) increased in Pb groups following 5 and 10 injections: Control 10 injections: 2.08±0.47 0.46 mg/kg 10 injections:5.30±0.94*	(Tapisso et al., 2009)
Not measured	Swiss mice (male, number not found), lead acetate, 200, 400 mg/kg diet, 5 days	**CA** in bone marrow cells (%) sign.(*) increased: Control: 4.0±0.31 200 mg/kg diet: 10.1±1.95* 400 mg/kg diet: 20.6±2.17* Administration of $CaCl_2$ (40 or 80 mg/kg bw by gavage for 3 days, 2 weeks after Pb administration, did not show an increase in CA.	(Aboul-Ela, 2002)
Not measured	Swiss mice (6 animals per sex and dose), lead nitrate, single intraperitoneal injection, 0, 0.625, 1.25, 2.5, 5, 10, 20, 40, 80 mg/kg bw, investigation 12, 24, or 36 h after injection	**MN** frequency no dose-related increase	(Jagetia and Aruna, 1998)
Not measured	C57B1 mice, lead acetate, 0.5, 1% in diet, 3 months	**CA:** no severe chromosome or chromatid aberrations **MN** (MNPCE): not increased	(Jacquet et al., 1977) not ordered

7.6.3 In vitro data

Formation of reactive oxygen species

AGS (2017) summarised the available data as follows: "High mutation frequencies and mutation spectra similar to those induced by reactive oxygen species were found in a study of Yang et al. (1996) in CHO K1 cells at cytotoxic concentrations. Among other aspects it is described that via an inhibition of the aminolevulinic acid dehydratase an accumulation of aminolevulinic acid was prompted with concomitant generation of ROS and oxidative DNA damage (Beyersmann and Hartwig, 2008; IARC, 2006). Zhang et al. report ROS-related DNA strand breaks as a confirmed mechanism (Zangh et al., 2014)."

A more recent study specifically examined the possibility of oxidative DNA damage (Hernández-Franco et al., 2011). Human embryo liver cells (WRL-68 cell line) were treated for 1 month with 5 and 30 µM lead acetate. The exposure level was chosen such that it corresponded to the occupational exposure to lead. The viability of the cells was little affected (only in the third week at the higher concentration of 30 µM). Compared to the control sample, significantly increased ROS production was observed. Catalase and superoxide dismutase activities were elevated accordingly, but they changed in line with the time of exposure. Membrane lipid peroxidation was likewise found at both concentrations, but as the exposure time was increased it was no longer detectable. Significant DNA damage in the Comet Assay was found in the fourth week (and only then). The authors report direct oxidative changes in the first few weeks induced by lead exposure which are then partly corrected by anti-oxidative mechanisms, in which case the oxidative status is considered to be relevant and potentially problematic in terms of resulting toxicity when other external stimuli prevail at the same time or when the anti-oxidative barriers do not deploy their full effect (Hernández-Franco et al., 2011).

Mutagenicity

DFG (2009) summarised the data as follows: "The data on the genotoxicity of lead have been summarised in several review articles (Hartwig 1994; IARC 1980, 1987; Silbergeld et al., 2000). Whereas lead salts (with the exception of lead chromate) are generally non-mutagenic in bacterial test systems, mutagenicity tests in mammalian cells show predominantly positive effects. However, the extent of the mutagenic effects and the applied concentrations vary considerably and are dependent both on the cell line and on incubation conditions. Only weak mutagenic effects were observed for the most part in classical mutagenicity tests (HPRT test with V79 or CHO cells). On the other hand, more recent studies with AS52 cells show a marked concentration-dependent mutagenicity even at very low, submicromolar concentrations (0.1–1 µM) (Ariza and Williams 1996, 1999; Ariza et al., 1998). Whereas principally base pair substitutions were induced in the lower concentration range between 0.1 and 0.5 µM, deletions predominantly occurred between 0.5 and 1 µM. The most important difference to earlier studies is found in the test system: AS52 cells were used, in which the inherent hprt gene was inactivated and a bacterial gpt gene integrated. This test system also detects larger deletions, which in classical test systems result in cell death via a loss of vital genes. The AS52 cells were thus found to be especially sensitive to substances causing mutagenicity via reactive oxygen species, including a large number of metal compounds. In addition, lead ions >0.05 µM caused the induction of micronuclei (Thier et al., 2003) and co-mutagenic effects in combination with UV radiation in the submicromolar range (Hartwig et al., 1990)"

Micronuclei

AGS (2017) summarised the data as follows: "Bonacker et al. (2005) examined the occurrence of micronuclei in V79 cells after exposure to lead chloride and lead acetate at low concentrations. In the case of lead acetate already at 50 nM a distinct increase was found compared to the control group, and with lead acetate at 1.1 µM and higher. It was demonstrated that those micronuclei are essentially the consequence of an aneugenic effect of the lead salts (CREST analysis). Despite different potency for forming micronuclei and different dose-effect relationship, it was only at somewhat higher (and identical) concentrations (approx. 10 µM) that lead acetate, lead chloride and lead nitrate led to inhibition of the microtubule function. The cytotoxicity of lead chloride and lead acetate on V79 cells was also virtually identical."

Chromosomal aberrations

AGS (2017) summarised the data as follows: "Asakura et al. (2009) did not find dose-related chromosomal aberrations in cultivated mammal cells, even at high concentrations (7 % and 4 %, respectively, at 500 and 1000 µg/ml at +S9mix, structurally aberrant chromosomes). Chromosome aberrations (achromatic lesions, chromosome fragments) were observed after treatment of human leucocytes with lead acetate. But other studies also yielded negative findings (García-Lestón et al., 2010)."

Wozniak and Blasiak (2003) found single and double strand breaks and DNA protein crosslinks after application of 1 to 10 µM lead acetate. In the Comet Assay with human lymphocytes, however, a distinct shortening of the tail length (also compared to the control sample) was visible after administering 100 µM. According to the authors' interpretation DNA crosslinks were potentially formed at 100 µM which will not generate tails. Surprisingly there was no evidence of oxidative DNA damage. The authors discuss whether the repair enzymes were possibly damaged by lead exposure which could potentially have caused the observed strand breaks. As an interesting aspect, Zhang et al. (2014) confirmed in more recent studies that the crosslinks only occur in vitro at concentrations of 100 µM Pb^{2+} whereas other findings in the Comet Assay are already recognisable at 1 to 10 µM.

Disturbance of DNA repair

AGS (2017) summarised the data as follows: "Lead inhibits all essential repair systems (Gastaldo et al., 2007; Hartwig, 1994; Hartwig et al., 1990; McNeill et al., 2007). The inhibition of nucleotide excision repair (NER) was described in 1990 and this went hand in hand with a clearly comutagenic effect in combination with UVC radiation (Hartwig et al., 1990). The substance (Li et al., 2008; Lin et al., 2003) induces mutations in cells with reduced repair enzyme capacity (NER-deficient cells). McNeill et al. showed a disturbance of the Base Excision Repair (BER) in low micromolar concentrations. Gastaldo et al. report delayed occurrence of double strand breaks after application of lead nitrate and disturbances in repair ("non-homologous end-joining repair process"). Zhang et al. mention disturbances of NER and of BER by lead as a confirmed mechanism (Zhang et al., 2014)."

Comet assay

AGS (2017) summarised the data as follows: "Human embryo liver cells (WRL-68 cell line) were treated with 5 and 30 µM lead acetate for 1 month. In the Comet Assay significant DNA damage was found in the fourth week (and only then). The authors see direct oxidative changes in the first few weeks, induced by lead exposure, which are subsequently corrected in part by antioxidative mechanisms in which case in their opinion the oxidative status is relevant and potentially problematic when other external stimuli prevail simultaneously or when the antioxidative barriers do not deploy their full effect (Hernández-Franco et al., 2011)."

DNA structure

Zhang et al. (2014) found that Pb^{2+}could bind to DNA with four binding sites to form Pb^{2+}–DNA complex by minor groove binding effects and electrostatic forces, resulting in damage to the structure of DNA double helix.

7.6.4 Summary

A large number of studies on the genotoxicity of lead are available, the majority of which report a clastogenic effect (ATSDR, 2019, AGS, 2017, IARC, 2006). The data base is quite robust for demonstrating clastogenic effects such as DNA damage and increased MN and CA frequencies in exposed groups with mean PbB levels above 300 µg/L (e.g., Chinde et al., 2014; Grover et al., 2010; Garcia-Leston et al., 2012). There are fewer studies in workers with mean PbB levels between 200 and 300 µg/L that reported increased DNA damage and DNA repair (Jannuzzi and Alpertunga, 2016), DNA damage (Danadevi et al., 2003), and DNA damage and increased MN frequency (Kasuba et al., 2012). Due to the limited number of studies available that investigate clastogenic effects of lead in the exposure range below 300 µg/L and due to methodological limitations of such studies such as small number of workers investigated, lack of adjustment for other relevant exposures, uncertainty about the role of individuals with exposure above the mean, the database in the mean exposure range below 300 µg/L is considered too uncertain for a conclusion.

Based on the results of studies investigating lead-induced genotoxic effects in workers by Vaglenov et al. (2001), Olewinska et al. (2010), Garcia-Leston et al. (2012), Chinde et al. (2014) and Jannuzzi and Alpertunga (2016), AGS (2017) concluded on a LOAEL of 300 µg/L.

7.7 Carcinogenicity

IARC (2006) evaluated the carcinogenic risks of "Inorganic and organic lead compounds" to humans and concluded the following:

- There is *limited evidence* in humans for the carcinogenicity of inorganic lead compounds.

- There is *inadequate evidence* in humans for the carcinogenicity of organic lead compounds.
- There is *sufficient evidence* in experimental animals for the carcinogenicity of inorganic lead compounds.
- There is *sufficient evidence* in experimental animals for the carcinogenicity of lead acetate, lead subacetate, lead chromate, and lead phosphate.
- There is *inadequate evidence* in experimental animals for the carcinogenicity of lead oxide and lead arsenate.
- There is *inadequate evidence* in experimental animals for the carcinogenicity of organic lead compounds.
- There is *inadequate evidence* in experimental animals for the carcinogenicity of tetraethyl lead.
- There is *inadequate evidence* in experimental animals for the carcinogenicity of lead powder.

Overall, IARC (2006) concluded that

- Inorganic lead compounds are *probably carcinogenic to humans (Group 2A)*.
- Organic lead compounds are *not classifiable as to their carcinogenicity to humans (Group 3)*.

The IARC Working Group noted that organic lead compounds are metabolised, at least in part, to ionic lead both in humans and animals. To the extent that ionic lead, generated from organic lead, is present in the body, it will be expected to exert the toxicities associated with inorganic lead.

7.7.1 Human data

The approach in this section is to summarize the latest assessments made by IARC (2006), ATSDR (2007), EFSA (2010, updated 2013), NTP (2012) and US EPA (2013b) and to describe the more recent individual studies that have been published since 2010 focusing on the cancer sites that were identified as being of interest by IARC. These were also the cancer sites investigated in most of the recent studies.

As explained above, IARC (2006) concluded that there is *limited evidence* in humans for the carcinogenicity of inorganic lead compounds. From the extensive human data (cohort and case-control studies and meta-analyses) IARC identified four cancer sites of interest (lung, stomach, kidney and brain) but ended up with the above-mentioned conclusion of limited evidence.

ATSDR (2007) was published more or less same time as IARC (2006) and was thus based mainly on the same data. EFSA (2010, updated 2013) referred to the IARC (2006) conclusions and summarised the animal data but stated for human data that "In accordance with the IARC(2006) classification of lead as a class 2A carcinogen (insufficient evidence of human carcinogenicity), cancer epidemiology will not be considered here". The NTP (2012) assessment of health effects of low level lead did not assess carcinogenicity.

US EPA (2013b) reviewed the human cancer data and concluded that the evidence is inconsistent.

More recent human data

Summaries of the recent (after 2010) epidemiological studies on brain, kidney, stomach and lung cancer are presented in Table 54, Table 55, Table 56 and Table 57 of Appendix 6.

Brain cancer (Table 54, Appendix 6)

Parent et al. (2017) reported a population-based case-control study combining data from seven countries. There were 1800 glioma cases and 5160 controls. Gliomas represent about 75% of all malignant brain tumors. Exposure to lead, cadmium, nickel, chromium

and iron as well as to welding fumes was assessed based on life-time working histories and a job exposure matrix. Although the analyses were adjusted for age and a number of socio-economic variables, they were not adjusted for exposure to the other metals studied. The risk was not increased by lead exposure ever/never (OR 0.8: 95% CI 0.7 – 1.0) nor in any category of cumulative or of duration of exposure.

The cohort studies of McElvenny et al. (2015) and Chowdhury et al. (2014) also reported the risk of brain cancer mortality in 9122 and 56 368 UK and US workers, respectively, identified from among subjects who had undergone past blood lead monitoring due to their occupational exposure. Neither study found an increased brain cancer mortality among the exposed. However, as these cohorts were included in the pooled analysis by Steenland et al. (2017) they are not described here (for further details see Table 54, Appendix 6).

Steenland et al. (2017) analysed mortality by pooling data from three cohorts of lead-exposed workers with PbB data from health surveillance schemes (USA, Finland, UK) including over 88 000 workers and over 14 000 deaths. Both internal comparisons (> 400 µg/L , 300 – 399 µg/L and 200 – 299 µg/L vs less than 200 µg/L) and external comparisons to national mortality rates were performed. In the internal comparison, the risk of brain cancer was not statistically significantly increased in any of the exposure categories while the trend by exposure was of borderline significance (p = 0.09). In the external comparison the SMR for brain cancer was below one in each exposed category.

Liao et al. (2016) followed 73 363 women and 61 379 men of the Shanghai Women's Health Study and Shanghai Men's Health Study, respectively. Exposure to lead was estimated based on life-time working history and a job exposure matrix. Combining data for both sexes, the risk of brain cancer was increased for ever exposed, but without statistical significance (RR = 1.8; 95% CI 0.7 – 4.8) based on 10 exposed cases. However, the risk was not increased in those with high exposure. The authors also found an increased risk for meningioma among women (RR 2.4; 95% CI 1.1 – 5.0) based on 9 exposed cases, while no risk estimate could be calculated for men as all 12 cases occurred in unexposed workers. No PbB data was available.

Gwini et al. (2012) followed 4114 male Australian workers who had undergone medical surveillance including PbB measurements due to their employment in "scheduled lead occupations". Overall the risk of brain cancer was not increased compared to regional rates (SMR 1.05; 95% CI 0.47 – 2.33). All cases occurred in the group with PbB below 300 µg/L and no risk estimate could be calculated for those with a PbB $\geq$ 300 µg/L (expected N of cases was one, based on regional rates).

Ilychova and Zaridze (2012) followed 1432 men and 3102 women employed at least 2 years in the printing industry in Moscow. Overall the mortality from brain cancer was not increased either in men (SMR = 1.24; 95% CI 0.39 – 3.84) or women (SMR = 0.71; 95% CI 0.23 – 2.19). PbB data was not available.

Bhatti et al. (2011) conducted a case-control study of 355 glioma and 151 meningeoma patients and 505 controls in the US analyzing also effect modification of ALAD (aminolevulinate dehydratase) genotype on Pb exposure related risk of cancer. Based on questionnaire information on work history, exposure to lead was assessed both with a job exposure matrix (JEM) and by an expert in industrial hygiene. There was no evidence of an overall association between lead exposure and glioma or of effect modification of the relationship between lead and glioma by ALAD genotype using either method of exposure assessment. There was evidence of an association between lead exposure and meningioma among individuals with the highest category of expert assessed cumulative lead exposure (OR = 2.7 (95% CI: 1.0, 7.8), but no similar evidence was found when examining the JEM cumulative exposure metric (OR = 0.9 (95% CI: 0.3, 2.8). Also for meningioma, the metric based on expert-assessment indicated borderline evidence of effect modification by ALAD genotype with ever exposure to occupational lead (p = 0.09) and statistically significant evidence of effect modification with cumulative lead exposure (p = 0.04) and the risk being

increased for ALAD2 carriers. Neither metric derived from the JEM showed any evidence of effect modification of meningioma risk with ALAD genotype.

If the studies of McElvenny et al. (2015) and Chowdhury et al. (2014) are also considered, even if they overlap with Steenland et al. (2017), there are eight recent studies. Five of them did not find any association between exposure to lead and risk of brain cancer. The study by Steenland et al. (2017) found a borderline significant trend in internal comparisons ($p = 0.09$), while the comparison to external mortality rates did not indicate an effect. The study by Liao et al. (2016) found some indication of an association when considering exposure ever/never, while there was no indication of a dose-response relationship when comparing low and high exposure. It is difficult to characterize the intensity of exposure in that study as the definition of low and high was not based on total lead exposure but on the combination of lead dust and fume and their medians. The study of Bhatti et al. (2011), although not finding consistent evidence that overall the risk of glioma or meningioma would be increased by increasing exposure, found, however some indication that with presumably more accurate exposure assessment (by an expert instead of JEM) there is some indication of an increased risk of meningioma and also of an effect modification of this Pb related risk by ALAD genotype. All in all, the data set seems quite similar to the data set available at the time of IARC (2006) evaluation and there is no consistent epidemiological evidence in the cohort studies of an association and most of the studies are based on small numbers of cases among the exposed.

Kidney cancer (Table 55, Appendix 6)

Michalek et al. (2019) conducted a nested case-control study of 59778 cases and 298890 controls from Finland, Iceland and Sweden. Cases were identified from cancer registries for 1961-2005. A job exposure matrix (JEM) was applied to the job title history of each case and control. The JEM covered 29 substances. There was no indication of an increase risk by increasing cumulative lead exposure overall, or in men or women (p for trend 0.58, 0. 78 and 0.87, respectively and ORs close to 1).

Callahan et al. (2019) reported a study with 1217 cases of kidney cancer and 1235 controls. Exposure to lead was assessed by industrial hygienists based on occupational histories and responses to questionnaires regarding workplace tasks. There was no evidence of an increased risk by any of the lead exposure parameters (p for trend ranging from 0.32 to 0.98 and ORs in all exposure categories close to 1). There was also no evidence of effect modification by variants of the ALAD gene involved in lead toxicokinetics. However, there was some indication of an increased risk from exposure to lead among never smokers.

The above-mentioned pooled analysis (Steenland et al., 2017) covering 88 000 exposed workers with PbB data did not find an increased risk either in internal comparisons (p for trend 0.79) or external comparisons (SMRs below one in all exposure categories). Neither did the UK or US sub-cohorts of this study find an association between PbB level and risk of kidney cancer ((Chowdhury et al., 2014, McElvenny et al., 2015), (see Table 55, Appendix 6).

Bertke et al. (2016) followed 1900 US lead smelter workers. Based on 11 cases of kidney cancer, the SMR was increased, but without statistical significance (SMR 1.56; 95% CI 0.78 – 2.79) and there was no indication of a dose-response relationship (p for trend 0.87).

In the general population Shanghai health surveillance cohorts (Liao et al., 2016) the risk was statistically significantly increased in the high exposure group in men based on 8 cases (RR 2.3; 95% CI 1.1 – 4.7) but not in women (RR 1.2; 95% CI 0.5 – 3.4). As explained above for brain cancer, there was no PbB level data.

In the Australian cohort of 4114 exposed male workers from a health surveillance scheme (Gwini et al., 2012), there were only 6 cases of kidney cancer and the risk was not

increased (SMR 0.65; 95% CI 0.29 – 1.46). There were no cases among those with PbB above 300 µg/L, but also the expected number based on national rates was low.

Southard et al. (2012) conducted a nested case-control study among Finnish male smokers participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. PbB was measured at start of the cancer prevention study. The adjusted OR showed a dose-response by quartiles of PbB (p = 0.022) with an OR of 2.0 (95% CI 1.0 – 3.9) in Q4 (≥ 46.6 µg/L as compared to Q1 (< 25 µg/L) adjusted for age at randomization, smoking, systolic blood pressure, body mass index, alcohol, serum calcium and Calbindin D28K promoter (-366)(rs1800645) genotype

Ilychova and Zaridze (2012) followed 1432 men and 3102 women employed at least 2 years in the printing industry in Moscow. Overall the mortality from kidney cancer was not increased either in men (SMR = 1.26; 95% CI 0.46 – 2.75) or women (SMR = 1.42; 95% CI 0.57 – 2.93). In the highest category of cumulative exposure, there was some indication of an increased risk (SMR=2.12; 95% CI 1.10 – 4.07, both sexes combined). However, there was no adjustment for effect of potential confounding factors. PbB data was not available.

Boffetta et al. (2011) conducted a hospital-based case-control study in the Czech Republic, Poland, Romania and Russia. Exposure to As, Cd, Cr(III), Cr(VI), Pb and Ni was estimated from questionnaire-based work histories in terms of duration (years) and cumulative exposure (µg/m^3 - years). The ORs were adjusted for age, gender, centre, residence, tobacco, body mass index, hypertension and the other metals. The risk was increased for ever exposed to lead, OR 1.55 (95% CI 1.10 – 2.19), but there was no clear dose-response relationship by duration of exposure or cumulative exposure (p for trend not reported). However, the OR was statistically significantly increased in the highest quartile of cumulative exposure (2.25: 95% CI 1.21 – 4.19).

If the studies of (McElvenny et al., 2015) and (Chowdhury et al., 2014) are also considered even if they overlap with Steenland et al. (2017) there are eleven recent studies. Seven of them did not find any association between exposure to lead and risk of kidney cancer. The study by Liao et al. (2016) found some indication of an association in high exposure men, but based on a small number of cases. It is difficult to characterize the intensity of exposure in that study as the definition of low and high was not based on total lead exposure but on a combination of lead dust and fume and their medians. The study of Boffetta et al. (2011) found some evidence of increased risk in the highest quartile of cumulative exposure, while there was no clear dose-response by duration of exposure or cumulative exposure. Southard et al. (2012) found a statistically significant trend by increasing exposure and a statistically significantly increased risk in the highest PbB compared to the lowest and using a comprehensive adjustment for confounding in a nested (matched) case-control design. Ilychova and Zaridze found some indication of an increased risk in the highest exposure category, but there was no adjustment for potential confounders. All in all, the data set seems quite similar to the data set available at the time of the IARC (2006) evaluation and there is no consistent epidemiological evidence in the cohort studies of an association and most of the studies are based on small numbers of cases among the exposed.

Stomach cancer (Table 56, Appendix 6)

The above-mentioned pooled analysis (Steenland et al., 2017) covering 88 000 exposed workers with PbB data did not find an increased risk either in internal comparisons (p for trend 0.93) or external comparisons (SMRs below or close to one in all exposure categories). Neither did the UK or US sub-cohorts of this study find an association between PbB level and risk of kidney cancer (McElvenny et al., 2015, Chowdhury et al., 2014).

In the follow-up of 1900 US lead smelter workers, the SMR was 1.31 (95% CI 0.67 – 2.28, based on 12 cases) and there was no indication of a dose-response relationship (p for trend 0.21) (Bertke et al., 2016).

In the general population Shanghai health surveillance cohorts (Liao et al., 2016) the risk was statistically significantly increased in the high exposure group in men (RR 1.6; 95% CI 1.0 – 2.4) but not in women (RR 0.8; 95% CI 0.5 – 1.5). As explained above for brain cancer, there was no PbB level data.

Kim et al. (2015) followed 81 067 South Korean exposed workers who had undergone PbB testing as part of their health surveillance. The comparison was made to those who had PbB level below 100 µg/L and the risk was not increased in those men with PbB levels of 100-200 or > 200 µg/L, while for women the numbers of cases were too low for meaningful comparisons.

In the Australian cohort of 4114 exposed male workers from a health surveillance scheme (Gwini et al., 2012), there were only 8 cases of stomach cancer and the risk was not increased (SMR 1.04; 95% CI 0.52 – 2.07). There were no cases among those with PbB above 300 µg/L, but also the expected number based on national rates was low.

Ilychova and Zaridze (2012) followed 1432 men and 3102 women employed for at least 2 years in the printing industry in Moscow. Overall the mortality from stomach cancer was not increased either in men (SMR = 0.84; 95% CI 0.55 – 1.22) or women (SMR = 0.96; 95% CI 0.69 – 1.34). PbB data was not available.

If the studies of (McElvenny et al., 2015) and (Chowdhury et al., 2014) are also considered even if they overlap with Steenland et al. (2017) there are eight recent studies. Six of them did not find any association between exposure to lead and risk of stomach cancer. The study by Bertke et al. (2016) found a somewhat, but statistically non-significantly increased SMR overall, but no indication of a dose-response relationship (p for trend 0.21). The study by Liao et al. (2016) found some indication of an association in high exposure men, but this was based on a small number of cases. It is difficult to characterize the intensity of exposure in that study as the definition of low and high was not based on total lead exposure but on a combination of lead dust and fume and their medians. All in all, these new studies seem to differ slightly from the data set available at the time of the IARC (2006) evaluation and provided somewhat less convincing evidence than the conclusion by IARC *"In four of these five studies, there was a fairly consistent excess of 30–50% of stomach cancer compared with external reference populations"*.

Lung cancer (Table 57, Appendix 6)

The above-mentioned pooled analysis (Steenland et al., 2017) covering 88 000 exposed workers with PbB data found an increased risk especially in the internal analysis where comparison was made to those with less than 200 µg/L (p for trend < 0.0001) with relative risks of 1.39, 1.54 and 1.78 among those with 200-299, 300-399 or >400 µg/L, respectively. However, the risk estimates were not adjusted for smoking or for workplace exposures other than lead. Smoking habits were known in a subset of 112 study participants that were invited to bone lead analysis and there was no correlation between pack-years of smoking or frequency of never/ex-smokers and PbB thus not indicating a confounding effect at least in this subpopulation. It is also noteworthy that confounding by smoking is considered less likely when comparing workers with workers (such as the internal comparisons by Steenland and colleagues) than when comparing workers with the general population (Siemiatycki et al., 1988b). Furthermore, the observed relative risk in the highest exposure category was quite high in comparison to what is generally considered as a magnitude of potential excess from confounding by smoking in diseases strongly associated with smoking (Siemiatycki et al., 1988a, Kriebel et al., 2004).

The US sub-cohort of this study also found an association between PbB level and risk of lung cancer when the comparison was made with the lowest exposure category. When comparing to the general population the SMR overall was not increased while there was a small increase in the highest exposure category (Chowdhury et al., 2014). It is to be noted that there was an evident healthy worker effect in the cohort as overall mortality was clearly below 1 (SMR 0.69; 95% CI 0.66 – 0.71) and all major causes of death (except

lung cancer in the highest exposure category) had SMRs below 1. In the UK sub-cohort there was also an excess of lung cancer, although it was not clearly correlated to the PbB level (McElvenny et al., 2015). Neither study adjusted the results for smoking.

In the follow-up of 1900 US lead smelter workers, the SMR was 1.94 (95% CI 1.64 – 2.27) but there was no indication of a dose-response relationship (p for trend 0.39) (Bertke et al., 2016).

In the general population Shanghai health surveillance cohorts (Liao et al., 2016) the risk was increased in the high exposure group in men (RR 1.4; 95% CI 1.0 – 2.0) but not in women (RR 0.8; 95% CI 0.35 – 1.). These risk estimates are adjusted for smoking. As explained above, there was no PbB level data.

Wynant et al. (2013) conducted a pooled analysis of two case-control studies in Montreal (1593 men with lung cancer and 1426 male controls). Exposure to organic and inorganic lead and other relevant substances at work was estimated based on job history. No PbB data was available. Adjustment for potential confounders, including smoking was done. There was no indication of increased risk of lung cancer from exposure to organic lead (ever/never) or inorganic lead (ever/never, or substantial/never).

Kim et al. (2015) followed 81 067 South Korean exposed workers who had undergone PbB testing as part of their health surveillance. Comparison was made to those who had PbB level below 100 µg/L and the risk was not increased in those men with PbB level of 100-200 or > 200 µg/L, while for women the numbers of cases were too low for meaningful comparisons.

In the Australian cohort of 4114 exposed male workers from a health surveillance scheme (Gwini et al., 2012), the risk was not significantly increased (SMR 1.25; 95% CI 0.92 – 1.69). The data by PbB level did not indicate any obvious trend. The risk estimates were not adjusted for smoking.

Ilychova and Zaridze (2012) followed 1432 men and 3102 women employed at least 2 years in the printing industry in Moscow. Overall the mortality from lung cancer was not increased either in men (SMR = 0.94; 95% CI 0.69 – 1.28) or women (SMR = 0.48; 95% CI 0.23 – 0.99). PbB data was not available.

If the studies of (McElvenny et al., 2015) and (Chowdhury et al., 2014) are also considered even if they overlap with Steenland et al. (2017), there are nine new studies. Five of them did not find any association between exposure to lead and risk of lung cancer. The study by Steenland et al (2017) found quite a clear trend of increasing risk associated with increasing PbB but the results were not adjusted for smoking. Some incation of increased risk were also found in the studies by Chowdbury et al. (2014) and McElvenny et al. (2015) which were also part of the study by Steenland and also did not adjust for smoking. The study by Bertke et al (2016) found an increased SMR overall, but no indication of a dose-response relationship and the results were not adjusted for potential confounders. All in all, these new studies seem to differ slightly from the data set available at the time of the IARC (2006) evaluation which summarised the findings as follows *"Overall, with the exception of the smelter workers in Sweden, these studies were consistent in showing no or a slight excess of lung cancer compared with external reference populations. Observed excesses were quite small and well within the range that might be explained by chance or confounding by smoking. Few or no data for dose–response analyses and no smoking data were available for these cohorts"*. More specifically, the recent studies provided more often information on (and sometimes indication of) a dose-response relationship. However, the problem of lack of adjustment for smoking and other potential confounders remains.

Other cancers

The above-mentioned pooled analysis (Steenland et al., 2017) covering 88 000 exposed workers with PbB data found an increased risk of laryngeal cancer especially in the internal analysis where comparison was made to those with PbB less than 200 µg/L. Those with

PbB > 400 µg/L had a HR of 2.69 (95% CI 1.07 – 6.76) and there was a borderline significant trend (p for trend = 0.09). However, as explained above for lung cancer, the risk estimates were not adjusted for smoking or for workplace exposures other than lead.

Gaudet et al. (2019) analysed data from three case-control studies investigating breast cancer risk by blood cadmium and lead level. There were 1435 cases and 1433 controls. Lead content in stored erythrocytes was used as the exposure metric and the study population was divided into quintiles. The lead levels were not congruent between the studies and were not combined in a meta-analysis. There was no association between the erythrocyte lead level and risk of breast cancer in any of the three studies (p for trend was 0.40, 0.24 and 0.75).

White et al. (2019) studied the risk of breast cancer in a cohort of 50 884 women. Exposure to various metals was estimated by linking the residence data to EPA's national census-tract estimates of metal concentrations in air and dividing these into quintiles in the statistical analyses. There were 2587 cases of breast cancer and there was a slightly increased risk of breast cancer when comparing highest and lowest quintiles of lead exposure (HR 1.1; 95% CI 0.98 – 1.30) but no indication of a trend by quintiles (p = 0.5). However, for post-menopausal breast cancer there was a borderline significant trend (p = 0.07).

Testicular germ cell tumor (TGCT) accounts for 98% of testicular cancer and it is presumed that the precursor of TGCT, germ cell neoplasia *in situ*, is derived from primordial germ cells that failed to differentiate *in utero*. Togawa et al. (2016) studied the risk of TGCT of the offspring by parental occupational exposures to heavy metals and welding fumes in a registry based case control study in Finland, Norway and Sweden. There were 8112 cases and 26 264 controls and the maternal and paternal exposure estimates were generated linking the occupational information from census (every 5 years) to a job exposure matrix and were divided into no exposure, low exposure and high exposure. The cutoff between low and high exposure was 0.30 µmol/L (i.e. about 60 µg/L). There was no indication of an association between risk of TGCT and the paternal (p for trend 0.88) or maternal (p for trend 0.77) exposure to lead.

Overall conclusions on human data

The recent ATSDR (2019) draft report (also assessing non-occupational populations) concluded that *numerous epidemiological studies have investigated associations between Pb exposure and cancer. Studies include exposure of workers and general populations, with many studies reporting PbB. In most studies, mean PbBs in these studies are <10 µg/dL. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent and interpretation may be limited due to confounding factors. Many studies of occupational cohorts and cancer risks do not report PbB data. These studies have reported associations between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder. However, results are inconsistent and interpretation may be limited due to confounding factors.*

ECHA considers that the epidemiological data are inconsistent as regards an increased risk of cancer by inorganic lead compounds and that the original IARC (2006) conclusions are still valid, i.e. that the evidence for the carcinogenicity of inorganic lead compounds in the human data is *limited*.

7.7.2 Animal data

SCOEL (2002)(2002) summarised that some lead compounds have been shown to be carcinogenic in animals, producing kidney tumours in particular, including carcinomas, at exposure levels that cause chronic renal tissue damage. Tumours at other sites have also been reported. IARC (1987) concluded that there was "*sufficient evidence in experimental animals for the carcinogenicity of lead*". The mechanism(s) of carcinogenicity is not clearly

established; cytotoxicity may well be involved, although the genotoxic potential of lead remains uncertain.

According to EFSA (2010, updated 2013): "Oral exposure to lead acetate has been shown to be carcinogenic in the rat kidney in several studies, producing adenomas and adenocarcinomas after chronic exposure in males and females. The doses in these studies were high compared to human intake. In three of these studies the lowest dose was 3 or 5 mg lead/kg feed and in the remaining studies the doses was either 500 or 1,000 ppm in the feed equivalent to about 20 or 40 mg/kg b.w. per day for adult rats. In the two studies suitable for the purpose, i.e. there were more than two dose groups, a dose-response relationship was demonstrable. In a study where rats were given lead acetate in the feed to achieve a daily dose of 3 mg per animal for two months followed by a daily dose of 4 mg lead per animal for 16 months, tumours were found in several organs, with a statistically significant increase in the incidence of tumours of the adrenal gland, testes and prostate in males and adrenal gland in females (IARC, 2006). In another study, of a mixed population of male and female rats, oral exposure to 3 mg lead acetate/rat per day was associated with tumours of the lung, pituitary, prostate, mammary gland and adrenal gland (IARC, 2006). In a study where primigravid mice (20 in each group) were given lead acetate in doses of 0, 500, 750 and 1,000 mg/L in the drinking water during gestation and lactation, renal tumours were observed in the offspring. The kidney tissue adjacent to the tumours appeared to be normal in most cases, or had only a mild degree of aging nephropathy similar to that of control mice (Waalkes et al., 1995). A study in metallothionein double knockout mice showed that these mice are more susceptible to lead induced kidney carcinogenesis than wild type mice. Renal lead-containing nuclear inclusion bodies were frequently observed in wild type mice but did not form in metallothionein-null mice. Metallothionein was often found associated with the outer portion of these inclusion bodies. Thus, the metallothionein-null mice cannot form renal inclusion bodies, even after protracted lead exposure, and this increases the carcinogenic potential of lead. Poor production of metallothionein may predispose some individuals to lead carcinogenicity (Waalkes et al., 2004). Brain gliomas were observed after oral exposure to lead acetate in rats in two separate studies (dose 3 mg lead/rat per day). Also, lead subacetate induced renal cancer in rats and mice after oral administration in doses of 0.1 % in the feed. In one study, hamsters exposed orally to lead subacetate did not develop tumours. In four separate studies, injection of lead phosphate subcutaneously, or combined subcutaneously and intraperitoneally, was shown to produce renal cancers in rats. Three experiments showed that oral exposure to lead subacetate enhanced N-ethyl-N-hydroxyethyl-nitrosamine-induced renal carcinogenesis in male rats. Oral exposure to lead nitrate increased the incidence of N-nitrosodimethylamine-induced renal tumours in male rats while intraperitoneal injections of lead subacetate enhanced N-nitrosodimethylamine-induced lung tumour multiplicity in mice (IARC, 2006)."

Overall, EFSA (2010, updated 2013) concluded that extensive experimental evidence shows that various water-soluble and –insoluble lead compounds in high doses can induce tumours at different sites in rodents. In addition, one study showed that renal tumours may occur with minimal lead-induced nephropathy (Waalkes et al., 1995). It is also noteworthy that brain gliomas, which are rarely spontaneous, were induced after oral exposure to lead in rats (IARC, 2006). Lead proved to be a renal tumour carcinogen/promoter in rats and mice exposed to various organic renal carcinogens. As lead is not a direct acting genotoxin and the doses used to induce tumours in the rodent experiments are very high compared to human intake the CONTAM Panel considered human exposure to lead through food unlikely to represent a significant cancer risk.

Reliable carcinogenicity studies with oral administration in rats and mice are summarised in Table 32 and Table 33, respectively.

Table 32: Selected carcinogenicity studies in rats with lead compounds

Lead Dose			Tumour incidences		Description of study and results	References
ppm	mg/kg bw/d	Total g	Males (M)	Females (F)		
3	0.12 (M) 0.15 (F)	0.06	0/20	0/20	**Lead acetate**, diet, 104 weeks Rats (not further specified), 20, 50 or 100 animals per sex and dose Kidney tumours: mainly adenomas but also carcinomas (not further specified) in M ≥548 ppm (42.3 mg/kg bw/d), NOAEL 141ppm (5.6 mg/kg bw/d); in F LOAEL at 2102 ppm (162 mg/kg bw/d) Increased mortality especially at the high dose (80%)	Azar et al. (1973) cited in US EPA (1989) and OEHHA (2002)
5	0.22 (M) 0.25 (F)	0.06	0/100	0/100		
18	0.72 (M) 0.9 (F)	0.2	0/50	0/50		
62	2.5 (M) 3.1 (F)	0.8	0/100	0/100		
141	5.6 (M) 7.1 (F)	2	0/50	0/50		
548	22 (M) 27 (F)	7	**5/50 (10%)**	0/50		
1130	45 (M) 56 (F)	14	**10/20 (50%)**	0/20		
2102	84 (M) 105 (F)	26	**16/20 (80%)**	7/20 (35%)		
0		0	0	0	**Lead acetate**, diet, 22 months, Rats (CD), 50 animals per sex and dose Kidney: non-neoplastic nodular and adenomatous tubulus hyperplasia, neoplasms reported in cortical epithelium but not further specified	API (1971) cited in AGS (2017)
10		0.1	0	0		
50		0.6	**1**	0		
100		1.2	**4/14**	0		
1000		12	**7/15**	3/15		
0	0		0/55	—	**Lead acetate**, drinking water, up to 104 weeks Rats (Fischer), 80 males per dose **Kidney**: adenoma and carcinoma in male rats at ≥250 ppm (10 mg/kg bw/d); NOAEL 50 ppm (2 mg/kg bw/d)	Fowler and Lipsky (1999) cited in AGS (2017) and OEHHA (2002)
50	2		0/42	—		
250	10		**5/52 aden.** **5/52 carc.**	—		
1000	40		**22/41 aden.** **24/41 carc.**	—		
0			0/213	0/214	**Lead acetate**, diet, up to 2 years Rats (F344), controls: 213 males, 214 female, exposed: 24 animals per sex and dose **Kidney**: only malignant tumours reported; only 24 animals per sex and dose	Fears et al. (1989) cited in AGS (2017)
500			0/24	0/24		
2000			**11/24**	1/24		
8000			**19/24**	4/24		
0	1		0/16	—	**Lead acetate**, drinking water,	Koller et al.

Lead Dose			Tumour incidences		Description of study and results	References
ppm	mg/kg bw/d	Total g	Males (M)	Females (F)		
2600	130		**13/16**	—	76 weeks Rats (Sprague Dawley), 16 male rats **Kidney**: renal tubule carcinomas; no other tumours *Comment: only 76 weeks exposure and only 16 animals exposed*	(1985)
0 1000 10 000	0 15 (M) 18 (F) 146 (M) 183 (F)		0/14 **5/16** **6/13**	0/15 6/16 6/11	**Lead subacetate**, diet, 104 weeks (high dose), 126 weeks (low dose) Rats (Wistar), 11-16 rats per sex and dose **Kidney**: adenomas and carcinomas *Comment: only 11-16 animals per sex and dose*	van Esch et al. (1962)
0 10 000	0 146	73	0/30 **13/29**	— —	**Lead subacetate**, diet, 78 weeks Rats (Sprague Dawley), 30 male rats per dose **Kidney**: adenomas and carcinomas; no other tumours *Comment: only 78 weeks exposure and only 16 animals exposed*	Kasprzak et al. (1985)
0 10 000	0 146	97	 **31/34**	— —	**Lead subacetate**, diet, 99 weeks Rats (Wistar), control 20 male rats, exposed 30 male rats **Kidney**: adenomas and carcinomas; no other tumours *Comment: only one high toxic dose*	Mao and Molnar (1967)

Table 33: Selected carcinogenicity studies in mice with lead compounds

Lead Dose			Tumour incidences		Description of study and results	References
ppm	mg/kg bw/d	Total g	Males	Females		
0 500 750	 100 150		1/25 hyperpl. 3/25 hyperpl. 0/25 aden. **1/25 carc.** 5/25 hyperpl. 0/25 aden. **1/25 carc.**	0/25 0/25 **1/25 aden.**	**Lead acetate**, drinking water, in utero up to week 112 Mice (B6C3F1), 25 - 35 animals per sex and dose **Kidney**: dose-related increase in effects (atypical hyperplasia and/or adenoma and/or	Waalkes et al. (1995)

Lead Dose			Tumour incidences		Description of study and results	References
ppm	mg/kg bw/d	Total g	Males	Females		
1000	200		7/25 hyperlp. **0/25 carc. 5/25 aden.**	4/25 hyperpl.	carcinoma) Other tumours: incidences not increased	
0			0/25	—	**Lead acetate**, drinking water, 104 weeks	Waalkes et al. (2004)
1000			1/24 hyperpl.	—	Mice (Wild type MT+) 25 male mice per dose	
2000			3/25 hyperpl.	—	**Kidney**: hyperplasia and ≥1000 ppm, 1/24 animals with adenoma at 4000 ppm	
4000			4/24 hyperpl. **1/24 aden.**	—		
0			0/25	—	**Lead acetate**, drinking water, 104 weeks	Waalkes et al. (2004)
1000			8/25 hyperpl. **2/25 aden.**	—	Mice (**metallothionein-knock-out MT-**), 25 male mice per dose	
2000			9/25 hyperpl. **3/25 aden. 1/25 carc.**	—	**Kidney**: hyperplasia and adenoma at all doses ≥1000 ppm, 1/25 animals with carcinoma at 2000	
4000			10/25 hyperpl. **5/25 aden.**	—		
0	0		0/25	0/25	**Lead subacetate**, diet, 104 weeks	Van Esch and Kroes (1969)
1000	44		**2/25 aden. 4/25 carc.**	1/25 aden.	Mice (Swiss), 25 animals per sex and dose	
10 000/ 5000			toxic	Toxic	**Kidney**: adenoma and carcinoma; no other tumours increased	

Abbreviations: aden.: adenoma; carc.: carcinoma; hyperpl.: hyperplasia

Lead induces kidney tumours in male rats (e.g., Azar et al., 1973; Api et al., 1971; Fowler and Lipsky 1999; Fears et al., 1989; Koller et al., 1985; van Esch et al., 1962). The lowest dose that induced kidney tumours (specified as adenomas and carcinomas) was 250 ppm lead acetate in drinking water (10 mg/kg bw/d). No tumours were observed at 50 ppm lead acetate in drinking water (2 mg/kg bw/d; Fowler and Lisky 1999).

In studies with mice, the lowest concentration tested of 500 ppm lead acetate in drinking water (about 100 mg/kg bw/day) resulted in an increase in atypical hyperplasia and 1 carcinoma in males (Waalkes et al., 1995).

7.7.3 Summary

Human data

ECHA considers that the epidemiological data are inconsistent as regards increased risk of cancer from inorganic lead compounds and that the original IARC (2006) conclusions are still valid, i.e. that the evidence for the carcinogenicity of inorganic lead compounds in the human data is *limited*.

Animal data

Lead was shown in various studies to induce kidney tumours in male rats (e.g., Azar et al., 1973; Api et al., 1971; Fowler and Lipsky 1999; Fears et al., 1989; Koller et al., 1985; van Esch et al., 1962). The lowest dose that induced kidney tumours (specified as adenomas and carcinomas) was 250 ppm lead acetate in drinking water (10 mg/kg bw/d). No tumours were observed at 50 ppm lead acetate in drinking water (2 mg/kg bw/d; Fowler and Lisky 1999). In studies with mice, the lowest concentration tested of 500 ppm lead acetate in drinking water (about 100 mg/kg bw/day) resulted in an increase in atypical hyperplasia and 1 carcinoma (Waalkes et al., 1995).

EFSA (2010, updated 2013) concluded that extensive experimental evidence shows that various water-soluble and –insoluble lead compounds in high doses can induce tumours at different sites in rodents. In addition, one study showed that renal tumours may occur with minimal lead-induced nephropathy (Waalkes et al., 1995). It is also noteworthy that brain gliomas, which are rarely spontaneous, were induced after oral exposure to lead in rats (IARC, 2006). Lead proved to be a renal tumour carcinogen/promoter in rats and mice exposed to various organic renal carcinogens.

7.8 Reproductive toxicity

7.8.1 Human data

Exposure to lead may affect libido and semen quality, observed as reductions in sperm count, sperm motility, sperm viability, and sperm integrity and as an elevation in morphological abnormalities and reduced sperm DNA integrity. These alterations may lead to effects such as reducing fertility potential and chances of miscarriages, and preterm birth in the partner. Lead exposure impairs hormonal synthesis and hormonal regulation in both sexes. Lead exposure may also affect female reproduction such as impaired menstruation, reduced fertility potential, delayed conception time, altering hormone production, thereby affecting pregnancy and its outcome (Kumar, 2018).

Male fertility

SCOEL (2002)(2002) summarised that a few epidemiological studies have been performed on the association between paternal exposure to lead and adverse reproductive outcome. The results suggest an increased risk of spontaneous abortion, perinatal death and low birth weight following paternal occupational lead exposure (Lindbohm et al., 1991; Kristensen et al., 1993; Anttila and Sallmén, 1995; Min et al., 1996). In a Finnish study, a significant increase was observed in the risk of spontaneous abortion among the wives of men whose PbB was 300 µg/L or higher during spermatogenesis (Lindbohm et al., 1991). Reduced fertility has also been reported for men with a long duration of lead exposure (Lin et al., 1996).

SCOEL (2002) further summarised that there is limited evidence of an association between reduced semen quality (reduced sperm count and motility and increased morphologically abnormal sperm) and PbB in excess of about 400 µg/L (Alexander et al., 1996; Assenato et al., 1986; Lancranjan et al., 1975). From a review on male reproductive toxicity of lead (Apostoli et al., 1998), it seems evident that only Pb levels above 400 µg/L in blood are associated with a decrease in sperm count, volume and morphological alterations. SCOEL (2002) concluded that signs of male reproductive toxicity appear consistently at PbB levels above 400 µg/L. These effects should be considered as adverse.

Studies investigating male fertility are also described by IARC (2006). It was concluded that the studies reviewed show 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.

In Table 34 more recent studies (year ≥2000) are summarised in which effects on the fertility of workers with PbB levels ≤400 µg/L were investigated.

Table 34: Selected studies on fertility in lead-exposed male workers

Blood lead (µg/L)	Cohorts	Reported effects	Reference
402±128	80 battery workers	PbB level 400 µg/L associated with **increased percent abnormal sperm** and **sperm head morphology,** and **DNA denaturation**, but not with sperm count, semen volume, or motility.	(Hsu et al., 2009) cited from NTP 2012
<200 to >400	251 Pb factory workers, Italy, grouped according PbB level <200, 200-290, 300-390, >400 119 controls	Only PbB levels ≥400 µg/L resulted in a statistically significant **longer Time-To-Pregnancy**	(Apostoli et al., 2000)
531 347 85	29 workers (Sn and Pb works) 20 workers (Sn and Pb works) 14 controls	PbB level 531 µg/L: **reduced sperm motility** likely due to lipid peroxidation (increased malondialdehyde levels)	(Kasperczyk et al., 2008)
<200 to ≥400 Non-exposed	153 currently employed married male lead battery workers, Taiwan, grouped according to PbB levels: <200, 200-290, 300-390, ≥400	PbB levels ≥300 µg/L resulted in a statistically significant **longer Time-To-Pregnancy** (prolonged for 0.15 cycles by a 10 µg/L increase in blood lead)	(Shiau et al., 2004)
367 (119-659) 103 (67-208)	98 industrial workers (Croatia), 20-43 years old, 5 (2-21) years exposed 51 referents (industrial workers)	PbB levels associated with **decreased testosterone** and **estradiol**, not LH, FSH and PRL *Large exposure range without sub-grouping of workers to identify a reliable threshold*	(Telisman et al., 2000)
310 (46-645) 44 (max. 98)	362 workers (battery company or lead smelter in Belgium, Italy, UK) 141 referents	PbB level 500 µg/L: **reduced sperm concentration** (by 49%) 440 µg/L: likely threshold for reduced sperm concentration no effects on sperm chromatin	(Bonde et al., 2002)
309 (102-591) 34 (5-90)	68 Pb smelter workers, Belgium 91 referents	**Reduced sperm concentration** (correction for age and period of abstinence), higher serum inhibin B levels *Large exposure range without sub-grouping of workers to identify a reliable threshold*	(Mahmoud et al., 2005); working group Bonde et al.,
317±120 293±146 292±98 372±155	1104 men from 4 countries (Belgium, Finland, Italy, England), 22 companies, of whom 638 were occupationally exposed to lead	No consistent association of **Time To Pregnancy** with current PbB levels was found in any of the exposure models, although reduced fertility was reported in individual categories of two models considering total duration of work and cumulative exposure	(Joffe et al., 2003)
311 41	77 male Pb workers (62 active, 15 retired) 26 referents	No effect on basal **serum hormones** (e.g., testosterone, cortisol, thyroid hormones, LH, PRL, FSH); in a challenge test, stimulated follicle-stimulating hormone levels significantly lower	(Erfurth et al., 2001)

Abbreviations: FSH: follicle stimulating hormone; LH: luteinizing hormone; PbB: blood lead levels; PRL: prolactin

Several more recent studies listed in Table 34 confirmed effects on sperm at PbB levels of 400 µg/L or higher (Apostoli et al., 2000; Bonde et al., 2002; Hsu et al., 2009; Kasperczyk et al., 2008). In the cross-sectional study of Bonde et al. (2002) in which 503 workers were investigated, indications for a threshold for an effect on semen quality was identified at a concurrent PbB level of 440 µg/L.

Indications for reduced fertility, measured as prolonged Time-To-Pregenancy, was reported in a study in 153 workers with PbB levels ≥300 µg/L (Shiau et al., 2004). However, in a larger cross-sectional study (Joffe et al., 2003) in 638 men occupationally exposed to lead (292±98 µg/L up to 372±155 µg/L) from 4 countries and 22 companies, no consistent association of Time To Pregnancy with current PbB levels was found in any of the exposure models applied. Reduced fertility was observed in this study in individual categories of two models that considered total duration of work and cumulative exposure. This indicates that the reduced fertility might be associated with previous higher PbB exposure of workers.

Therefore, the currently available data support the conclusion from SCOEL (2002) that signs of male reproductive toxicity appear at PbB levels above 400 µg/L.

However, it has to be noted that the available studies are of limited power due to small number of workers in the studied exposure groups and might be subject to bias issues such as selection bias and some had relatively low response rates.

Female fertility

SCOEL (2002) noted that there are no data on female fertility relating to modern occupational exposure levels. Lead is transferred across the placenta during the 12th to 14th weeks of pregnancy.

Only one study in female workers exposed to lead has been identified.

Paredes Alpaca et al. (2013) assessed the effects of lead exposure on reproductive health (miscarriage, fertility, multiple births, sex ratio at birth, incidence of some diseases during pregnancy), in a cohort of 2,067 female workers exposed to lead in the ceramic tile industry in Italy that repeatedly underwent PbB level testing in the period 1998-2004. Follow-up was performed for each subject for the 12 months following any PbB testing. Thirty-one miscarriages and 212 live births were recorded. The miscarriage rate (5.42‰) among the study subjects was statistically not different from the regional reference (5.00‰), while the fertility rate (37.05‰) was lower (RR: 0.72; 95%CI 0.63-0.83). The frequency of multiple births (1.9%) was similar to the regional rate (1.2%). Eighty-six females (40.57%) and 126 males (59.43%) were born, compared to regional percentages of 49% females and 51% males. Of all the indicators examined, only miscarriage showed a positive trend among women exposed to lead (3.31%, 5.87%, 5.68% for ≤50 µg/L, >50-≤150 µg/L, >150 µg/L, respectively). In addition, women exposed to lead had a higher frequency of hypertension during pregnancy (RR: 1.34; 95%CI 1.07-1.68), pre-ecampsia/eclampsia (RR: 1.47; 95% CI 1.08-2.00), prolonged pregnancy (RR: 1.37; 95%CI 1.09-1.73), and problems with the amniotic cavity (RR: 1.16; 95%CI 1.02-1.33). The relative risk for prolonged pregnancy was significantly increased >50 µg/L, the relative risks for the other effects at >150 µg/L.

Developmental toxicity

SCOEL (2002) commented that at birth the blood lead concentration in the umbilical cord of the child is close to the blood lead level of the mother (80 to 90%). Consequently, the child of a pregnant woman employed in the lead industry may have at birth a blood lead level exceeding considerably that of the unexposed population. Blood lead levels have also been observed to increase during pregnancy despite unchanged or decreasing

environmental lead levels. The mobilisation of lead from bone during pregnancy probably explains the increase.

SCOEL also noted that effects of maternal lead exposure cannot be distinguished from early childhood exposure due to other sources but toxicokinetic considerations indicate that effects on neurological and psychomotor development is a possible but uncharacterisable risk from maternal exposure to the fetus or breast-fed infant. SCOEL also pointed out that in the studies on mental child development, umbilical blood lead levels, but not maternal levels throughout pregnancy have been determined.

In several published evaluations, increased PbB levels have been associated with a decrease of intelligence quotient (IQ) in children as reviewed by EFSA (2010), NTP (2012), EPA (2013), ATSDR (2019). EPA (2013) stated the PbB-associated IQ decrements were found in child populations with mean PbB levels of 50 to 100 µg/L. NTP (2012) concluded that there is sufficient evidence that PbB levels <50 µg/L are associated with decreases in IQ in children 4 to 13 years of age. ATSDR (2019) stated that in children a decreased cognitive function including full scale IQ (FSIQ) has been associated with PbB levels ≤ 100 µg/L and that collectively, the studies provided evidence for effect sizes ranging from -1 to -6 IQ points in association with a 10-fold increase in PbB and larger effect sizes in cohorts or cohort strata having a lower mean PbB.

As lead passes the placenta and is stored in bones, it is likely that maternal occupational exposure to lead could contribute to such effects either during in utero development of the nervous system or during infancy as a consequence of release of lead stored in fetal bone during the pregnancy.

Intelligence tests employ a variety of tasks probing cognitive abilities including memory, verbal and spatial reasoning, planning, learning, and the comprehension and use of language. The raw IQ score is then mathematically transformed to provide a rank of that score in the IQ standardisation sample (based on a Gaussian distribution). The IQ distribution is normalised to have a population mean of 100. As scores in IQ tests have been increasing by about 3 to 5 points per decade (the so-called Flynn effect), IQ tests are routinely re-normalised. As discussed by EFSA (2010), it is unlikely that childhood lead exposure impairs intelligence. Instead, any impairment measured by IQ scores most likely arises due to the particular constellation of cognitive functions the individual tests required (e.g., use of language, attention, or speed of performance). According to EPA (2013), neither epidemiologic nor toxicological evidence has identified an individual critical lifestage or duration of Pb exposure within childhood that is associated with cognitive function decrements, while the mode of action for Pb-associated cognitive function decrements is supported by observations of Pb-induced impairments in neurogenesis, synaptogenesis and synaptic pruning, long term potentiation, and neurotransmitter function in the hippocampus, prefrontal cortex, and nucleus accumbens.

When studying the potential effect of maternal Pb exposure (e.g. by using maternal or umbilical cord PbB as exposure metric) on the IQ development of the child one needs to adjust for maternal and paternal IQ, lead exposure of the child since birth and various environmental and socio-economic factors influencing cognitive development. As explained above, the relevant time windows to measure these potential confounders are unknown. This makes such studies methodologically challenging and the results have been inconsistent. After reviewing the studies, the NTP (2012) stated that no clear evidence exists that maternal or umbilical cord PbB levels < 100 µg/L are associated with decreased IQ in children. More recently ATSDR (2019) noted that a large number of studies showing decrements in neurological function in children have been published. Collectively, these studies support the concept that Pb affects cognitive function in children prenatally exposed to PbB levels ≤ 100 µg/L, with numerous studies providing evidence for effects at PbB levels ≤ 50 µg/L.

7.8.2 Animal data

Generation reproductive toxicity studies

Varnagy et al. (2002) performed a one-generation reproductive toxicity study (OECD TG 415) in rats (30 females and 15 males per group) exposed to 1000, 5000 mg Pb acetate/kg diet. In the parental generation, no effects were observed on copulation, fertility, or gestation. At ≥1000 mg/kg diet a significant reduction in the body weight gain of females was observed. 5000 mg/kg diet led to a significant reduction in body weight gain of males and no body weight gain in females during pregnancy and lactation. In the offspring generation, no effects were reported on viability, lactation, and weaning but a significant reduction in body weight gain during lactation at ≥1000 mg/kg diet.

Dumitrescu et al. (2008) exposed female rats (n=21 in 6 groups) to 50, 100, 150 ppb Pb acetate in drinking water, starting 3 months before mating until end of lactation. Male rats were exposed 3 months before mating. Reduced litter size, modification of sex ratio (increased number of female pups), delay of vaginal opening and decrease of body weight at vaginal opening in female F1 offspring was reported. The low number of animals investigated is not be noted.

Studies investigating male fertility

Studies investigating male fertility of lead-exposed experimental animals are summarised in Table 35.

Table 35: Selected studies in experimental animals investigating effects of lead on male fertility

Blood lead (µg/L)	Exposure	Reported effects	Reference
Monkeys			
430	Cynomolgus monkeys, 1500 µg Pb acetate/kg bw/day from birth (n=4) or from postnatal day 300 (n=5) to 9 years 3 vehicle controls	**Histological or ultrastructural effects in seminal vesicles**; subtle effect on the **pituitary** and **Sertoli cell function** (sign. decrease in the inhibin/follicle stimulating hormone (INH/FSH) ratio; sign. lower gonadotropin releasing hormone stimulated levels of luteinizing hormone)	(Cullen et al., 1993) (Foster et al., 1993)
320- 360	Cynomolgus monkeys (n=4), 1500 µg Pb acetate/kg bw/day from birth to 10 years (lifetime) Controls (n=3)	**Persistent ultrastructural alterations** in the **testis** and **seminiferous tubules**	(Foster et al., 1998)
Rabbits			
200, 400, 500, 700, 800, 900, 1100	Dutch Belt rabbits (7-15 males per group), 3.85 mg Pb acetate/kg bw, s.c., 15 week, controls	160 to 240 µg/L threshold for **impact on semen quality** (sperm count, ejaculation volume, percentage motile sperm swimming velocity, morphology); rabbits 3.75 times more sensitive than humans	(Moorman et al., 1998)

Blood lead (µg/L)	Exposure	Reported effects	Reference
Rats			
720 540 190 530 300	Male rats Male rats Male rats Female rats Female rats	In male rats **reduced sperm counts** at 720 µg/L but not at 540 µg/L, at 190 µg/L **increased prostate weights**. In female rats at 300 µg/L unbalanced estrus cycle at 530 µg/L ovarian cycts	Review by (Assi et al., 2016) citing inter alia (Chowdhury et al., 1984)
600±40 340±30 <70	Wistar rats (males), 52 day old rats, 0.1 and 0.3% lead acetate in drinking water, controls	Correlation between PbB and effects on **sperm quality** and **sperm production** and **testosterone** (serum and intratestiular)	(Sokol et al., 1985)
340-370 <70	Wistar rats (males), 42, 52, 70 day old rats, 0.1% lead acetate in drinking water Controls	**Reduced serum testosterone** and **sperm concentration** in adult animals (52 and 70 days old), not in prepubertal rats (42 days old)	(Sokol and Berman, 1991)
67±28 18±8	Wistar rats (7 animals per sex and group), lead acetate, 25 mg/kg bw, 7 i.p. injections once every two days	Number of **abnormal sperm** sign.* increased compared to control: Control: 54 (7.7%) 25 mg/kg bw: 106 (15.1%)* NOTE: also MN frequency increased, serum thyroid hormones reduced and serum cortisol increased	(Piao et al., 2007)
52.7±0.6 42.6±0.9	Wistar rats (8 males per group), 3 months exposure, lead acetate, 25 mg/kg bw/d, gavage Controls	**Histological or ultrastructural damage to the male reproductive organs** *Comment*: PbB levels were almost similar for Pb exposed rats ("intoxicated") and control rats; this makes the quantitative information not reliable	(El Shafai et al., 2011)
Mice			
(Pb measured in serum and testis)	Kunming mice (15 males per group), 60 days exposure, 0.5, 1.0 and 1.5 g Pb acetate/L in drinking water (0, 89, 183, 279 mg Pb acetate/kg bw/d),	**Decreased male fertility** at 1.0 and 1.5 g/L; Pb also inhibited **spermatogenesis** and **sperm developmen**t, and significantly downregulated expressions of Ddx3y gene expression in testis	(Wang et al., 2013)

The available studies investigating male fertility in experimental animals as presented in Table 35 demonstrated ultrastructural effects in testes and seminiferous tubules of monkeys exposed to Pb acetate for up to 10 years (Cullen et al., 1993; Foster et al., 1993, 1998) with PbB levels of 320 to 360 µg/L. In rabbits with subcutaneous injection of Pb acetate, the threshold for impact on semen quality was established at 160 to 240 µg Pb/L blood; however, the authors noted that rabbits are 3.75 times more sensitive than humans (Moorman et al., 1998). In rats, reduced seminal vesicles and ssubtle effects on the pituitary and Sertoli cell function were reported at PbB levels of 340 to 370 µg/L (Sokol and Berman, 1991). Mice exposed for 60 days to Pb acetate showed inhibited spermatogenesis and sperm development and reduced fertility.

Studies investigating female fertility

Nampoothiri and Gupta (2008) administered female rats (14 animals per group) a subcutaneous dose of 0.05 mg Pb acetate/kg bw per day starting before mating (proestrous stage), and continued during mating and gestation. No significant changes in reproductive performance was observed (body weight gain, litter size, number of dead/resorbed foetuses, total litter weight, ovarian weight, placental weight). Key

steroidogenic enzymes of ovary and placenta along with gonadal steroids showed minimal changes. Biomolecules were affected (glycogen, protein, RNA, DNA, and protein content). Also general parameters of toxicity were altered but within the normal range (alkaline phosphatase, serum glutamate pyruvate transaminase, creatinine).

Developmental toxicity

There is a vast amount of studies in experimental animals investigating effects of lead on the developing offspring. In more recent studies, lead exposure has been shown to lead to delayed onset of female puberty at PbB levels of 13 and 130 µg/L (Iavicoli et al., 2006), to haematological, renal and hepatic effects at 40 µg/L (Teijon et al., 2006), to effects on neurotransmitter, dopamine homeostasis, physical development, or to obesity in adult males at ≥ 100 µg/L (Leasure et al., 2008), or to retinal aberrations at 120 µg/L (Fox et al., 2008).

7.8.3 Summary

Lead exposure impairs hormonal synthesis and regulation in both sexes. Exposure of male workers to lead may affect semen quality and sperm DNA integrity that could lead to reduced fertility and miscarriages or preterm birth in the partner. Recent data in lead-exposed workers support the conclusion from SCOEL (2002) that adverse effects on male reproduction could appear at PbB levels above 400 µg/L. With regard to female fertility, one recent study in female lead-exposed workers (Paredes Alpaca et al., 2013) indicates an increased risk for miscarriages at PbB levels >50 µg/L. Lead-related effects in children can be observed at PbB levels <50 µg/L.

7.9 Mode of action (MoA) considerations

Disruption of Calcium (Ca^{2+}) homeostasis by Pb has been observed in a number of different cell types and cell-free environments, indicating that this is a major mode of action for Pb-induced toxicity on a cellular level. Ca^{2+} is one of the most important carriers of cell signals and regulates virtually all aspects of cell function, including energy metabolism, signal transduction, hormonal regulation, cellular motility, and apoptosis. Ca^{2+} homeostasis is maintained through a tightly regulated balance of cellular transport and intracellular storage (US EPA, 2013).

Ca^{2+} homeostasis is particularly important in bone cells, as the skeletal system serves as the major dynamic reservoir of Ca^{2+} in the body. Bone cells also are unique in that they exist in a microenvironment that is high in Ca^{2+} and potentially high in Pb concentrations (US EPA, 2013).

Pb has been shown to disrupt the normal movement of Ca^{2+} ions, as well as other physiologically important ions through interactions with these transport mechanisms (US EPA, 2013).

Pb demonstrates Ca^{2+}-mimetic properties in enhancing neurotransmitter release from cells in the absence of Ca^{2+} and Ca^{2+}-induced depolarization (US EPA, 2013).

Pb has been shown to displace metal cations from the active sites of multiple enzymes and proteins, and thus to alter the functions of those proteins. These alterations in protein function have implications for numerous cellular and physiological processes, including cell signaling, growth and differentiation, gene expression, energy metabolism, and biosynthetic pathways (US EPA, 2013).

7.9.1 Neurological effects

Among the most important ways that inorganic lead can affect the nervous system are those involving interference with calcium-dependent reactions and/or disruption of calcium homeostasis. It has also been suggested that lead-induced increase in neuronal calcium levels may cause an excessive calcium influx into mitochondria, resulting in the production

of free radicals and in the opening of the membrane transition pores, thus damaging the neurones (see EFSA 2010, updated 2013).

The particular vulnerability of the fetus and infant to the neurotoxicity of lead may be due in part to immaturity of the blood-brain barrier and to the lack of the high-affinity lead binding protein in astroglia that enables them to trap divalent lead ions in adults. In addition, other membrane changes may affect the blood-brain barrier and brain cells. Lead has been found to accumulate in brain myelin of rats and myelin membrane fluidity was higher in such rats than in controls. Myelin from lead intoxicated animals showed gross morphological alterations, and altered composition (higher phosphatidylethanolamine content and altered glycoproteins) when compared to the controls. It seems likely that similar changes may occur in human brain. Further, Adonaylo and Oteiza (1999) have shown from studies on liposomes that lead may cause lipid rearrangement in the lateral phase of the phospholipid bilayer of the cell membrane. Exposure to lead causes lipid clustering in liposomes and increases the rate of iron-initiated lipid oxidation and consequent membrane damage. The dopaminergic system has a role in aspects of cognitive function since lesions of dopaminergic neurones impair performance of various learning and cognitive tasks. There is evidence that suggests that lead may affect regulation of dopamine synthesis and release, indicating a presynaptic site of action (see EFSA 2010, updated 2013).

The cholinergic system plays a role in learning and memory processes. In general, it is clear that lead blocks the evoked release of acetylcholine and diminishes cholinergic function (Cooper et al., 1984; Silbergeld, 1977; Shih and Hanin, 1978; Suszkiw et al., 1984). This has been demonstrated in central and peripheral synapses. Studies with the neuromuscular junction have shown that lead reduces acetylcholine release by blocking calcium entry into the terminal. Chronic exposure of rats to lead resulted in decreased muscarinic-receptor expression in the hippocampus. Whether lead exposure during development alters muscarinic receptor sensitivity is unclear as there are reports with conflicting results. The preponderance of the binding data suggests Among the most important ways that inorganic lead can affect the nervous system are those involving interference with calcium-dependent reactions and (or) disruption of calcium homeostasis. One process that has been studied in detail is the activation of protein kinase C (PKC). Picomolar concentrations of lead activate preparations of PKC in vitro (Markovac and Goldstein, 1988). The PKC family is made up of 12 isozymes, each with different enzymatic cofactor requirements, tissue expression, and cellular distributions. The gamma-isoform is one of several calcium ion dependent forms of PKC that is a likely target for lead neurotoxicity; it is neurone-specific and is thought to be involved in spatial learning, and memory processes. It has also been suggested that lead-induced increase in neuronal calcium levels may cause an excessive calcium influx into mitochondria, resulting in the production of free radicals and in the opening of the membrane transition pores (Sidhu and Nehru, 2003), thus damaging the neurones.

The particular vulnerability of the fetus and infant to the neurotoxicity of lead may be due in part to immaturity of the blood-brain barrier and to the lack of the high-affinity lead binding protein in astroglia that enables them to trap divalent lead ions in adults (Lindahl et al., 1999). In addition, other membrane changes may affect the blood-brain barrier and brain cells. Lead has been found to accumulate in brain myelin of rats and myelin membrane fluidity was higher in such rats than in controls (Dabrowska-Bouta et al., 1999). Myelin from lead intoxicated animals showed gross morphological alterations, and altered composition (higher phosphatidylethanolamine content and altered glycoproteins) when compared to the controls (Dabrowska-Bouta et al., 1999, 2008). It seems likely that similar changes may occur in human brain. Further, Adonaylo and Oteiza (1999) have shown from studies on liposomes that lead may cause lipid rearrangement in the lateral phase of the phospholipid bilayer of the cell membrane. Exposure to lead causes lipid clustering in liposomes and increases the rate of iron-initiated lipid oxidation and consequent membrane damage. The dopaminergic system has a role in aspects of

cognitive function since lesions of dopaminergic neurones impair performance of various learning and cognitive tasks. There is evidence that suggests that lead may affect regulation of dopamine synthesis and release, indicating a presynaptic site of action (Cory-Slechta, 1995).

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7.9.2 Haematological effects

Pb has been observed to interfere with Ca^{2+} homeostasis in erythrocytes, platelets and white blood cells shown to displace metal cations from the active sites of multiple enzymes and proteins, and thus to alter the functions of those proteins (US EPA 2013).

The haematological effects of lead can result in increased urinary levels of porphyrins, coproporphyrins, ALA, erythrocyte protoporphyrin (EP), free erythrocyte protoporphyrin (FEP) and zinc protoporphyrin (ZPP). The most serious haematological effect is anaemia. Lead interferes with haem biosynthesis by altering the activity of three enzymes: δ-aminolevulinic acid synthetase (ALAS), δ-aminolaevulinic acid dehydratase (ALAD) and ferrochelatase. Lead indirectly stimulates the mitochondrial enzyme ALAS, which catalyses the condensation of glycine and succinyl-coenzyme A to form ALA. The activity of ALAS is the rate-limiting step in haem biosynthesis; an increase in ALAS activity occurs through feedback derepression (see EFSA 2010, updated 2013).

Lead inhibits noncompetitively the zinc-containing cytosolic enzyme ALAD, which catalyzes the condensation of two units of ALA to form porphobilinogen. Lead also inhibits noncompetitively the activity of the zinc-containing mitochondrial enzyme ferrochelatase, which catalyzes the insertion of iron(II) into the protoporphyrin ring to form haem. It has been postulated that metals bind to thiol groups of allosteric sites and, according to their structure, provoke allosteric transitions to the active or inactive form of the enzymes. As a result of the inhibition of ALAD and ferrochelatase, there is increased production and excretion of the precursors ALA and coproporphyrin (COPRO) with increased circulatory protoporphyrin (PROTO) usually bound to zinc. Diminished synthesis of haem-containing monooxygenases (cytochromes P450) may reduce oxidation of xenobiotics (see EFSA 2010, updated 2013).

Lead interference with haem synthesis causes a reduction in haemoglobin concentration in blood. Decreased haemoglobin production, coupled with an increase in erythrocyte destruction, results in a hypochromic, normocytic anaemia with associated reticulocytosis (see EFSA 2010, updated 2013).

7.9.3 Renal effects

A characteristic histological feature of lead nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule. Inclusion bodies contain lead complexed with protein. The toxicological consequences of the formation of inclusion bodies are not clear, but it may reflect a disposition mechanism, involving metallothionein. Cytosolic proteins can serve as carriers of lead or intermediary ligands for uptake of lead into the nucleus. These proteins can also participate in ligand exchange reactions with other cytosolic

binding sites, including δ-aminolevulinic dehydratase, which binds to lead and is inhibited by it (see EFSA 2010, updated 2013).

Other high-affinity lead-binding proteins (affinity constant (Kd) approximately 14 nM) have been isolated from human kidney. Characteristic of lead-induced nephropathy is the occurrence of structural abnormalities of mitochondria of the renal proximal tubule cells (see EFSA 2010, updated 2013).

Mitochondria isolated from lead intoxicated rats contain lead, principally associated with the intramembrane space or bound to the inner and outer membranes. Such mitochondria also show abnormal respiratory function, including decreased respiratory control ratios during pyruvate/malateor succinate-mediated respiration. The mitochondrial effects may be the result of membrane changes similar to those described in the section on neurotoxic effects (see EFSA 2010, updated 2013).

7.9.4 Cardiovascular effects

SCOEL (2002) summarised that the effect of lead on blood pressure has been widely investigated in recent years. Experiments have demonstrated that lead effects the soft muscles of the vessels by interfering with the Na-K system, cAMP, Ca^{2+}-mediated signalling and the renin angiotensin system. The biological plausibility of a causal relationship between elevated blood pressure and lead exposure has been mainly investigated in animal experiments and in vitro tests. The most likely mechanisms include interference with the balance between the renin-aldosterone axis and the renal kallikrein system, direct action at the level of the vascular smooth muscle cell and the potentiation of sympathetic stimulation. The available literature suggests that there is a positive association between systolic blood pressure and the blood lead concentration. By contrast, the correlation with diastolic blood pressure was much less consistent across the various studies and in the overall analysis attained statistical significance only because of one strongly positive survey (Gartside, 1988). Whether the association between systolic pressure and blood lead is causal in terms of morbidity or mortality is not proven.

Increased blood pressure is observed with chronic exposure to lead. Lead exerts direct constrictive effects on vascular smooth muscle. These effects may be mediated by inhibition or Na-K-ATPase activity and associated elevation of intracellular Ca^{2+} levels, possibly with activation of protein kinase C. Lead-induced hypertension is accompanied by depletion of nitric oxide (NO), which plays an important role in regulating blood pressure, through peripheral (i.e., vasodilation, natriuresis) and central (anti-sympathetic) mechanisms (see EFSA 2010, updated 2013).

7.9.5 Genotoxicity

The toxicity of lead and its compounds has been well known for many centuries, with anemia and developmental disturbances being most prominent. Nevertheless, the exact mechanisms are still unclear, but as with most other metals and their compounds, indirect mechanisms like the induction of oxidative stress and the interaction with DNA repair processes appear to be relevant (see Beyersmann and Hartwig 2008).

Genotoxic effects

Genotoxic effects of lead compounds are well documented in in vitro systems, experimental animals and in lead-exposed humans (summarised in IARC 2006b). Equivocal results have been published with respect to the mutagenicity of water soluble lead compounds in mammalian cells in culture; in most classical test systems, effects were rather weak and/or restricted to toxic doses. Nevertheless, when applying mammalian AS52 cells carrying a single copy of an E. coli gpt gene, which are suited for the detection of small and large deletions, lead chloride induced mutations in a dose-dependent manner, starting at the non-cytotoxic concentration of 0.1 µM (Ariza and Williams 1996; Ariza et

al., 1998; Ariza and Williams 1999). High mutant frequencies and mutation spectra similar to those induced by reactive oxygen species were also observed in another study in CHO K1 cells (Yang et al., 1996). Furthermore, two studies revealed an increase in mutation frequency in combination with UVC irradiation and MNNG, indicative of a disturbance of DNA repair processes (see below). In contrast to the equivocal results of gene mutation studies, chromosomal damage and micronuclei have been observed consistently in mammalian cells in culture, in experimental animals and in several cases also in lead-exposed humans; however, with respect to population-based studies, confounding exposures cannot be ruled out (reviewed in IARC 2006b). At low concentrations realistic for human exposure, two mechanisms may underlie lead-induced genotoxicity, namely a disruption of the pro-oxidant/anti-oxidant balance and an interference with DNA repair systems (see Beyersmann and Hartwig 2008).

Induction of oxidative stress

At different experimental levels, there are strong indications for the involvement of reactive oxygen species (ROS) in lead-induced genotoxicity. Proposed molecular mechanisms include enhanced lipid peroxidation, inhibition of antioxidant defense systems, catalysis of Fenton-type reactions and, interestingly, also the long-known inhibition of aminolevulinic acid dehydratase. The latter reaction leads to the accumulation of the heme precursor aminolevulinic acid, with the subsequent generation or ROS and oxidative DNA damage (reviewed in IARC 2006b) (see Beyersmann and Hartwig 2008).

DNA repair inhibition

A further mechanism, which has been quite well documented during the last few years, is the interaction of lead with two major DNA repair systems, that is nucleotide excision repair and base excision repair, and comutagenic effects have been observed in combination with UVC radiation and MNNG (reviewed in IARC 2006b). As one molecular target of lead with respect to base excision repair, lead has been shown to inhibit the apurinic/apyrimidinic endonuclease (APE1) in the low micromolar concentration range both in an isolated enzymic test system and in cultured AA8 cells, leading to an accumulation of apurinic sites in DNA and an increase in MMS-induced mutagenicity (McNeill et al., 2007). Furthermore, lead interferes with the repair of DNA double strand breaks via interaction with the stress response pathway induced by ATM (a phosphoinositol-3-kinase related kinase) (Gastaldo et al. 2007). Due to its high affinity for sulfhydryl groups, one mechanism for lead interaction with proteins could be the displacement of zinc from zinc binding structures. In support of this assumption, in cell-free systems lead has been shown to reduce DNA binding of transcription factors TFIIIA and Sp1 (Hanas et al. 1999; Huang et al. 2004). However, no impact was seen on the zinc-containing DNA repair proteins Fpg or XPA (Asmuss et al. 2000). Thus, zinc binding proteins cannot be considered a general target, but interactions depend on the actual protein (see (Beyersmann and Hartwig, 2008)).

Deregulation of cell proliferation

Low concentrations of lead have been shown to stimulate cell growth (reviewed in IARC 2006b). A probable mechanism consists of the mobilization of free intracellular Ca2+ and the activation of protein kinase C (PKC) by lead, which triggers a signal transduction cascade finally leading to the stimulation of DNA synthesis. In animals, lead significantly increases proliferative lesions in the kidney below cytotoxic concentrations, indicating that genotoxicity and accelerated growth stimuli may act in concert in lead-induced carcinogenicity (see Beyersmann and Hartwig 2008).

7.9.6 Carcinogenicity

SCOEL (2002) concluded that based on experimental data it seems plausible that the carcinogenicity of lead is based on indirect, rather than on direct genotoxic mechanisms (Silbergeld *et al.,* 2000). This could imply the existence of a practical threshold for the

carcinogenic effects, and would argue in favour of the possibility of setting a health-based OEL for lead. However, further research into the mechanisms of lead genotoxicity and carcinogenicity should be encouraged in order to strengthen this avenue of argumentation.

AGS (2017) noted that it is to be assumed that lead and its inorganic compounds feature genotoxicity and that this characteristic plays a role for carcinogenesis. The exact mechanism of carcinogenicity, however, has not yet been elucidated. A primary genotoxic mechanism does not seem to be predominant. Secondary genotoxic mechanisms such as the disturbance of DNA synthesis and repair (Beyersmann and Hartwig, 2008) and an interaction with DNA-binding proteins and tumour suppressor proteins (Beyersmann and Hartwig, 2008; García-Lestón et al., 2010; NTP, 2011) as well as inflammation mechanisms (Chou et al., 2011) are probably of high significance.

7.9.7 Reproductive effects

IARC (2006) concluded that it is not yet clear whether the mechanism inducing effects on fertility and sperm count 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 (Hertz-Picciotto & Croft, 1993). Developmental toxicity to the fetus is also possible.

Doumouchtsis et al. (2009) reviewed the effects of lead on endocrine function and summarised these as follows: Although evidence is conflicting, it has been reported that accumulation of lead affects the majority of the endocrine glands. In particular, it appears to have an effect on the hypothalamic-pituitary axis causing blunted TSH (thyroid-stimulating hormone), GH (growth hormone), and FSH/LH (follicle stimulating hormone/ luteinizing hormone) responses to TRH (thyrotropin-releasing hormone), GHRH (growth hormone-releasing hormone) and GnRH (gonadotropin-releasing hormone) stimulation, respectively. Suppressed GH release has been reported, probably caused by reduced synthesis of GHRH, inhibition of GHRH release or reduced somatotrope responsiveness. Higher levels of PRL in lead intoxication have been reported. In short-term lead-exposed individuals, high LH and FSH levels are usually associated to normal testosterone concentrations, whereas in long-term exposed individuals' low testosterone levels do not induce high LH and FSH concentrations. These findings suggest that lead initially causes some subclinical testicular damage, followed by hypothalamic or pituitary disturbance when longer periods of exposure take place. Similarly, lead accumulates in granulosa cells of the ovary, causing delays in growth and pubertal development and reduced fertility in females. In the parenchyma of adrenals histological and cytological changes are demonstrated, causing changes in plasma basal and stress-mediated corticosterone concentrations and reduced cytosolic and nuclear glucocorticoid receptor binding. Thyroid hormone kinetics are also affected. Central defect of the thyroid axis or an alteration in T4 metabolism or binding to proteins may be involved in derangements in thyroid hormone action. Lead toxicity involves alterations on calcitropic hormones' homeostasis, which increase the risk of skeletal disorders.

7.10 Lack of specific scientific information

To appropriately evaluate adverse effects (such as genotoxicity) of lead on workers without the confounding impact of previous higher Pb exposure, prospective studies (following a group over time) would be required in workers with PbB levels consistently in the lower PbB range ≤300 µg/L, ≤200 µg/L and ≤100 µg/L.

8. Cancer Risk Assessment and exposure limit values

8.1 Published approaches for cancer risk assessment

SCOEL (2002) concluded that the observed experimental carcinogenicity of lead salts is, in the first instance, directed towards the kidneys as the target tissue. Most probably, these effects are to a great extent based on the renal toxicity of high doses of lead. There is an ongoing discussion on the human carcinogenicity of lead and lead compounds. Based on experimental findings it seems plausible that lead has no direct genotoxic effect which argues in favour of existence of practical thresholds of carcinogenicity. Hence an OEL based on avoiding functional CNS alterations is expected also to protect against peripheral nervous system and renal toxicity, including possible renal cancer development.

8.2 Exposure Limit Values

As described in section 7, exposure to lead is associated with various health endpoints and the studies investigating the exposure-effect associations within those endpoints have used a variety of outcome markers ranging from early effect markers (for which the long-term predictive value is not fully understood) to clinical disease and mortality. The international and national bodies proposing occupational limit values since the latest EU recommendation (SCOEL 2002) have used various argumentations but have all ended up basing their overall recommendation mostly on human data on adult neurotoxicity with some variation as regards how other health effects among women at childbearing age have been dealt with. All these recommendations use a biological limit value (BLV), more specifically PbB, as the relevant exposure metric. Those that also recommend an occupational exposure limit value (OEL) for workplace air to support achieving the desired BLV targets, have derived an OEL that best corresponds to the established BLV. Lead is unique in this regard, since for most substances with a national or international BLV, the BLV is derived from the OEL instead. The assessments are summarised below, starting from the previous EU level recommendation by SCOEL (2002). Regardless of the units used in the original documentation, all PbB values below have been expressed as "µg/L".

Table 36: Summary of proposed PbB limit values for the occupational setting.

Insitution	BLV (µg/L)		OEL (µg/m³)	Comment
	workers	Females of reproduct. Capacity		
SCOEL 2002	300	-	100	400 µg/L: subtle effects in neurobehavioral tests
Sweden 2019	300	100	-	
ACGIH 2017	200	-	-	200 µg/L: Various neurological and neurobehavioral effects and effects of reproduction can be seen down to 200 µg/L
Safe Work Australia 2014	200-300 (BLRL)	-	-	BLRL (blood lead removal level) based on LOAELs 250-300 µg/L after considering neurotoxicity, hypertension, reproductive toxicity and carcinogenicity
ANSES 2016	180	-	-	180 µg/L: NOAEL for impairment in performance in neurobehavioral tests (Schwartz et al 2001, 2005)
Germany (AGS proposal 2017)	150	-	-	300 µg/L: LOAEL for neurotoxicity

SCOEL 2002

SCOEL (2002) concluded:

- The leading toxic effect of lead in males and females is impairment of performance in neurobehavioural tests. Most authors agree that a long-term PbB level of 400 µg/L probably represents a LOAEL in this respect; since subtle effects have been experienced by some individuals at PbB levels of 400 µg/L.
- Other endpoints of lead toxicity, namely PNS (peripheral nervous system) and renal toxicity, are relevant for exposure levels which are consistently higher. The observed experimental carcinogenicity of lead salts is, in the first instance, directed towards the kidneys as the target tissue. Most probably, these effects are to a great extent based on the renal toxicity of high doses of lead. There is an ongoing discussion on the human carcinogenicity of lead and lead compounds. Based on experimental findings it seems plausible that lead has no direct genotoxic effect which argues in favour of the existence of practical thresholds of carcinogenicity. Hence an OEL based on avoiding functional CNS alterations is expected also to protect against PNS and renal toxicity, including possible renal cancer development. Similar conclusions may probably be drawn with respect to other systemic toxicities, for example on haem biosynthesis and on blood pressure, although there is a discrepancy in opinions and more research is needed in this direction.
- There is considerable uncertainty concerning impairment of reproductive function by lead. For males, there are valid indications that only PbB levels above 400 µg/L are connected with impairment of fertility. In females, however, it is relevant that cognitive deficits of the offspring are dose-dependently associated with lead exposure. The question of reversibility of such deficits is not yet satisfactorily resolved. On the basis of the present data no definite NOAEL can be deduced, which calls for a minimization of exposure.
- Another aspect to be observed is the existing background levels which result from environmental sources, even without overt occupational exposures. In most EU countries, the background PbB levels have decreased during the last 20-30 years from ~200 µg/L to ~50 µg/L. However, there are areas where higher levels are still being found, mainly due to the former use of lead materials in water installations (e.g., in some areas of Eastern Germany).

On this basis, SCOEL recommended a biological limit value for PbB of 300 µg/L with the following note: "It should be kept in mind that the recommended BLV is not seen as being entirely protective of the offspring of working women. No threshold for potential central nervous system effects in new born and infants can be identified at present. The exposure of fertile women to lead should therefore be minimised."

With regard to Occupational Exposure Limits (OEL), SCOEL noted that "Only part of the occupational exposure occurs by inhalation and a considerable portion is incorporated after oral ingestion. Lead ingestion varies as a function of personal hygiene of the individual and the overall cleanliness of the work environment. In consequence, the setting of an OEL for airborne lead is more difficult than for other compounds. Based on the field studies on lead battery workers by Lai et al. (1997) and others (see Kentner and Fischer 1993) and using the preferred values approach of SCOEL, an OEL for airborne exposure of 100 µg/m^3 (8-hour TWA) is recommended as consistent with the above biological limit value." SCOEL did not propose a STEL.

French ANSES 2017

The French ANSES (2017b) Expert Committee reviewed the scientific literature and proposed both a biological limit value (BLV) and biological reference values (BRV) for lead.

The former being established on the basis of health data and the latter referring to concentrations in the general population.

ANSES considered that neurological effects have been widely documented for exposures above 400 µg/L. Based on studies of Schwartz et al. 2001 and 2005 among Korean lead workers ANSES concluded on a LOAEL of 210 µg/L and a NOAEL of 180 µg/L for neurobehavioral effects.

In the occupational setting the clinically relevant adverse kidney or cardiovascular effects were considered to occur only above the NOAEL identified for neurotoxicity. Also the NOAEL for male reproductive toxicity was higher (450 µg/L) and effects on the immune system or haematological effects were considered unlikely below 400 µg/L.

ANSES proposed a BLV of 180 µg/L.

ANSES, however, acknowledged that reproductive toxicity effects on intrauterine growth, risk of spontaneous abortion and delayed post-natal development as well as effects on blood pressure and hypertension during pregnancy have been observed at maternal PbB below 100 µg/L. ANSES also acknowledged that from existing studies it is difficult to identify a threshold for these effects.

Based on 95th percentiles from data of the French general population aged 18-74 years ANSES proposed the following biological reference values (BRVs):

- 45 µg/L for women of childbearing age
- 60 µg/L for women
- 85 µg/L for men

It was further stated that "for women of childbearing age, the OEL Committee recommends not exceeding the BRV of 45 µg/L insofar as it is not possible to identify a precise threshold with no effect on reproduction".

As regards an OEL for airborne lead, ANSES (2017a), in their draft proposal, referred to Safe Work Australia (2014) and considered that of the six studies used in the Australian approach, two can be selected on the basis of metrological quality to calculate an air slope factor (ASF) correlating the air and blood concentrations . ANSES correlated a BLV of 180 µg/L with an OEL (8-hour TWA) of 30 µg/m^3. As regards a STEL, ANSES noted that there is no evidence of particular acute effects and consequently applied the national standard approach for such situations by proposing a STEL 5 times that of an 8-hour TWA.

German AGS 2017

Considering the available data base on neurological effects, AGS (2017) determined a LOAEC of 300 µg/L with reference to bone lead and blood lead levels. An assessment factor of 2 was considered appropriate to extrapolate to a NAEC of 150 µg/L because the observed effects were only weak and the usual extrapolation factor of 3 from a LOAEC to a NAEC for air values corresponds, in the case of lead, to a factor of 2 in blood because of non-linearity.

AGS concluded on a BLV of 150 µg/L.

Other endpoints (such as immunotoxicity, cardiovascular effects, reproductive toxicity and nephrotoxicity) are partly found at similar blood lead concentrations as neurotoxicity. The derivations are likewise affected by the relevant uncertainties, however, so that it is sufficient to derive an OEL on the basis of the clearly acknowledged neurotoxic effects.

AGS noted that the blood lead concentrations measured in the studies evaluated are associated with relevant uncertainties. In this context, it is of central importance that the measured blood lead value does not fairly reflect the chronic exposure and should therefore be regarded as an unsatisfactory auxiliary measure for assessing chronic neurotoxicity. Only if the blood lead concentration is calculated on the basis of cumulative

blood lead index (CBLI; assuming an exposure period of 40 years for the scenario considered here) this value can provide reasonable information on the estimated exposure level for chronic lead impact at the workplace.

AGS further noted that the concrete blood lead concentration reported from a study is not conclusive in particular if

- significant changes over time (former exposure, current exposure) are to be assumed,
- the exposure dates back, for example if effects on retired individuals are to be found and assessed,
- in parallel with occupational exposure, very high (former) non-occupational lead exposures have to be included,
- the exposure time is short so that the blood lead level essentially only reflects the acute lead concentration.

On the other hand, AGS noted that the neurological behavioural tests performed (with different weightings) reflect both: they are the result of chronic and acute damage through lead; but the chronic effects correlate better either with the *cumulative* weighted blood lead concentration or alternatively with the concentration of lead in bones. Therefore, AGS concluded that is why all mentioned effect concentrations which are directly based on the evaluation of blood lead levels at the workplace are very uncertain, lead to inconsistent LOAEC data and are therefore contentious.

Considering genotoxicity of lead, AGS concluded that cytogenetic effects are to be assumed at blood lead concentrations of 300 µg/L. This conclusion was based on several studies. However, AGS also noted that even if no genotoxic effect is anticipated when the determined blood lead level of 150 µg/L is complied with, it should additionally be emphasised that no qualified method is available for extrapolating an unambiguous effect threshold at about 300 µg PbB/L on the basis of cytogenetic effects. For these reasons it is recommended that the mentioned blood lead level of 150 µg/L (Biological Value) should preferably be undercut. In particular it is uncertain if the margin of safety for developmental-toxicity effects is sufficient.

In the case of lead, however, the observed effects of secondary genotoxicity receive additional relevance. Besides the classic "non-carcinogenic endpoints" these effects take on an "intermediate position". Even if they cannot be sufficiently associated, quantitatively and qualitatively, with tumour development, an increase in DNA damage or the impairment of DNA repair capacity is an adverse effect from which an OEL should protect. That is why the endpoint of genotoxic effects was included as a separate assessment criterion.

AGS did not derive an OEL for lead in the air. AGS considered the uncertainties inherent in establishing an airborne lead concentration limit to be so significant that a value of sufficient scientific quality could not be derived. AGS referred to a recent estimate of the concentration of airborne lead based on blood lead values from a pharmacokinetic model (OEHHA, 2013). Based on these data, a BLV of 150 µg/L would correlate to an 8 h TWA of 11.5 µg/m^3. However, AGS noted the high uncertainty for a correlation between PbB levels and Pb concentrations in air and that data were missing in the lower exposure range. Due to this uncertainty, AGS did not derive an OEL for lead in air. Neither did AGS derive a STEL.

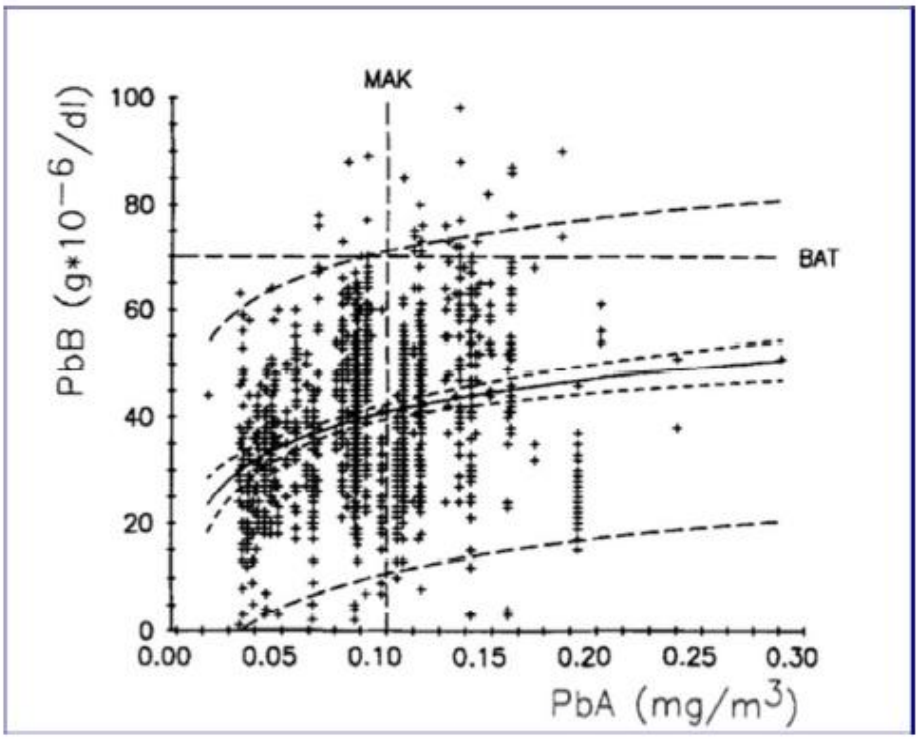

Figure 1: Correlation between air lead and blood lead levels (AGS, 2017)

US ACGIH 2017

ACGIH 2017 noted the data summarised by IARC (2006), NTP (2012) and EPA (2013) and further considered the data on the following effects: neurological and neurobehavioral effects in adults, neurobehavioral effects on the fetus and early childhood, cardiovascular effects, renal effects, reproductive effects, genotoxic effects and general mortality.

ACGIH stated that *various studies report that neurological and neurobehavioral effects and reproductive effects can be seen at PbB down to 200 µg/L.* ACGIG (2017) recommended a biological exposure index (BEI) of 200 µg/L.

As regards prenatal lead exposure and infant development, ACGIH BEI Committee noted that lead passes the placenta and can be transferred to the infant in breast milk and therefore to keep the PbB of the fetus and the infant below 50 µg/L, the PbB of the mother would need to be limited to 50 µg/L. The Committee, however, referred to the US EPA (2013) assessment and concluded: *At this time, BEI Committee does not believe the PbB of the workforce needs to be controlled to 50 µg/L because the evidence for a persistent relationship between prenatal lead exposure and infant development is mixed.* The BEI Committee, however, noted the CDC (2010) guidelines recommending follow-up and intervention beginning at PbB ≥ 50 µg/L in pregnant women. More specifically it was stated that persons applying the BEI of 200 µg/L *are encouraged to counsel women in child-bearing age, about the risk of delivering a child with a PbB over the current CDC reference value, the importance of closely monitoring the child's PbB, and the need to take steps appropriate to minimize the child's post-natal exposure to lead.*

Safe Work Australia 2014

Safe Work Australia (2014) reviewed the latest International and National assessments and selected the EPA (2013) assessment as a starting point to decide the relevant endpoints. EPA (2013) used a weight of evidence based approach on causality using the following categories: Causal relationship, Likely to be a causal relationship, Suggestive of

a causal relationship, Inadequate to infer a causal relationship, Not likely to be a causal relationship.

Safe Work Australia considered that where EPA (2013) had judged that evidence was only considered to be 'suggestive' or 'inadequate', it was assumed the studies are unlikely to provide sufficient information to support derivation of a workplace exposure standard for lead, and were therefore not further discussed. The health effects considered by US EPA (2013) to have a 'causal' or 'likely causal' relationship with lead exposure in adults were the focus of further analyses, i.e. the nervous, cardiovascular and male reproductive systems (please see separate considerations below for women at childbearing age).

It was acknowledged that some subtle endpoints pursued in the general population epidemiology studies have not been examined as thoroughly in the occupational setting. However, it was considered that the information on worker cohorts was more relevant for informing decisions regarding standards for workplace exposure than the information from the general population.

For the above-mentioned selected health effects further literature was reviewed and summarised and the following was concluded:

1. The most sensitive effects on the central nervous system for which there is consistent evidence are cognitive deficits in neurobehavioural tests and have been reported in workers with mean PbB of >300 µg/L.
2. Several studies have reported results as an estimated increase in blood pressure associated with a particular increase in PbB. The association is strongest for increases in systolic blood pressure. The effect on blood pressure is not a health outcome per se but a risk factor for cardiovascular and cerebrovascular disease. This risk is small for many individuals, however in a population it may be important, since it could shift a population's distribution to increase the percentage of individuals considered hypertensive. Some quantitative correlations in the general population between increases in blood pressure and mortality from cardiovascular disease were noted, but there was uncertainty how they would apply to worker populations.
3. Consistent associations in studies of occupational populations with concurrent PbB levels of 250 µg/L and greater, report detrimental effects of Pb on sperm; however, uncertainties remain regarding the timing, frequency, duration and level of Pb exposures contributing to the effects observed in epidemiologic studies.

For PbB, Safe Work Australia concluded the following:

1. The epidemiology data indicates a worker population mean PbB concentration of 300 µg/L can be regarded as a low observed adverse effect level (LOAEL), and a mean of 200 µg/L as a defensible no observed adverse effect level (NOAEL). Contemporary risk assessment methods recommend a lower bound estimate of the NOAEL be used as the point of departure for setting health protective standards (NHMRC 2006, enHealth 2012). Hence to avoid adverse health effects in females not of reproductive capacity and in males, a BLRL of 200 µg/L would be precautionary and protective. Nevertheless it should be recognised that the above 'critical' PbB's are not lower bound estimates that will necessarily protect nearly all workers in these categories, but instead they are closer to central estimates (i.e. average) for groups of workers in lead related jobs. Consequently a PbB of 200 µg/L does not result in certain preclusion of subtle health effects for a 'sensitive' individual (Section 4.6), particularly if these PbB concentrations are present for a long time.
2. For pregnant females and females of reproductive capacity (which by definition also includes females who are breastfeeding), a PbB target of 100 µg/L is suggested to keep cumulative lead stores in the body low enough to protect the

neurological development of the yet to be conceived and unborn child. This is consistent with the recommendations of the National Health and Medical Research Council (NHMRC, 2009).

As regards the last bullet, ECHA notes, that the literature on developmental neurotoxicity was not further reviewed in the report.

Safe Work Australia analysed the relationship between PbB concentrations and PbAir concentrations, the so called air slope factor (ASF) that reflects the incremental increase in PbB for each unit increase in air concentration and has been defined with the unit $(\mu g/dL)(\mu g/m^3)^{-1}$. Safe Work Australia considered that "ASF is non-linear and the relative contribution of PbAir to PbB is greater at low air concentrations relative to high concentrations. The factors influencing ASF include, but are not limited to, particle size, solubility, personal versus area PbAir data, the temporal relationship of PbAir measurements with PbB measurements, accuracy of PbAir measurements for exposure, PbAir being total lead or respirable lead, smoking status, hygiene practice (i.e. likelihood of hand mouth interaction), length of employment, inter-individual variability in lead absorption, etc. Furthermore, although worker PbB levels are likely to primarily be the result of lead exposure in the workplace they also include a contribution from background lead exposure. Currently this background exposure mainly comes from lead in the diet but in the past when leaded petrol was widely used, lead in ambient air was a major contributor to background PbB". Safe Work Australia considered various ASFs and their merits and implications and suggested an airborne work exposure standard of 0.05 mg/m^3 to achieve a PbB level of 200 µg/L. Safe Work Australia did not propose a STEL.

8.2.1 Occupational Exposure Limits (OELs)

8.2.1.1 Inorganic compounds

The current binding occupational limit value for "inorganic lead and its compounds" is 0.15 mg/m^3 (8 hours TWA) and the binding biological limit value for "lead and its ionic compounds" is 70 µg lead/100 mL blood, corresponding to 700 µg/L, as listed in Annex I and II of the Directive 98/24/EC respectively.

Given that health effects have been linked to significantly lower blood lead levels, the current binding biological limit value cannot be considered as sufficiently protective for workers. To control occupational exposure, measurement of Pb concentrations in the air is important. However, proposing an OEL value for air is more complicated than for other compounds as the derivation of the OEL is based on a correlation to the established BLV. Lead is unique in this regard as for most substances with a national and international BLV, the BLV is derived from the OEL.

More recent approaches such as those by AGS (2017), Safe Work Australia (2014) and ANSES (2017a), have established an occupational exposure limit value (OEL) for lead and are described above.

National OEL levels for inorganic lead compounds in the EU vary between 50 and 150 ug/m^3 (see Table 12). It should be noted, however, that as explained above the correlation between air concentration and blood concentration is influenced by various factors and is therefore not constant over various occupational settings. ECHA notes that the current values set in the Annexes of CAD are 150 $\mu g/m^3$ (8 hours TWA) and 700 µg/L. Using this correlation, the recommended BLV of 150 µg/L would correspond to a 8 hour TWA of 30 $\mu g/m^3$ (150 µg/L / 700 µg/L * 150 $\mu g/m^3$ = 32 $\mu g/m^3$). ECHA notes that this correlation between air and blood limit values is close to the ones above, used by ANSES and Safe Work Australia.

It is important to note that the BLV as the primary tool for protecting workers from lead toxicity has to be complied with. In order to help to achieve PbB below 150 µg /L, **ECHA also recommends setting an 8 hour TWA of 30 $\mu g/m^3$**.

8.2.1.2 Organic compounds

It is noted that the alkyl lead compounds are of higher acute (neuro) toxicity compared to the inorganic lead compounds.

Tetraethyl lead was demonstrated to be more neurotoxic compared to tetramethyl lead.

ECHA notes that national OEL levels for tetraethyl lead (Table 14) and tetramethyl lead (Table 15) in the EU are available which vary between 5 and 100 µg tetraethyl lead/m^3 and 50 to 150 µg tetramethyl lead/m^3.

Therefore, **ECHA also recommends an 8 hr TWA of 30 µg/m^3** for organic compounds (alkyl lead compounds), which is the same value as proposed for inorganic lead compounds.

It is important to note that the BLV as the primary tool for protecting workers from lead toxicity has to be complied with.

8.2.2 Short Term Exposure Limits (STELs)

ECHA does not propose a STEL because the leading toxic effects for lead and inorganic compounds are chronic systemic effects and there is no evidence of acute effects at these levels. This is in line with the recent assessments by Safe Work Australia, ANSES and AGS as well as the SCOEL recommendation (2002).

National STEL values for lead and inorganic compounds are listed in Table 12.

8.2.3 Biological Limit Value (BLV)

8.2.3.1 Inorganic compounds

Lead is widely distributed throughout the body and stored in bones. Therefore, lead related effects (mimicking calcium action and/or disrupting calcium homeostasis) can be observed in every organ system (ATSDR 2019). Due to this mode of action, lead-related effects are a continuum ranging from severely toxic effects to changes on a cellular basis and it is expected that there would not be a threshold for lead-related effect acting at the cellular level. Within this document adversity of lead-related effects is used for evaluation of information related to occupational exposure.

To derive a BLV for workers, statistically significant adverse effects in cohorts of lead exposed workers are considered, whereas in studies investigating large number of individuals of the general population changes in measured parameters and their dose-response-relationship are identified. However, such usually small changes based on a population basis are not necessarily relevant to derive an occupational exposure limit for workers.

Carcinogenicity

It is assumed that the carcinogenic activity of lead is based on an indirect role in carcinogenesis, for example in inhibiting DNA repair, rather than in causing alterations in DNA directly (Silbergeld *et al.,* 2000). Based on this assumption, several bodies have derived an occupational exposure limit for lead such as ACGIH (2017), AGS (2017), ANSES (2017), or Safe Work Australia (2014).

Genotoxicity

A large number of studies on the genotoxicity of lead are available, the majority of which report a clastogenic effect (ATSDR, 2019, AGS, 2017, IARC, 2006). The data base is quite robust demonstrating clastogenic effects such as DNA damage and increased MN and CA frequencies in exposed groups with mean PbB levels above 300 µg/L (e.g., Chinde et al., 2014; Grover et al., 2010; Garcia-Leston et al., 2012). There are fewer studies in workers with mean PbB levels between 200 and 300 µg/L that reported increased DNA damage

and DNA repair (Jannuzzi and Alpertunga, 2016), DNA damage (Danadevi et al., 2003), and DNA damage and increased MN frequency (Kasuba et al., 2012). Due to the limited number of studies available that investigate clastogenic effects of lead in the exposure range below 300 µg/L and due to methodological limitations of such studies such as small number of workers investigated, lack of adjustment for other relevant exposures, uncertainty about the role of individuals with exposure above the mean, the database in the mean exposure range below 300 µg/L is considered too uncertain for a conclusion.

Based on the results of studies investigating lead-induced genotoxic effects in workers (such as Vaglenov et al., 2001, Olevinska et al., 2010, Garcia-Leston et al. 2012, Chinde et al., 2014, and Januzzi and Alpertunga 2015), AGS (2017) concluded on a LOAEL of 300 µg/L.

Neurological effects

The reviewed meta-analyses investigating neurological effects concluded on a LOAEL for nerve conducting velocity of 330 µg/L (Krieg et al., 2008), on subtle neurobehavioral deficits between 370 and 520 µg/L (Seeber et al., 2002) and on changes in cognitive and sensomotoric parameters in lead exposed workers with blood lead concentrations of 340.8±136.3 µg/L (Vlasak et al., 2019). Based on data from previous reports using a BMD approach, the critical blood lead level for effects on the nervous system was calculated to be between 107 and 175 µg/L (Murata et al., 2009). Iwata et al. (2005) calculated a $BMD_{95\%}$ of 144 (121-173) µg/L for an effect on postural balance.

The most reliable information is from Schwartz et al. (2001) which suggested a threshold for neurobehavioral effects of 180 µg/L based on a cross-sectional study in 938 workers. It has to be noted that such effects are subtle.

Renal effects

In studies investigating workers, serum creatinine, as an indicator of the glomerular filtration rate, was slightly increased in cross-sectional studies at PbB levels of 700 µg/L (Onuegbu et al., 2011) and 400 µg/L (Hernandez-Serrato et al., 2006) but not at 390 µg/L (Orisakwe et al., 2007). In a larger longitudinal study investigating 537 workers, changes in renal function (blood urea nitrogen, serum creatinine, calculated creatinine clearance) were reported at mean PbB levels measured over 3 years between 313 and 326 µg/L (Weaver et al., 2009). However, in men the associations indicated lower creatinine and higher glomerular filtration rate during the course of study regardless of whether PbB increased or decreased. In the other longitudinal study that investigated only 30 workers with current PbB levels of about 300 µg/L and previous higher levels (ca. 600 µg/L), the effect on renal function (creatinine) was unclear (Hsiao et al., 2001). Early biological effect markers such as N-acetyl-β-D-glucosaminidase (NAG) was increased at 625 µg/L (Gao et al., 2010) with no effects at 390 µg/L (Orisakwe et al., 2007, Garcon et al., 2007). A $BMDL_{10}$ of 253 µg/L for changes in NAG was calculated (Lin and Tai-Yi, 2007).

The reviewed data indicate that the lowest $BMDL_{10}$ value of 253 µg/L for sub-clinical changes from an effect marker for renal impairment (NAG) could be considered as the non-adverse effect level.

Cardiovascular effects

In working populations a LOAEL around 300 µg/L has been observed for small (0.5-2 mmHg) increases in systolic or diastolic blood pressure (Glenn et al 2006, Weaver et al 2008). In the general population, similar effects have been observed at even lower PbB levels. However, an effect on blood pressure is not a health outcome per se but a risk factor for cardiovascular and cerebrovascular disease. Considering increases of an order of 1 to mmHg of systolic or diastolic blood pressure the risk is small at an individual level and there are no studies that have assessed in a working population the long-term predictive value of such small blood pressure increases for cardiovascular morbidity or mortality.

Some of the recent studies, especially in their internal comparisons by exposure level (Steenland et al., 2017, Bertke et al., 2016, Kim et al., 2015, McElvenny et al., 2015, Chowdbury et al 2014), provide some indication of an association between past exposure to lead and cardiovascular mortality. In the studies reporting PbB as an exposure metric, the effect was typically seen at levels above 200 - 400 µg/L. However the studies did not adjust for potential confounding effects of non-occupational risk factors.

Haematological effects

SCOEL (2002) summarised that lead inhibits enzymes of haem synthesis in a dose-dependent manner (both as regards prevalence and severity) and there are a number of related parameters for which it is possible to tentatively identify PbB levels at which changes cannot be detected (NOAELs):

- coproporphyrin: 400 µg/L;
- urinary and blood δ-aminolevulinic acid levels: 300 to 350 µg/L;
- inhibition of iron chelation: 200-250 µg/L;
- zinc protoporphyrin: 200 µg/L;
- δ-aminolevulinic acid dehydrase (ALAD): 100 µg/L.

More recent investigations indicate that PbB levels below 50 µg/L inhibited enzymes such as ALAD involved in haeme synthesis in workers (Murata et al., 2009).

SCOEL (2002) concluded that subclinical changes in parameters of haem synthesis may occur below 400 µg Pb /L blood, but these are not regarded as "adverse". SCOEL also noted that although the data-base is weak, there appears to be a risk of developing lead-induced anaemia (haemoglobin concentration < 140 g/L) at PbB in excess of about 500 µg/L. Karita et al. (2005) estimated a $BMD_{95\%}$ for an increased probability of abnormal haemoglobin to be at 195 µg Pb/L blood.

Male fertility

SCOEL (2002) concluded that adverse effects on male reproduction appear consistently at PbB levels above 400 µg/L. More recent studies investigating the fertility of lead-exposed workers support this conclusion.

Female fertility

The data with regard to female fertility is very limited. One recent study in female lead-exposed workers (Paredes Alpaca et al., 2013) indicates an increased risk of miscarriages at PbB levels >50 µg/L.

Developmental toxicity

ATSDR (2019) summarised that PbB levels <100 µg/L are associated with adverse effects, particularly in children. Currently, it is accepted that adverse effects occur at PbB levels <50 µg/L and for the most studied endpoints (neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental) and no safe blood lead level in children has been identified.

Derivation of a BLV

Taking into account the reviewed studies on lead-exposed workers, Table 37 summarizes the lowest relevant PbB levels reported for the relevant endpoints of Pb toxicity in workers.

Table 37: Summary of PbB levels with lowest effect levels, thresholds or calculated BMDL for the relevant endpoints of Pb toxicity in workers

PbB (µg/L)	Effects
>400	Adverse effects on sperm quality (Apostoli et al., 2000; 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
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	Threshold (NOAEL) for subtle neurobehavioral effects in workers (Schwartz et al., 2001)

[1)] In the general population, similar effects have been observed at even lower PbB levels. However an effect on blood pressure is not a health outcome per se but a risk factor for cardiovascular and cerebrovascular disease. Considering increases of an order of 1 to mmHg of systolic or diastolic blood pressure the risk is small at an individual level and there are no studies that have assessed in a working population the long-term predictive value of such small blood pressure increases for cardiovascular morbidity of mortality

AGS (2017) specifically noted that "In the case of lead, however, the observed effects of secondary genotoxicity receive additional relevance. Besides the classic "non-carcinogenic endpoints" these effects take on an "intermediate position". Even if they cannot be sufficiently associated, quantitatively and qualitatively, to the cancer process, an increase in DNA damage or the impairment of DNA repair capacity is an adverse effect from which an OEL should protect. That is why the endpoint of genotoxic effects was included as a separate assessment criterion."

AGS (2017) used a point of departure of 300 µg/L as the LOAEC based on a weight of evidence assessment from several studies and considered an assessment factor of 2 as sufficient to extrapolate to a NAEC. AGS also concluded on an extrapolated value (NAEC) for neurotoxicity and low risk of secondary genotoxicity of 150 µg/L. Consequently, AGS concluded on a BLV of 150 µg/L.

ECHA comes to a similar conclusion with an overall LOAEL of 300 µg/L for adverse effects on sperm quality and clastogenic effects. ECHA considered that NOAELs were >150 µg/L for subtle neurobehavioral effects, sub-clinical renal effects and anemia.

ECHA notes that the basis for a BLV is human data and consequently there is no need for an assessment factor for interspecies variation. Furthermore, ECHA notes that the human data base for lead related health effects is extremely large both in terms of study populations covered and health endpoints addressed and these data are considered to adequately address the variability among workers when selecting as starting point a NOEAL from this data base. Therefore no assessment factor for interindividual variation is considered to be needed. The extensive human data base also includes numerous studies in working populations with a long-term exposure, furthermore the exposure metric used (PbB) is also partially reflecting long-term exposure through bone release and ECHA considers that an assessment factor for duration of exposure is not needed. ECHA notes that a similar approach has been followed by the national bodies recently proposing BLVs

for lead. These bodies only applied an assessment factor for LOAEL to NOAEL extrapolation if their starting point was a LOAEL, but did not apply other assessment factors.

ECHA proposes a BLV of 150 µg Pb/L blood.

National biomonitoring values for lead in blood OEL vary between 150 and 300 µg/L (see Table 36).

This BLV is not protective for the offspring of female lead-exposed workers at childbearing age (see below).

Special considerations for women at childbearing age

As described in section 7.8.1 an increased PbB has been associated with a decrease of intelligence quotient (IQ) in children (EFSA 2010, NTP 2012, EPA 2013, ATSDR 2019). As lead passes the placenta and is stored in bones, it is possible that maternal occupational exposure to lead could contribute to such effects either during in utero development of the nervous system or during infancy as a consequence of release of lead stored in fetal bone during the pregnancy.

When studying the potential effect of maternal Pb exposure (e.g. by using maternal or umbilical cord PbB as the exposure metric) on the IQ development of the child one needs to adjust for maternal and paternal IQ, lead exposure of the child since birth and various environmental and socio-economic factors influencing cognitive development. As explained in section 7.8.1, the relevant time windows to measure these potential confounders are unknown. This makes such studies methodologically challenging and the results have been inconsistent. Most recently ATSDR (2019) noted that a large number of studies showing decrements in neurological function in children have been published. Collectively, these studies support the concept that Pb affects cognitive function in children prenatally exposed to PbB ≤100 µg/L, with numerous studies providing evidence for effects at PbB ≤50 µg/L.

Based on the above ECHA considers that it does not seem possible to directly identify a maternal PbB that would exclude the possibility of any effect on cognitive function development of the newborn. Therefore ECHA recommends to RAC to consider the following three options in their opinion development to address this effect:

Option 1: A BLV of < 50 µg/L is proposed for women of childbearing age;

Option 2: The PbB level for women of childbearing age should not be higher than the reference values of the respective general populations not occupationally exposed to lead;

Option 3: It is recommended to make qualitative statement in the Chemical Agents Directive that the exposure of fertile women to lead should be minimised or avoided in the workplace because the BLV for lead is not protective of the offspring of women of childbearing age.

8.2.3.2 Organic compounds

DFG (1995) summarised that the excretion of the specific tetraethyl lead metabolite, diethyl lead, can be regarded as the most suitable parameter for the evaluation of internal tetraethyl lead TEL exposure. A BAT value of 25 µg diethyl lead/L urine (calculated as Pb) was derived, that correlated with the MAK value for tetraethyl lead of 50 µg/m^3. However, DFG noted that the determination of diethyl lead required a complicated method that was not validated at that time.

Therefore, DFG (1995) also proposed a BAT value of 50 µg total Pb/l urine, which correlated only unsatisfactorily with the current occupational exposure to tetraethyl lead, possibly due to earlier exposure to Pb compounds and the resulting accumulation of Pb in the organism.

No valid information could be retrieved that allows an appropriate correlation between Pb in blood and Pb in urine for the organic lead compounds to verify if the proposed biomonitoring value (PbB) for inorganic lead would be applicable also for the organic lead compounds.

However, since the higher acute (neuro) toxicity of tetraethyl and tetramethyl lead compared to the inorganic lead compounds is accounted for by the OEL, the body burden resulting from any exposure to a lead compounds is addressed by measuring systemic lead exposure as blood lead. Therefore, it is proposed to apply the BLV for inorganic lead compounds also for the organic lead compounds.

Consequently, a BLV of 150 µg Pb/L blood is proposed for inorganic and for organic lead compounds.

8.2.4 Biological Guidance Value (BGV)

Since a BLV is proposed**, no BGV is derived**. However, it is recommended that national data are used to establish background levels of PbB.

From the German Environmental Specimen Bank, the following statistically derived reference levels were identified: 40 µg/L for adult men, 30 µg/L for adult women and 35 µg/L for children (HBM4EU, 2019).

8.3 Notation

There is no reported evidence of lead being a skin sensitiser or respiratory sensitiser.

Therefore, **no notation for 'Skin' or 'Sensitisation' is required**.

However, some substances containing lead might be skin or respiratory sensitisers due to the properties of the other constituents of the substances.

9. Groups at Extra Risk

Women of child bearing capacity and pregnant women

Considering the workplace, women of child bearing capacity and pregnant women require specific considerations. BLV is not seen as protective of the offspring of working women. No threshold for potential central nervous system effects in new born and infants can be identified at present. The exposure of fertile women to lead should therefore be minimised.

Age

According to ATSDR (2019) Children and the elderly are likely to have increased susceptibility to Pb compared to non-elderly adults.

Pb crosses the placenta and is distributed to the foetus; neonates are also exposed to Pb in breast milk. Epidemiological studies show that umbilical cord PbB (reflective of neonatal PbB) and PbB in infants are associated with adverse health outcomes during childhood, including decrements in neurological function. Results of a few studies that have followed children to early adulthood show an association between child PbB and behavioural and neuroanatomical changes in adults, suggesting a possible role of exposures in childhood to adult outcomes. Children are likely to be more susceptible than adults to Pb for the following reasons: (1) it is generally accepted that developing systems are more susceptible than mature systems; (2) absorption of Pb is higher in children compared to adults (see Section 3.1.1, Absorption); and (3) children exhibit behaviours that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity, pica behaviour [the compulsive, habitual consumption of non-food items]), proximity of the breathing zone to entrained surface dust).

Regarding the elderly, ATSDR (2019) noted that it is well-established that physiological functions (e.g., renal, neurological, cardiovascular) decline with age. Thus, populations with age-related compromises in physiological function would be anticipated to be more susceptible to Pb than younger populations. Furthermore, because aging is associated with bone loss, Pb is mobilized into blood, resulting in potential increases in PbB.

Sex

ATSDR (2019) summarised that some epidemiological studies examined health outcomes in populations stratified by sex. However, studies have not demonstrated clear sex-related susceptibilities to Pb-induced toxicity for any health effect outcome. In women, pregnancy, lactation, and post-menopausal status may increase bone demineralization, mobilizing bone Pb into the blood and potentially redistributing Pb to other tissues.

Pre-existing Conditions, Diseases, and Exposure to Other Substances.

ATSDR (2019) summarised that because health effects associated with Pb are observed in every organ system, it is assumed that any condition or disease that compromises physiological functions could cause increased susceptibility to Pb. Examples of underlying conditions include diseases of the kidney (e.g., glomerular nephritis), neurological system (e.g., autism), hematological system (e.g., anemia, thalassemia), and cardiovascular system (e.g., hypertension, cardiac conduction disorders). Similarly, increased susceptibility to Pb would be anticipated due to use of alcohol, tobacco, or any other substance that causes deficits in physiological function.

Genetic Polymorphisms

Numerous genetic polymorphisms that may alter susceptibility to Pb through altered toxicokinetics (i.e., absorption, distribution, and retention of Pb) or toxicodynamics (e.g., effects) have been identified. The most well-studied polymorphisms are δ-ALAD and the Vitamin D receptor (VDR). Several other polymorphisms that may alter susceptibility to Pb have been identified, although little data are available. In addition to the references listed below, information also was obtained from a recent review by Broberg et al. 2015.

ALAD: Pb binds to and inhibits δ-ALAD, causing decreased hemoglobin formation, measurable decreases in blood hemoglobin concentration, and anemia. δ-ALAD is the major binding site for Pb in the blood (see Section 3.1.2). As such, polymorphisms of ALAD have the potential to alter Pb toxicokinetics, and thereby alter health effects. Many studies have evaluated the potential effects of ALAD polymorphisms on Pb distribution and toxicity (ATSDR 2019).

VDR: The VDR is located in the nucleus of intestinal, renal, and bone cells. It is involved in maintaining calcium and phosphate homeostasis and regulating bone metabolism. Binding of vitamin D3 (the active form of vitamin D) to the VDR activates genes that encode for various calcium-binding proteins involved in intestinal absorption and accumulation of calcium in bone. The VDR regulates the production of calcium-binding proteins, and accounts for up to 75% of the total genetic effect on bone density. Because Pb can replace and mimic calcium, the VDR plays a critical role in the accumulation of Pb in bone. The VDR has several polymorphic forms that are defined based on restriction enzyme digestion; these include FokI with three genotypes (FF, Ff, and ff) and BsmI with three genotypes (BB, Bb, bb). The FF genotype has been associated with higher PbB and increased bone mineral density and calcium uptake. The BB genotype has been associated with higher PbB and bone Pb. However, the role of VDR polymorphisms in the Pb uptake into bone remains to be fully elucidated (ATSDR 2019).

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Appendix 1 Tabulated Summaries for Substance identification and Physico-chemical properties of lead compounds

Table 38: Inorganic lead compounds

Name	EC/list number	CAS number	Description	Molecular formula
Lead	231-100-4	7439-92-1		Pb
Lead monoxide	215-267-0	1317-36-8		OPb
Tetralead trioxide sulphate	235-380-9	12202-17-4		O_7Pb_4S
Pentalead tetraoxide sulphate	235-067-7	12065-90-6		O_8Pb_5S
Orange lead	215-235-6	1314-41-6		O_4Pb_3
Lead dinitrate	233-245-9	10099-74-8		$NO_3Pb_{½}$
Trilead dioxide phosphonate	235-252-2	12141-20-7		HO_5PPb_3
Lead sulfochromate yellow	215-693-7	1344-37-2	This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77603.	
Lead chromate molybdate sulfate red	235-759-9	12656-85-8	This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77605.	
Lead dichloride	231-845-5	7758-95-4		Cl_2Pb
dicalcium tris(lambda2-lead(2+)) tetracarbonate sulfate	931-722-2	-		
Lead titanium zirconium oxide	235-727-4	12626-81-2		
Silicic acid, lead salt	234-363-3	11120-22-2		
Lead carbonate	209-943-4	598-63-0		CO_3Pb
Lead hydroxide	243-310-3	19783-14-3		H_2O_2Pb
Lead bis(tetrafluoroborate)	237-486-0	13814-96-5		$BF_4Pb_{½}$
Lead cyanamidate	244-073-9	20837-86-9		CN_2Pb
Trilead diarsenate	222-979-5	3687-31-8		$AsO_4Pb_{3/2}$
Lead telluride	215-247-1	1314-91-6		PbTe

Name	EC/list number	CAS number	Description	Molecular formula
Pyrochlore, antimony lead yellow	232-382-1	8012-00-8	This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77588.	
Lead titanium trioxide	235-038-9	12060-00-3		O_3PbTi
Lead sulphide	215-246-6	1314-87-0		PbS
Lead selenide	235-109-4	12069-00-0		PbSe
Lead diazide	236-542-1	13424-46-9		N_6Pb
copper lead silver	931-607-7	-		
Trilead bis(carbonate) dihydroxide	215-290-6	1319-46-6		$C_2H_2O_8Pb_3$
Lead dioxide	215-174-5	1309-60-0		O_2Pb
Lead sulphate	231-198-9	7446-14-2		O_4SPb
Lead oxide sulfate	234-853-7	12036-76-9		O_5Pb_2S
Sulfurous acid, lead salt, dibasic	263-467-1	62229-08-7		
Lead chromate	231-846-0	7758-97-6		CrO_4Pb

Table 39: Inorganic lead compounds – physico-chemical properties[32]

Substance name	EC/list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility
Lead monoxide	215-267-0	solid	9.96	888[33]	70 mg/L (pH 11) 0.1 mg/L (pH 8.4)
Tetralead trioxide sulphate	235-380-9	solid	6.84	>500	102 mg/L (pH 8
Pentalead tetraoxide sulphate	235-067-7	solid	7.15	>600	32.7 mg/L (pH 8.7)
Orange lead	215-235-6	solid	8.93	>550	67.3 mg/L (pH 10.8)
Lead dinitrate	233-245-9	solid	4.5	458	486 g/L
Trilead dioxide phosphonate	235-252-2	solid	6.74	230 (decomp)	12.2 mg/L (pH 8)

[32] All properties are obtained from registration data published on https://echa.europa.eu/information-on-chemicals except where indicated otherwise.

[33] Property value obtained from scifinder (scifinder.cas.org).

Substance name	EC/list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility
Lead sulfochromate yellow	215-693-7	solid	5.6	n/a	insoluble
Lead chromate molybdate sulfate red	235-759-9	solid	3.8 – 6	> 800	< 0.1 mg/L
Lead dichloride	231-845-5	solid	5.98	501	10 g/L (pH 4.2; 20 °C) 12.5 g/L (pH 4.1; 32 °C)
dicalcium tris(lambda2-lead(2+)) tetracarbonate sulfate	931-722-2	solid	7.4	634	n/a
Lead titanium zirconium oxide	235-727-4	solid	1533	n/a	3.4 mg/L (pH 6.3)
Silicic acid, lead salt	234-363-3	solid	6.6	>675 - <717	< 0.07 mg/L
Lead carbonate	209-943-4	solid	6.1	315 (decomp)[33]	insoluble
Lead hydroxide	243-310-3	solid	n/a	n/a	n/a
Lead bis(tetrafluoroborate)	237-486-0	solid	1.7 (50% aq. solution)	n/a	> 500 g/L
Lead cyanamidate	244-073-9	solid	5.8	> 400	n/a
Trilead diarsenate	222-979-5	solid	5.8	n/a	sparingly soluble
Lead telluride	215-247-1	solid	8.2[33]	924	< 0.1 mg/L
Pyrochlore, antimony lead yellow	232-382-1	solid	7.8	> 1300	ca. 6 mg/L
Lead titanium trioxide	235-038-9	solid	8.1	ca. 1756	0.075 mg/L (pH 6.5)
Lead sulphide	215-246-6	solid	7.6[33]	1114	insoluble < 0.1 mg/L
Lead selenide	235-109-4	solid	8.1	1078	insoluble < 0.1 mg/L
Lead diazide	236-542-1	solid	4.2	n/a	ca. 0.5 g/L
copper lead silver	931-607-7	solid	9.1	> 450	n/a
Trilead bis(carbonate) dihydroxide	215-290-6	solid	7.0	> 500	2.2 mg/L (pH 6.2)
Lead dioxide	215-174-5	solid	9.38[33]	290 (decomp)	<11.3 ug/L (pH 6-7)
Lead sulphate	231-198-9	solid	6.3[33]	1170[33]	ca. 42 mg/L
Lead oxide sulfate	234-853-7	solid	6.3	>600	19.2 mg/L (pH 7.1)
Sulfurous acid, lead salt, dibasic	263-467-1	solid	7	>350	34 mg/L(pH 6-6.6)
Lead chromate	231-846-0	solid	6.3[33]	844[33]	n/a

Table 40: Inorganic substances only used during production and recycling of lead and its compounds[34]

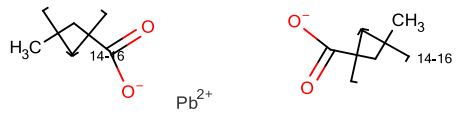
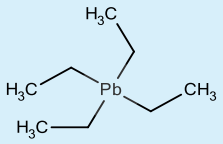
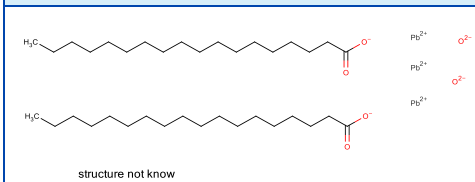
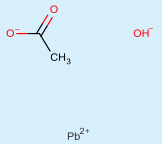
Name	EC/list number	CAS number	Description
Slags, copper refining	266-970-4	67711-94-8	Mainly copper, copper oxides, some oxides of lead and minor metals, skimmed from the anode furnace and returned to the converter.
Matte, copper	266-967-8	67711-91-5	Product of smelting roaster calcines concentrates or cement copper with flux in reverberatory or electric furnaces. Composed primarily of copper and copper, iron and lead sulfides with minor sulfides of other metals.
Flue dust, zinc-refining	273-760-6	69012-63-1	By-product of refining of zinc ores consisting primarily of zinc, lead and iron.
Leach residues, zinc ore, lead-contg.	293-314-4	91053-49-5	Insoluble substance obtained during dissolution of zinc ores or concentrate in sulfuric acid for the production of zinc sulfate solutions after physical separation such as flotation and filtration.
Slags, lead smelting	273-825-9	69029-84-1	Slag formed as the feed progresses through the blast furnace in lead smelting. Consists primarily of metallic elements and oxides of calcium, magnesium and silicon.
Lead, bullion	308-011-5	97808-88-3	nan
Slags, lead reverbatory smelting	273-800-2	69029-58-9	By-product from the smelting of lead ores, scrap lead or lead smelter dross. Consists primarily of oxides and silicates of antimony and lead.
Wastes, lead battery reprocessing	305-445-7	94551-99-2	Material obtained during the recycling of exhausted lead storage batteries. Consists primarily of oxides and sulfates of lead and lead alloys.
Calcines, lead-zinc ore conc.	305-411-1	94551-62-9	A thermally agglomerated substance formed by heating a mixture of metal sulfide concentrates, limestone, sand, furnace dross, miscellaneous zinc, lead and copper bearing materials, together with already roasted material to a temperature of 1000°C to 1200°C (538°F to 649°F).
Matte, lead	282-356-9	84195-51-7	Substance resulting from the smelting of lead and its alloys obtained from primary and secondary sources and including recycled plant intermediates. Composed primarily of iron and lead (mainly in sulfide form) and may contain other residual non-ferrous metals and their compounds.
Flue dust, lead-refining	273-809-1	69029-67-0	By-product of refining lead ores obtained from baghouse and electro-static precipitator and as slurry from scrubbers.
Lead, dross	273-796-2	69029-52-3	nan
Lead, dross, copper-rich	273-925-2	69227-11-8	A scum formed on the surface of molten copper.
Slimes and Sludges, copper electrolytic	266-972-5	67711-95-9	A complex combination of insoluble compounds which precipitate during copper electrolytic refining.
Zinc, desilverizing skims	273-802-3	69029-60-3	Crusts formed on the surface of cooling molten lead during the desilverizing of lead.

[34] Due to the complexity and variability of these substances, physico-chemical properties are not readily available and also not very meaningful and have therefore been omitted.

Name	EC/list number	CAS number	Description
Residues, zinc smelting	273-824-3	69029-83-0	Residues remaining after refining and smelting of zinc from primary and secondary sources. Consists primarily of zinc compounds and may contain large amounts of iron and lead and their oxides as well as minor amounts of other metals and/or their compounds.
Lead alloy, base, Pb,Sn, dross	273-701-4	69011-60-5	Oxides formed during melting, refining, and casting of solders. Major constituents are oxides of tin, lead and antimony; minor constituents are iron, nickel, sulfur, arsenic, copper and silver.
Lead, dross, antimony-rich	273-791-5	69029-45-4	A scum or slag formed on the surface of molten lead during the process of removing antimony along with arsenic by oxidation with air. It consists of antimony, arsenic and lead oxides.
Slimes and Sludges, precious metal refining	308-516-0	98072-61-8	nan
Speiss, lead	282-366-3	84195-61-9	Substance resulting from the smelting of lead and its alloys obtained from primary and secondary sources and including recycled plant intermediates. Composed primarily of arsenic, lead and iron and may contain other residual non-ferrous metals and their compounds.
Lead, dross, bismuth-rich	273-792-0	69029-46-5	A scum formed on the surface of molten lead during the process of removing bismuth by the addition of calcium and magnesium. It consists of lead containing calcium and magnesium bismuthides.
Slimes and Sludges, battery scrap, antimony- and lead-rich	310-061-8	102110-60-1	A product obtained by the treatment of battery scraps to recover lead. Composed primarily of oxides and sulfates of antimony and lead.
Lead, antimonial, dross	273-795-7	69029-51-2	A scum formed on the surface of antimonial lead. Consists primarily of sodium arsenate and sodium antimonate with some lead oxide and free caustic soda.
Concentrates of lead and zinc compounds with sulfur resulting from hydrometallurgy (hot acid leaching, super-hot acid leaching and flotation)	936-276-2	-	
Slimes and Sludges, zinc sulfate electrolytic	273-742-8	69012-43-7	Product resulting from cleaning anodes and electrolyzing cells in an electrolytic zinc plant with zinc sulfate. Consists primarily of oxides of lead and manganese and calcium sulfate.
Leach residues, zinc ore-calcine, zinc cobalt	273-769-5	69012-72-2	Residue from treatment of calcined zinc ore concentrates with antimony trioxide, zinc dust, lead oxide and copper sulfate. Consists primarily of zinc and a composite of metallics: cobalt, copper and lead.
Waste solids, lead silver anode	305-449-9	94552-05-3	The slag or residue obtained when lead/silver anodes used in the electrolytic production of zinc are recast. Fusion of the alloys of lead and silver (manganese may also be present) and simultaneous oxidation occur.

Name	EC/list number	CAS number	Description
Flue dust, precious metal refining	308-496-3	98072-44-7	The dust obtained from the refining of materials from primary and secondary sources containing gold, iridium, osmium, palladium, platinum, rhenium, ruthenium and silver. Composed primarily of lead with traces of other metals.
Matte, precious metal	308-506-6	98072-52-7	
Slags, tellurium	273-828-5	69029-86-3	Product of treating molten lead with sodium salts. Consists primarily of sodium-tellurium salts in various states of oxidation.
Residues, precious metal refining cementation	310-051-3	102110-50-9	The residues obtained by the addition of aluminum or zinc to end liquors obtained from secondary refining of gold, iridium, osmium, palladium, platinum, rhenium, ruthenium or silver. Composed primarily of the precious metals, ammonium chloride and chlorides of aluminum, magnesium and zinc.
Residues, copper speiss acid leaching	309-643-4	100656-54-0	The product obtained by acid leaching of copper speiss. Composed primarily of antimony, arsenic and lead with high precious metal content.
Leach residues, tellurium	273-814-9	69029-73-8	Residues remaining after leaching various residues from lead refining with sodium hydroxide to recover tellurium. Consist primarily of Tl, Cu, Pb, Se, Ag, sodium sulfate, sodium silicate and sodium hydroxide.

Table 41: organic lead compounds

Structure	Name	EC/list number	CAS number
	Fatty acids, C16-18, lead salts	292-966-7	91031-62-8
	Tetraethyllead	201-075-4	78-00-2
	Dioxobis(stearato)trilead	235-702-8	12578-12-0
	Acetic acid, lead salt, basic	257-175-3	51404-69-4

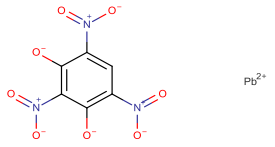
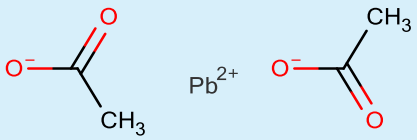
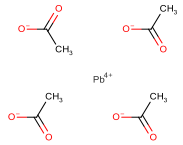
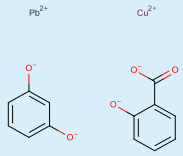
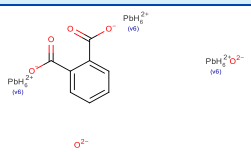
Structure	Name	EC/list number	CAS number
	Lead 2,4,6-trinitro-m-phenylene dioxide	239-290-0	15245-44-0
	Lead di(acetate)	206-104-4	301-04-2
	Lead tetraacetate	208-908-0	546-67-8
 structure not known	Copper Lead Resorcylate Salicylate Complex	614-455-3	68411-07-4
	[phthalato(2-)]dioxotrilead	273-688-5	69011-06-9

Table 42: organic lead compounds – physico-chemical properties[32]

Substance name	EC/list number	Physical state	Density [g/cm³ at 20°C]	Melting point [°C]	Water Solubility
Fatty acids, C16-18, lead salts	292-966-7	solid	1.46	101-105	10.4 mg/L (pH 7.8)
Tetraethyllead	201-075-4	liquid	1.65	-136	< 2.35 mg/L (pH 7)
Dioxobis(stearato)trilead	235-702-8	solid	1.95	290 (decomp)	1.76 mg/L (pH 9.3)
Acetic acid, lead salt, basic	257-175-3	solid	3.58	198-225	73.2 % w/w
Lead 2,4,6-trinitro-m-phenylene dioxide	239-290-0	solid	3.02	decomp.	0.7 g/L
Lead di(acetate)	206-104-4	solid	3.25	204	443 g/L
Lead tetraacetate	208-908-0	solid	2.2	175	n/a
Copper Lead Resorcylate Salicylate Complex	614-455-3	solid	2.7	decomp.	Slightly sol. <100 mg/L
[phthalato(2-)]dioxotrilead	273-688-5	solid	4.5	326 (decomp)	579 mg/L (pH 9.7)

Appendix 2 CLH Tables

Table 43: EU Classification: CLP (EC) 1271/2008, Annex VI listing of lead and its compounds

Index No	Chemical name	EC No	CAS No	Hazard Class and Category Code(s)	Hazard Statement Code(s)
009-014-00-1	lead hexafluorosilicate	247-278-1	25808-74-6	Repr. 1A Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H360Df H332 H302 H373 ** H400 H410
028-015-00-8	slimes and sludges, copper electrolyte refining, decopperised	305-433-1	94551-87-8	Carc. 1A Muta. 2 Repr. 1A STOT RE 1 Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H341 H360D *** H372 ** H334 H317 H400 H410
028-050-00-9	silicic acid, lead nickel salt	-	68130-19-8	Carc. 1A Repr. 1A STOT RE 1 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H350i H360Df H372 ** H317 H400 H410
082-001-00-6	lead compounds with the exception of those specified elsewhere in this Annex			Repr. 1A Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H360Df H332 H302 H373 **: C ≥ 0,5 % H400 H410 H361f: C ≥ 2,5 %[35]

[35] This classification is known to be inconsistent regarding the classification as Repr. 1A and the specific concentration limit for Repr. 2 and is due to be corrected.

Index No	Chemical name	EC No	CAS No	Hazard Class and Category Code(s)	Hazard Statement Code(s)
082-002-00-1	lead alkyls			Repr. 1A Acute Tox. 1 Acute Tox. 2 * Acute Tox. 2 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H360Df: C ≥ 0,1 % H310 H330 H300 H373 **: C ≥ 0,05 % H400 H410
082-003-00-7	lead diazide; lead azide	236-542-1	13424-46-9	Unst. Expl. Repr. 1A Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H200 H360Df H332 H302 H373 ** H400 H410
082-003-01-4	lead diazide; lead azide [≥ 20 % phlegmatiser]	236-542-1	13424-46-9	Expl. 1.1 Repr. 1A Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H201 H360Df H332 H302 H373 ** H400 H410
082-004-00-2	lead chromate	231-846-0	7758-97-6	Carc. 1B Repr. 1A STOT RE 2 Aquatic Acute 1 Aquatic Chronic 1	H350 H360Df H373 ** H400 H410
082-005-00-8	lead di(acetate)	206-104-4	301-04-2	Repr. 1A STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H360Df H373 ** H400 H410
082-006-00-3	trilead bis(orthophosphate)	231-205-5	7446-27-7	Repr. 1A STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H360Df H373 ** H400 H410

Index No	Chemical name	EC No	CAS No	Hazard Class and Category Code(s)	Hazard Statement Code(s)
082-007-00-9	lead acetate, basic	215-630-3	1335-32-6	Carc. 2 Repr. 1A STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H351 H360Df H373 ** H400 H410
082-008-00-4	lead(II) methanesulphonate	401-750-5	17570-76-2	Repr. 1A Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Skin Irrit. 2 Eye Dam. 1	H360Df H332 H302 H373 ** H315 H318
082-009-00-X	lead sulfochromate yellow; C.I. Pigment Yellow 34; [This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77603.]	215-693-7	1344-37-2	Carc. 1B Repr. 1A STOT RE 2 Aquatic Acute 1 Aquatic Chronic 1	H350 H360Df H373 ** H400 H410
082-010-00-5	lead chromate molybdate sulfate red; C.I. Pigment Red 104; [This substance is identified in the Colour Index by Colour Index Constitution Number, C.I. 77605.]	235-759-9	12656-85-8	Carc. 1B Repr. 1A STOT RE 2 Aquatic Acute 1 Aquatic Chronic 1	H350 H360Df H373 ** H400 H410
082-011-00-0	lead hydrogen arsenate	232-064-2	7784-40-9	Carc. 1A Repr. 1A Acute Tox. 3 * Acute Tox. 3 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H350 H360Df H331 H301 H373 ** H400 H410

Index No	Chemical name	EC No	CAS No	Hazard Class and Category Code(s)	Hazard Statement Code(s)
082-012-00-6	barium calcium cesium lead samarium strontium bromide chloride fluoride iodide europium doped	431-780-4	199876-46-5	Acute Tox. 4 * STOT RE 2 * Aquatic Chronic 2	H302 H373 ** H411
082-013-00-1	lead powder; [particle diameter < 1 mm]	231-100-4	7439-92-1	Repr. 1A Lact.	H360FD: C ≥ 0,03 % H362
082-014-00-7	lead massive: [particle diameter ≥ 1 mm]	231-100-4	7439-92-1	Repr. 1A Lact.	H360FD H362
609-019-00-4	lead 2,4,6-trinitro-m-phenylene dioxide; lead 2,4,6-trinitroresorcinoxide; lead styphnate	239-290-0	15245-44-0	Repr. 1A Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1 Unst. Expl	H360Df H332 H302 H373 ** H400 H410 H200
609-019-01-1	lead 2,4,6-trinitro-m-phenylene dioxide; lead 2,4,6-trinitroresorcinoxide; lead styphnate (≥ 20 % phlegmatiser)	239-290-0	15245-44-0	Expl. 1.1 Repr. 1A Acute Tox. 4 * Acute Tox. 4 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H201 H360Df H332 H302 H373 ** H400 H410

Appendix 3 REACH Registrations

Table 44: REACH Registrations – inorganic substances

EC/list number	Name	Intermediate registration	full registration
231-100-4	lead	10 000-100 000 (<5 reg)	>100 000 (131 reg)
215-267-0	lead monoxide	10 000-100 000 (5 reg)	>100 000 (60 reg)
235-380-9	tetralead trioxide sulphate	10 000-100 000 (<5 reg)	>100 000 (44 reg)
235-067-7	pentalead tetraoxide sulphate	10 000-100 000 (<5 reg)	10 000-100 000 (33 reg)
215-235-6	orange lead		10 000-100 000 (11 reg)
233-245-9	lead dinitrate	(<5 reg)	1000-10 000 (9 reg)
235-252-2	trilead dioxide phosphonate		1000-10 000 (8 reg)
215-693-7	lead sulfochromate yellow		1000-10 000 (8 reg)
235-759-9	lead chromate molybdate sulfate red		1000-10 000 (8 reg)
231-845-5	lead dichloride	10-1000 (<5 reg)	1000-10 000 (<5 reg)
931-722-2	Reaction product of lead chloride or lead sulphate with alkaline solution	1000-10 000 (<5 reg)	
235-727-4	Lead titanium zirconium oxide		10-1000 (5 reg)
234-363-3	Silicic acid, lead salt		10-1000 (<5 reg)
209-943-4	lead carbonate	10-1000 (<5 reg)	
243-310-3	lead hydroxide	10-1000 (<5 reg)	
237-486-0	lead bis(tetrafluoroborate)		10-1000 (<5 reg)
244-073-9	lead cyanamidate		10-1000 (<5 reg)
222-979-5	trilead diarsenate	10-1000 (<5 reg)	
215-247-1	lead telluride	10-1000 (<5 reg)	
232-382-1	pyrochlore, antimony lead yellow		10-1000 (<5 reg)
235-038-9	lead titanium trioxide		10-1000 (<5 reg)

215-246-6	lead sulphide	10-1000 (<5 reg)	
235-109-4	lead selenide	10-1000 (<5 reg)	
236-542-1	lead diazide		10-1000 (5 reg)
931-607-7	Lead Bullion, Platinum Group Metals rich		10-1000 (<5 reg)
215-290-6	trilead bis(carbonate) dihydroxide		<10 (<5 reg)
215-174-5	lead dioxide	 (<5 reg)	<10 (<5 reg)
231-198-9	lead sulphate	<10 (<5 reg)	
263-467-1	Sulfurous acid, lead salt, dibasic		<10 (<5 reg)
234-853-7	lead oxide sulfate		<10 (<5 reg)

Table 45: REACH Registrations – inorganic substances only used during production and recycling of lead and its compounds

EC/list number	Name	Intermediate registration	full registration
266-970-4	Slags, copper refining	>100 000 (11 reg)	>100 000 (<5 reg)
266-967-8	Matte, copper	>100 000 (9 reg)	>100 000 (<5 reg)
273-760-6	Flue dust, zinc-refining	>100 000 (29 reg)	
293-314-4	Leach residues, zinc ore, lead-contg.	10 000-100 000 (5 reg)	>100 000 (8 reg)
273-825-9	Slags, lead smelting	>100 000 (12 reg)	>100 000 (<5 reg)
308-011-5	Lead, bullion	>100 000 (14 reg)	>100 000 (11 reg)
273-800-2	Slags, lead reverbatory smelting	10 000-100 000 (<5 reg)	>100 000 (<5 reg)
305-445-7	Wastes, lead battery reprocessing	>100 000 (17 reg)	>100 000 (<5 reg)
305-411-1	Calcines, lead-zinc ore conc.	>100 000 (<5 reg)	
282-356-9	Matte, lead	10 000-100 000 (12 reg)	10 000-100 000 (5 reg)
273-809-1	Flue dust, lead-refining	10 000-100 000 (18 reg)	10 000-100 000 (5 reg)
273-796-2	Lead, dross	10 000-100 000 (18 reg)	1000-10 000 (7 reg)
273-925-2	Lead, dross, copper-rich	10 000-100 000 (8 reg)	10 000-100 000 (<5 reg)

266-972-5	Slimes and Sludges, copper electrolytic	10 000-100 000 (10 reg)	10 000-100 000 (7 reg)
273-802-3	Zinc, desilverizing skims	10 000-100 000 (7 reg)	1000-10 000 (<5 reg)
273-824-3	Residues, zinc smelting	10 000-100 000 (16 reg)	
273-701-4	Lead alloy, base, Pb,Sn, dross	1000-10 000 (8 reg)	10 000-100 000 (<5 reg)
273-791-5	Lead, dross, antimony-rich	10 000-100 000 (9 reg)	1000-10 000 (<5 reg)
308-516-0	Slimes and Sludges, precious metal refining	1000-10 000 (7 reg)	10 000-100 000 (7 reg)
282-366-3	Speiss, lead	1000-10 000 (<5 reg)	1000-10 000 (<5 reg)
273-792-0	Lead, dross, bismuth-rich	1000-10 000 (5 reg)	1000-10 000 (<5 reg)
310-061-8	Slimes and Sludges, battery scrap, antimony- and lead-rich	1000-10 000 (6 reg)	
273-795-7	Lead, antimonial, dross	1000-10 000 (8 reg)	1000-10 000 (<5 reg)
936-276-2	Concentrates of lead and zinc compounds with sulfur resulting from hydrometallurgy (hot acid leaching, super-hot acid leaching and flotation)		1000-10 000 (<5 reg)
273-742-8	Slimes and Sludges, zinc sulfate electrolytic	1000-10 000 (7 reg)	
273-769-5	Leach residues, zinc ore-calcine, zinc cobalt	1000-10 000 (6 reg)	
305-449-9	Waste solids, lead silver anode	1000-10 000 (6 reg)	
308-496-3	Flue dust, precious metal refining	10-1000 (<5 reg)	10-1000 (<5 reg)
308-506-6	Matte, precious metal	<10 (<5 reg)	1000-10 000 (<5 reg)
273-828-5	Slags, tellurium	1000-10 000 (<5 reg)	
310-051-3	Residues, precious metal refining cementation	10-1000 (6 reg)	10-1000 (6 reg)
309-643-4	Residues, copper speiss acid leaching	10-1000 (<5 reg)	
273-814-9	Leach residues, tellurium	10-1000 (<5 reg)	

Table 46: REACH Registrations – organic substances

EC/list number	Name	Intermediate registration	full registration
292-966-7	Fatty acids, C16-18, lead salts		1000-10 000 (9 reg)

201-075-4	tetraethyllead		1000-10 000 (<5 reg)
235-702-8	dioxobis(stearato)trilead		1000-10 000 (6 reg)
257-175-3	Acetic acid, lead salt, basic	10-1000 (<5 reg)	10-1000 (<5 reg)
239-290-0	lead 2,4,6-trinitro-m-phenylene dioxide		10-1000 (9 reg)
206-104-4	lead di(acetate)	10-1000 (<5 reg)	<10 (<5 reg)
208-908-0	lead tetraacetate		10-1000 (<5 reg)
614-455-3	Copper Lead Resorcylate Salicylate Complex		<10 (<5 reg)
273-688-5	[phthalato(2-)]dioxotrilead		<10 (<5 reg)

Appendix 4 Overview of recent epidemiological studies concerning exposure to lead and effects on kidney

Abbreviations

ALAD: delta-aminolevulinic acid dehydratase

CI: confidencr interval

CKD: chronic kidney disease

Cr: serum creatinine

CrCl: creatinine clearance

eGFR: estimated glomerural filtration rate

GFR: glomerural filtration rate

HR: Hazard ratio

NAG: N-acetyl-β-D-glucosaminidase

OR: Odds ratio

PbB: Blood lead level

Ref: reference group

RBP: retinol binding protein

RR: Risk ratio

SMR: Standardized mortality ratio

Table 47 Summary of the most relevant recent occupational cohort studies assessing the association between exposure to lead compounds and mortality from kidney disease. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
(Steenland et al., 2017)	Cohort of 88 000 workers (US, Finland, UK) who had undergone PbB testing as part of their medidal surveillanve due to their exposure	PbB level. Highest value in case several measurements	Mortality, chronic kidney disease. Both internal comparison to lowest PbB category and external comparison to national rates	µg/L < 200 200 – 299 300 – 399 ≥ 400 < 200 200 – 399 ≥ 400	 17 8 7 30 17 17 31	HR 1.00 ref 0.70 (0.30 – 1.65) 0.68 (0.27 – 1.70) 1.54 (0.77 - 3.08) SMR 0.84 (0.44 – 1.24) 0.58 (0.30 – 0.85) 1.19 (0.77 – 1.55)	p for trend = 0.25 Not adjusted for smoking or other known risk factors
(Bertke et al., 2016)	Cohort of 1990 US lead smelter workers. Only SMR results based on regional rates (Idaho) presented here as the authors state Idaho had lower cancer rates than the US overall	Cumulative exposure was estimated combining data based on personal and stationary air sampling data by department from 1973 to 1980 (the smelter ceased manfacture in 1982)	Mortality, chronic and unspecified nephritis and renal failure. Both internal comparison to lowest exposure category and external comparison to regional rates	All Cumulative exposure mg/m^3 days < 209 209 – 757 ≥ 757	17 19 22 23	SMR 1.83 (1.06 – 2.93) RR 1.00 ref 1.28 (0.69 – 2.37) 1.43 (0.78 – 2.83)	Not adjusted for smoking or for other known risk factors p for trend = 0.27
(McElvenny et al., 2015)	Cohort of 9 122 UK workers who had undergone PbB testing as part of their medical surveillanve due to their exposure	PbB level. Risks calculated both by mean and maximum PbB	Mortality, non-malignant kidney disease. Both internal comparison and external comparison to national rates	All Log mean PbB Log maximum PbB	16	SMR 1.29 (0.79 – 2.11) HR 1.24 (0.48 – 3.21) 1.05 (0.46 – 2.41)	Not adjusted for smoking or other known risk factors p = 0.66 p = 0.91

(Chowdhury et al., 2014)	Cohort of 58 368 US workers who had undergone PbB testing as part of their medidal surveillanve due to their exposure	PbB level. Highest value in case several measuremnets	Mortality, chronic renal disease. Both internal comparison to lowest PbB category and external comparison to national rates	All µg/L 0 – 49 50 – 249 250 – 399 ≥ 400 0 – 49 50 – 249 250 – 399 ≥ 400	31 2 3 10 16 2 3 10 16	SMR 0.65 (0.44 – 0.93) 0.78 (0.09 – 2.82) 0.31 (0.08 - 0.89) 0.52 (0.25 – 0.96) 1.01 (0.58 – 1.64) RR 1.00 ref 0.39 (0.09 – 1.77) 0.73 (0.20 – 2.64) 1.52 (0.43 – 5.38)	Not adjusted for known risk factors p for trend = 0.04

Table 48 Summary of the most relevant recent cross-sectional studies in occupational populations assessing the association between exposure to lead compounds and kidney function. Studies are listed in descending order by size of the study population.

Reference	Description	Exposure assessment	Outcome	Exposure N of cases Risk estimate (95% CI)	Comments
(Weaver et al., 2011)	Cross-sectional study in 712 Korean current and former lead smelter and lead battery plant workers. Mean age 47 (range 24 - 71) years. Mean PbB 214 (range 19 – 744) µg/L	Current PbB (µg/L), current Tibia-Pb (µg/g), current urinary Cd (µg/g creatinine)	Creatinine-based GFR measures as well as NAG	Mean values of glomerular filtration measures were within normal limits. When adjusted for PbB and tibia Pb as well as other risk factors of CKD higher urinary Cd showed an association with increasing estimated GFR, creatinine clearance and NAG, but lower serum creatinine. PbB and tibia lead were used only as covariates, while no risk estimates for them were presented.	
(Shelley et al., 2012)	Cross-sectional study in 684 Korean current and former lead smelter and lead battery plant workers. Mean age 47 (range 24 - 71) years. Mean PbB 215 (range 19 – 744) µg/L	Current PbB (µg/L), current Tibia-Pb (µg/g), current urinary Sb, Th and Cd (µg/g creatinine)	Both creatinine-based and cystatin-C-based GFR measures as well as NAG	Mean values of glomerular filtration measures were within normal limits. When adjusted for PbB and tibia Pb as well as other risk factors of CKD higher urinary Cd and higher urinary Th showed an association with increasing estimated GFR. PbB and tibia lead were used only as covariates, while no risk estimates for them were presented.	
(Chia et al., 2006)	Cross-sectional study in 459 Vietnamese and Singaporean lead battery and lead lead stabiliser factory workers. Mean age 39 years, mean PbB 190 µg/L	Current PbB (µg/L). ALAD genotype (ALAD2 heterozygous and homozygous combined, vs ALAD1 homozygous	Urinary albumin, urinary ß2 microglobulin, urinary α1 microglobulin, NAG	A significant, positive association between concurrent PbB and urine NAG was observed in linear regression models after adjustment for age, sex, race, exposure duration, ALAD polymorphism and the interaction between ALAD genotype and PbB. Those with ALAD2 genotype (heterozygous and homozygous combined) appeared to be more susceptible for renal lead effects especially at higher exposures (above 400 µg/L).	
(Sun et al., 2008)	Cross-sectional study in 155	Current PbB (µg/L).	Urinary albumin, NAG	There was a statistically significant association between PbB and each early biological effect marker. Urinary N-acetyl-β-D-glucosaminidase	

	storage battery factory workers (mean PbB 200 µg/L and age 44 years) and 36 male office workers of the same plant (mean PbB 90 µg/L and age 45 years) in Shanghai.		and hydroxyproline	(NAG) was found to be the most sensitive outcome with a PbB $BMDL_{05}$ of 101 µg/L.			
(Lin and Tai-Yi, 2007)	Cross-sectional study in 135 storage battery workers (mean PbB 422 µg/L and age 29 years) and 143 mechanics without occupational lead exposure (mean PbB 119 µg/L and age 27 years) in northern China	Current PbB (µg/L).	Urinary NAG (units/gCr), urinary ß2 microglobulin (µg/gCr), urinary total protein (mg/gCr)	Control Exposed Control Exposed Control Exposed	143 135 143 135 143 135	Urinary total protein 51.1 59.2 P < 0.05 Urinary ß2 microglobulin 65.5 117.1 P < 0.01 Urinary NAG 7.5 14.0 P < 0.01	No adjustment for other risk factors. Urinary NAG was found to be the most sensitive outcome with a PbB $BMDL_{10}$ of 253 µg/L while urinary total protein showed a$BMDL_{10}$ of 402 µg/L .
(Karimooy et al., 2010)	Cross-sectional study among 108 Iranian lead workers. Mean age was 37 years and mean duration of exposure 9.8 years.	Current PbB (µg/L). Graded into four categories with following mean values 170 µg/L 290 µg/L 575 µg/L 710 µg/L.	GFR	There was no significant correlation between PbB and GFR. However, it was reported that only 30 had a correctly collected 24-hour urine volume.			
(Khan et al., 2008)	Cross-sectional study among 87 lead smelter workers (median PbB 290 µg/L and mean age 40	Current PbB (µg/L).	serum urea (µmol/L), serum creatinine (µmol/L), serum uric acid	Lead exposed had a statistically significantly lower GFR (86.05 vs 94.81 ml/min, 0 = 0.009) and higher urea (5.09 vs 4.25 µmol/L, p < 0.001) than the controls. Creatinine was also slightly but not significantly higher (81.83 vs. 79.72 µmol/L, p = 0.3) and so was uric acid (357 vs 332 µmol/L, p = 0.058).			No adjustment for other risk factors.

	years) and 61 age and gender matched office workers of the same plant (median PbB 83 µg/L and mean age 38 years) in Pakistan		(µmol/L) and estimated GFR (ml/min)		
(Garcon et al., 2007)	Cross-sectional study in 57 non-ferrous smelter workers (mean PbB 390 µg/L and age 44 years) and 57 occupationally unexposed controls matched by age, gender, smoking, drug use and socioeconomic status (mean PbB 56 µg/L and age 44 years) in France.	Current PbB (µg/L), blood Cd, urine lead and urine Cd	Various renal early biological effect markers: retinol binding protein, α- and π-gluthatione S-transferase, NAG total, A and B)	NAG or RBP was not associated with blood or urine levels of lead or Cd. However, PbB was significantly associated with urine levels of alpha-glutathione S-transferase ($p < 0.05$)	No adjustment for other risk factors
(Onuegbu et al., 2011)	Cross-sectional study in 53 miscellaneous lead workers and 42 control subjects in a cross-sectional study in Nigeria. The mean age was 31 and 30 years and mean PbB 700 and 190 µg/L in lead workers and controls, respectively.	Current PbB (µg/L).	Plasma urea and creatinine	Creatine was slightly but significantly higher ($p < 0.05$) in lead exposed (97.4 µmol/L) than in controls (84.9 µmol/L). Urea was slightly but signifcantly ($p < 0.01$) higher ($p < 0.05$) in lead exposed (5.7 µmol/L) than in controls (4.7 µmol/L)	No adjustment for other risk factors.

(Orisakwe et al., 2007)	Cross-sectional study in 25 paint factory workers (mean PbB 390 µg/L) and 25 technical school students and staff members (mean PbB 170 µg/L) in Nigeria	Current PbB (µg/L).	Serum creatinine and urea	There was no difference in creatinine between the exposed (80.5 µmol/L) and unexposed (80.4 µmol/L) or urea (3.15 and 3.44 µmol/L, respectively).			No adjustment for other risk factors.

Table 49 Summary of the most relevant recent cross-sectional studies in the general population assessing the association between exposure to lead compounds and kidney function. Studies are listed in descending order by size of the study population.

Reference	Description	Outcome	Exposure	Effect on kidney function or risk estimate (95% CI)	p value	Commentds
(Navas-Acien et al., 2009)	Cross sectional study in 14 778 adults aged > 20 years of the NHANES 1999-2006 study analysing the association between PbB and Cd with CKD. The geometric means were 15.6 µg/L for PbB and 4.1 µg/L for blood Cd	Three measures of CKD were used; albuminuria (> 30 mg/g creatinine), reduced estimated GFR (< 60 mL/min per 1·73 m²) or both.	Current PbB (µg/L), quartiles (median) < 11 (8) > 11 – 16 (13) > 16 – 24 (19) > 24 (32) < 11 (8) > 11 – 16 (13) > 16 – 24 (19) > 24 (32) < 11 (8) > 11 – 16 (13) > 16 – 24 (19) > 24 (32)	OR (95% CI) Albuminuria 1.00 ref 0.83 (0.66 – 1.04) 0.92 (0.76 – 1.12) 1.19 (0.96 – 1.47) Reduced eGFR 1.00 ref 1.10 (0.80 – 1.51) 1.36 (0.99 – 1.85) 1.56 (1.17 – 2.08) Both 1.00 ref 1.53 (0.85 – 2.77) 1.57 (0.83 – 2.98) 2.39 (1.31 – 4.37)	 p<0.001 p<0.001 p not reported	The fully adjusted model included various socioeconomic and CKD risk factors as well as the blood concentration of the two metals. In models based on the product of the 2 log-transformed metals, there was also a significant interaction term between PbB and Cd for albuminuria (p = 0.003), but not for estimated GFR (p = 0.17) or both (p=0.22).
(Spector et al., 2011)	Cross-sectional study in 3941 US NHANES 1999-2002 participants > 20 years of age Geometric mean PbB of 17 µg/L	GFR was estimated with Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), cystatin C single variable, cystatin C multivariable and combined creatinine/cystatin C equations.	Current PbB (µg/L), tertiles < 13 13 – 22 > 22 Doubling of PbB < 13 13 – 22 > 22 Doubling of PbB	Cystatin C based estimated GFR compared to tertile 1 < 60 years of age 0.00 ref - 1.2 (-4.3 – 2.0) - 2.2 (-4.9 – 0.4) - 1.3 (-2.8 – 0.3) ≥ 60 years of age 0.00 ref -4.5 (-6.7 - -2.3) -7.8 (-10.3 - -5.2) -4.5 (-5.6 - -3.3)	P trend Doubling of PbB p = 0.09 p<0.001	For each method there was a statistically significant trend of decreasing GFR by increasing PbB among those aged 60 years or more, while for younger study subjects none of the GFR-methods showed a significant trend by PbB tertile. Only cystatin C based results shown.

						Adjusted for survey year, age, sex, race, BMI, education, smoking, cotinine, alcohol, hypertension, diabetes and blood Cd
(Lai et al., 2008)	Cross-sectional study in 2565 Taiwanese adults of > 40 years of age from a rural county who were offered a free health examination. Mean PbB ranged between 53 and 56 µg/L according to ethnic group and gender.	Increased serum creatinine (> 12 mg/L) was considered to indicate renal dysfunction and serum uric acid exceeding 70 mg/L in men and 60 mg/L in women were considered to indicate hyperuricemia.	Current PbB (µg/L) < 75 µg/L ≥ 75 µg/L < 75 µg/L ≥ 75 µg/L	OR (95% CI) Increased creatinine 1.00 ref 1.92 (1.18 – 3.10) Hyperuricemia 1.00 ref 2.72 (1.64 – 4.52)		Adjusted e.g. for age, gender, socio-economic variables, smoking, alcohol, hypertension and high lipid level There was also an increasing trend for both outcomes for PbB groups of < 50, 50-75 and > 75 µg/L. However those analyses were not adjusted for factors other than PbB.
(Lu et al., 2015)	Cross-sectional study in 1447 Chinese adults (general populaion of a lead polluted area). The mean PbB was 152 µg/L and 54% had a PbB of > 100 µg/L.	Bllod urea nitrogen (BUN) and creatinine clearance (CrCl)	In simple descriptive analysis BUN (4.42 vs 4.52 mmol/L, p<0.583) did not differ between PbB > 100 µg/L as compared to those with PbB of ≤ 100 µg/L. CrCl was hiher among the exposed (80 vs 73 ml/min) with borderline signifcance (p= 0.06). In multivariate analysis, a higher PbB level (continuous variable) was not associated with BUN (p=0.43) or CrCl (p=0.45) overall. There was also no statistically significant association between PbB and BUN or PbB and CrCl in any of the age categories studied (20-44, 45-59 and ≥ 60)			The analyses were adjusted for up to 8 variables including e.g. gender, age, body mass index
(Hernandez-Serrato et al., 2006)	Cross-sectional study among 413 Mexican adults over 15 years of age (mean 37 years). The mean PbB was 435 µg/L originating from both occupational and environmental sources.	Increased serum creatinine (> 1.5 mg/dL), hyperuricemia (serum uric acid > 7 mg/dL) and uremia (blood urea > 50 mg/dL) were defined as outcomes of interest.	Current PbB (µg/L) < 400 µg/L ≥ 400 µg/L < 400 µg/L ≥ 400 µg/L	OR (95% CI) Increased creatinine 1.00 ref 1.47 (0.41 – 5.17) Hyperuricemia 1.00 ref 1.75 (1.16 – 2.62)		Adjusted only for age and sex

			< 400 µg/L ≥ 400 µg/L	Hyperuremia 1.00 ref 2.04 (0.71 – 5.84)		

Appendix 5 Overview of recent epidemiological studies concerning exposure to lead and effects on blood pressure and Cardiovascular mortality and morbidity

Abbreviations

CI: confidencr interval

DPB = diastolic blood pressure

HR: Hazard ratio

OR: Odds ratio

PB = Blood pressure

PbB: Blood lead level

Ref: reference group

RR: Risk ratio

SPB systolic blood pressure

SMR: Standardized mortality ratio

Table 50 Summary of the most relevant recent epidemiological studies assessing the association between exposure to lead compounds and blood pressure and/or hypertension. Studies are listed in descending order by size of the study population.

Reference	Description	Outcome	Exposure	Increase in PB or risk of HT (95% CI)	p value	Commentds
(Han et al., 2018)	Cross-sectional study of 21688 Chinese exposed workers The geometric mean of PbB was 88 µg/L	BP was measured twice in sitting position with a 1-2 minute interval using a mercury sphygmomanometer. The mean of the two readings was used. HT was defined as SBP of > 140 mmHg and/or DBP of > 90 mmHg or self-reported use of antihypertensive medication.	Current PbB (µg/L), quartiles < 46 47 - 109 110 – 175 > 175 < 46 47 - 109 110 – 175 > 175 < 46 47 - 109 110 – 175 > 175	 SBP increase vs quartile 1 Ref 1.98 mm Hg (1.37 – 2.59) 1.81 mm Hg (1.51 – 2.10) 1.34 mm Hg (1.15 – 1.53) DBP increase vs quartile 1 Ref 0.65 mm Hg (0.22 - 1.09) 1.26 mm Hg (1.05 – 1.48) 0.70 mm Hg (0.56 – 0.84) OR of HT Ref 1.06 (0.97 – 1.15) 1.14 (1.08 – 1.20) 1.11 (1.08 – 1.15)	 p<0.001 p<0.001 p<0.001 p=0.004 p<0.001 p<0.001 p=0.181 p<0.001 p<0.001	The analyses were adjusted for up to 8 variables, including e.g. gender, age, factory type. However, no adjustment for confounding by known life-style risk factors of increased PB and HT.
(Faramawi et al., 2015)	Visit-to-visit BP variability in 13575 US adult participants (general population survey) of the NHANES III with a mean PbB of 34.4 µg/L	BP was manually measured at two visits with a one month interval. Three measurements were performed in both occasions and the mean of measurements for each visit was used to calculate visit-to-visit variability.	After controlling for age, gender, race, smoking and socioeconomic status, increasing PbB (continuous variable) was associated with increased SBP variability (p < 0.01) but not with increased DBP variability (p =0.08).			
(Hara et al., 2015)	Cross-sectional study among 12725 participants (general population) of the US NHANES IV (1999-2012) assessing more in detail also the interaction of gender and ethnicity (black, white, Hispanic) in	BP was determined as a mean of 1 to 3 readings. HT was defined as any of the following SBP of > 140 mmHg, DBP of > 90 mmHg or self-	 Women Men All Women	 SBP increase by doubling PbB 0.58 mm Hg (0.01 - 1.17) 0.79 mm Hg (0.30 - 1.27) 0.76 mm Hg (0.38 – 1.13) DBP increase by doubling PbB 0.43 mm Hg (0.07 - 0.80)	 p=0.05 p=0.0015 p<0.0001 p=0.021	The analyses were adjusted for 11 variables including e.g. age, body mass index, heart rate, serum total calcium, cotinine, dietary intake ratio of

	the association between PbB and PB. The geometric mean (and inter quartile range) of PbB varied from 12 (8 – 18) µg/L in Hispanic and white women to 19 (12 – 28) µg/L in Hispanic and black men.	reported use of antihypertensive medication.	Men All Women Men All	0.47 mm Hg (0.13 – 0.80) 0.43 mm Hg (CI 0.18 – 0.68) OR of HT by doubling PbB 0.95 (0.87 – 1.04) 0.95 (0.90 – 1.01) 0.95 (0.90 – 1.01)	p=0.0072 p=0.0007 p=0.26 p=0.17 p=0.11	sodium:potassium and education. For SBP all interaction terms of ethnicity and sex with PbB were significant. For DBP the interaction terms of ethnicity and sex with PbB were mostly nonsignificant. The risk of HT was not significantly increased by doubling of PbB in any of the ethnic groups in females or males.
(Zota et al., 2013)	Cross-sectional study among 9918 US NHANES (1988-2008) participants (general population) aged 40-65 years assessing more in detail the effect of stress-related allostatic load (AL) in the association between PbB and PB exceeding HT limits.	BP was determined as a mean of 3 readings. ORs were calculated for SBP > 140 mm Hg and DBP > 90 mm Hg by PbB quintile. Geometric mean PbB (µg/L) by quintiles Q1 7.6 Q2 12.5 Q3 16.7 Q4 22.5 Q5 38.8	Current PbB (µg/L), quartiles SBP All Q2 Q3 Q4 Q5 Low AL Q2 Q3 Q4 Q5 High AL Q2 Q3 Q4 Q5	OR (Q1 = ref) 0.87 (0.66 – 1.15) 1,00 (0.76 – 1.31) 1.03 (0.78 – 1.37) 1.23 (0.92 – 1.65) 0.81 (0.55 – 1.19) 0.86 (0.61 – 1.21) 0.88 (0.56 – 1.39) 1.14 (0.79 – 1.66) 0.96 (0.66 – 1.38) 1.20 (0.82 – 1.75) 1.23 (0.86 – 1.76) 1.40 (0.99 – 1.97)	 p for trend 0.06 p for trend 0.24 p for trend 0.03	Adjusted for age, sex, race, education, marital status, smoking, alcohol, use of antihypertensive medication

			DBP All Q2 Q3 Q4 Q5 Low AL Q2 Q3 Q4 Q5 High AL Q2 Q3 Q4 Q5	 1.22 (0.82 – 1.81) 1.56 (1.11 – 2.19) 1.80 (1.24 – 2.60) 1.77 (1.25 – 2.50) 0.85 (0.45 – 1.60) 1.51 (0.83 – 2.75) 1.73 (0.96 – 3.12) 1.46 (0.80 – 2.68) 1.66 (0.93 – 2.95) 1.67 (0.97 – 2.85) 1.92 (1.07 – 3.47) 2.28 (1.33 – 3.91)	 p for trend 0.0002 p for trend 0.03 p for trend 0.0002	
(Bushnik et al., 2014)	Cross-sectional study in 4550 participants (40 to 79 year old) of the Canadian Health Measures Survey (general population). The mean PbB level was 16.4 µg/L	BP was measured with an automatic electronic monitor with 6 readings for each individual. The average systolic and diastolic blood pressure was calculated from the last five readings. HT was defined as any of the following SBP of > 140 mmHg, DBP off > 90 mmHg, self-reported use of antihypertensive medication or self-reported health care provider diagnosis of hypertension.	Both SBP and DBP increased slightly with increasing PbB. When comparing 95th percentile (mean 64 µg/L) to the 5th percentile (5.4 µg/L) the mean SBP (mm Hg) increased from 111.9 (95% CI 108.8 to 114.9) to 122.8 (95% CI 119.1 – 126.4) and the mean DBP (mm Hg) from 72.1 (95% CI 69.9 – 74.3) to 75.4 (95% CI 73.2 – 77.5). For HT the association was less clear with relatively wide confidence intervals. The prevalence of hypertension was 32.8% (95% CI 22.9 – 44.6) in the 5th percentile PbB group, 35.5% (95% CI 27.0 – 45.0) in the 35th to 50th percentile and 44.8% (95% CI 35.3 – 54.7) in the 95th percentile group. All the above values are from analyses unadjusted for factors other than PbB. Based on multivariate analyses adjusted for the confounding factors and modelling for different age categories and PbB levels the SBP showed a significant association with PbB for 40-54 year olds but not for 55-79 year olds indicating a modifying effect for age. Among the 40-54 years old there was also a peculiar trend indicating that an increase of 10 µg/L in the range of PbB levels from 5.4 to 30 µg/L would result in a 2 mm Hg increase in SBP while a 10 µg/L increase in PbB in the range of 30 to 60 µg/L would result in a decrease of slightly less than 1 mm Hg. Similar results were achieved for diastolic blood pressure.			The analyses were adjusted for 12 variables including e.g. gender, age, body mass index, smoking, regular physical activity, indicators of diabetes or chronic kidney disease.

			For hypertension there was no clear association with PbB in the multivariate analyses.	
(Gambelunghe et al., 2016)	Cross-sectional study in 4452 Swedish adults in 1991-1994 and a follow-up of 2904 of them 16 years later (general population). Arithmetic mean of PbB at baseline was 28 µg/L (range 1.5 – 260)	BP was measured by a nurse using a standard mercury sphygmomanometer after supine rest of 10 minutes both as baseline and at follow-up. HT was defined as any of the following SPB of > 140 mmHg, DPB of > 90 mmHg or current use of antihypertensive medication prescribed by a physician.	At baseline comparisons were made between PbB quartile 4 (mean 47 µg/L) and quartiles 1 to 3 combined (means 15, 22 and 28 µg/L). In the multivariate analysis the following overall results were reported SBP (difference of Q4 from Q1-3) • Women 1.5 mm Hg, p=0.12 • Men 2.1 mm Hg, p=0.02 DBP (difference of Q4 from Q1-3) • Women 1.1 mm Hg, p=0.02 • Men 1.7 mm Hg, p=0.001 HT (OR Q4 vs Q1-3) • Women 1.4 (95% CI 1.1 – 1.7) • Men 1.2 (95% CI 0.96 – 1.5) • All 1.3 (95% CI 1.1 – 1.5) The associations remained significant when PbB was treated as a continuous variable with SBP (1.2 mm Hg) and DBP (1.0 mm Hg) being higher for a 20 µg/L increase in PbB. At baseline, while there was an association between hypertension and PbB (see above) there was no association between PbB (Q4 vs Q1-3) with hypertensive medication (OR 1.1; 95% CI 0.9 – 1.3). The above analyses comparing Q4 with the rest were repeated excluding individuals with PbB higher than 100 µg/L and the effect estimates for blood pressure and hypertension were essentially the same. When excluding individuals with PbB > 50 µg/L the effect estimates decreased but remained still significant for DBP and HT. The individuals in the highest PbB quartile at baseline did not have higher risk of antihypertensive medication at follow-up (OR 1.0; 95% CI 0.8 – 1.2) or risk of high blood pressure (OR 1.0; 95% CI 0.7 – 1.3). The individuals that did not participate in the follow-up had at baseline slightly higher effect estimates for blood pressure effects and a slightly higher baseline OR for hypertension by PbB than those that participated in the follow-up.	The analyses were adjusted for 7 variables including e.g. gender, age, smoking, alcohol, waist circumference.
(Lu et al., 2015)	Cross-sectional study in 1447 Chinese adults (general populaion of a lead polluted area).	BP was measured after 30 minutes of rest with two measurements in 3 minutes intervals in sitting position using a desk-model	In simple descriptive analysis SPB (127 vs 122 mmHg, p<0.001), DPB (95 vs 90 mmHg, p<0.001) and prevalence of HT (18.1% vs 12.3%, p=0.002) were higher among those with PbB > 100 µg/L as compared to those with PbB of $\leq$ 100 µg/L.	The analyses were adjusted for up to 8 variables including e.g. gender, age, body mass index.

	The mean PbB was 152 µg/L and 54% had a PbB of > 100 µg/L.	sphygmomanometer. The mean of the measurements was used. HT was defined as any of the following SPB of > 140 mmHg, DPB of > 90 mmHg or a previous diagnosis of HT.	In multivariate analysis, a higher PbB level (continuous variable) was associated with higher SBP (p = 0.001) and DBP (p = 0.004) among those with 20-44 years of age but not among those aged 45-59 (p = 0.45 and 0.13 for SBP and DBP, respectively) or those aged > 60 (p = 0.34 and 0.06 for SBP and DBP, respectively). PbB level was not associated with hypertension (p = 0.22).	
(Almeida Lopes et al., 2017)	Cross-sectional study in randomly selected 948 Brazilian adults of 40 years or older	BP was measured with a digital equipment at both arms 3 times with one-minute interval in seated position. The mean of the last two measurements was used. HT was defined as any of the following SBP of > 140 mmHg, DBP of > 90 mmHg or self-reported use of antihypertensive medication.	The overall geometric mean PbB was 19.7 µg/dL with quartile 1 of < 13.2 µg/L (mean 0.96) and quartile 4 of > 27.6 µg/L (mean 42.1). There was no clear association between PbB and SBP while participants of quartile 4 PbB were originally reported to have a DBP 0.06 mm Hg higher (95% CI 0.04 – 0.09) than those in quartile 1. When comparing 90th percentile (geometric mean PbB 60.3 µg/L) to 10th percentile (GM 7.4 µg/L) DBP was originally reported to be 0.07 mm Hg higher (95% CI 0.03 – 0.11). In a later commentary and correspondence it was explained that e.g. the above-mentioned 0.07 mm Hg difference actually corresponds to the coefficient between log transformed DBP and for easier understanding it should be exponentiated and would correspond to that group having DBP 1.07-fold to the comparison group (see (Yang and Staessen, 2018) and the related authors reply). However, no revised result tables were published. The adjusted OR for HT was 2.54 (95% CI 1.17 – 5.53) when comparing Q4 to Q1 and 2.77 (95% CI 1.41 – 5.46) when comparing 90th to the 10th percentile. However, in a later commentary, it was pointed out that for Q2 and Q3 compared to Q1 there was a clearly decreased risk (OR = 0.22 and OR 0.58) revealing a curvilinear association and no analyses were reported using PbB as a continuous variable or testing whether a linear model is appropriate (see Yang et al 2018).	The analyses were adjusted for 11 variables including e.g. gender, race, age, body mass index and smoking.
(Yang et al., 2018)	Comparison of PbB level association to ambulatory vs office-measured PB in a cross-sectional study of 236 newly hired workers. The geometric mean in the study population was 45	Office BP was measured by a nurse according to current guidelines with application of a stringent quality control program.	In multivariate analyses the effect sizes (SBP/DBP) for a doubling of PbB were 0.79/0.87 mm Hg (p = 0.11 / 0.04) for office measured blood pressure. For ambulatory monitored blood pressure the corresponding values indicated no effect from doubling of PbB: 0.29/-0.25 mm Hg for 24-hour ambulatory, 0.60/-0.10 mm Hg for awake ambulatory and -0.40/-0.43 mm Hg asleep ambulatory monitored blood pressure (p values for ambulatory ranging between 0.33 and 0.81).	The analyses were adjusted for age, body mass index, heart rate, waist-to-hip ratio, current smoking, g-glutamyltransferase,

	µg/L (interquartile range 26.0 – 91.5).	The ambulatory BP was recorded using validated oscillometric 24-hour monitors, which were programmed to obtain readings at 15-minute intervals during waking hours and every 30 minutes during sleep. Intra-individual means of the BP readings over 24 hours and during the awake and asleep periods were weighted by the time interval between successive readings Office HT as an office BP of at least 140 mm Hg SBP or 90 mm Hg DBP. The corresponding thresholds for ambulatory hypertension were 130 mm Hg SBP and 80 mm Hg DBP for the 24-hour BP and 135 mm Hg and 85 mm Hg and 120 mm Hg and 70 mm Hg for the awake and asleep BP, respectively.	A clinically meaningful white coat effect was defined as office blood pressure higher than ambulatory awake blood pressure by 20 mm Hg systolic or 10 mm Hg diastolic. Such and effect was observed in 45 (19.1%) and in all but one it was due to exceeding the diastolic threshold. Accounting for the presence of white coat effect reduced the association size of office DBP from 0.87 to 0.39 mm Hg. The doubling of PbB was not associated with hypertension assessed from office blood pressure measurements but was associated (borderline statistical significance) with hypertension assessed from ambulatory awake measurements (OR = 1.26; 95% CI 0.98 – 1.64, p=0.07).	total-to-HDL cholesterol ratio, and estimated glomerular filtration rate (eGFR)
(Barry et al., 2019)	211 adult men in a lead surveillance programme residing near New York City were enrolled. Current bone and blood lead, BP and estimated glomerular filtration rate (eGFR) were measured. Maximum past blood lead	SBP	Median (Inter quartile range) of bone, maximum past PbB and current PbB were 13.8 (9.4-19.5) µg/g, 290 (140-380) µg/L and 25 (15-44) µg/L, respectively. Maximum past and current blood lead were significantly associated with current bone lead in adjusted analyses (both p<0.0001), with associations driven by high blood lead. Bone lead was associated with increased continuous SPB (coefficient=0.36; 95% CI 0.05 to 0.67;	The association between bone and current blood lead was possibly driven by bone lead resorption into blood. Bone lead, but not past or current blood lead,

	was obtained from surveillance data. Regression models were used to determine associations of health with different lead measures.		p=0.02); categorical analyses indicated this was driven by the top two bone lead quartiles.	was associated with elevated systolic BP
(Taheri et al., 2014)	Cross-sectional study among 182 male Iranian battery workers. The mean PbB was 79.2 µg/L.	BP was measured twice in a seated position and the average of the readings was used.	Comparison was made between those with PbB > 100 µg/L and < 100 µg/L. In the multivariate model there was no statistically significant difference between the groups as regards SBP (p = 0.24) or DBP (p = 0.64). In univariate analysis both SBP (109 vs 114 mmHg, p=0.04) and DBP (67 vs 71 mmHg, p =0.02) were lower in the high exposure group than in the low exposure group.	The analyses were adjusted for 7 variables including e.g. age, waist circumference, smoking, physical activity.
(Camaj et al., 2018)	Cross-sectional study among 101 adults aged 25 in Kosovo (general population). The range of current PbB was 6.9 – 160 µg/L. One part of the cohort was from an area with high past environmental lead pollution and with mean PbB levels around 400 µg/L between 2 and 4 years of age.	BP was measured using an automated monitor three times at 1 minute intervals. The average of the two last measurements was used.	In the fully adjusted analysis SBP was 0.98 mm Hg higher (95% CI 0.09 – 1.86) and DBP 0.35 mm Hg higher (95% CI -0.11 to +0.81) per log unit increase of PbB. The study population was part of a cohort that had been followed since birth and PbB level measurements were available for various time points. The correlations between current BP and PbB levels related to 0-2, 2-4, 4-7 and 7-12.5 years of age were weaker than those between current BP and current PbB.	The analyses were adjusted for gender, smoking, body mass index, ethnicity and education

Table 51 Summary of the most relevant recent occupational cohort studies assessing the association between exposure to lead compounds and mortality or incidence of cardiovascular disease. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
(Steenland et al., 2017)	Cohort of 88 000 workers (US, Finland, UK) who had undergone PbB testing as part of their medidal surveillanve due to their exposure. Both internal comparison to lowest PbB category and external comparison to national rates	PbB level. Highest value in case several measuremnets	Mortality, ischeamic heart disease	µg/L < 200 200 – 299 300 – 399 ≥ 400 < 200 200 – 399 ≥ 400	 1109 657 413 1048 1109 1075 1059	HR 1.00 ref 1.14 (1.04 – 1.26) 1.16 (1.03 – 1.31) 1.41 (1.28 - 1.57) SMR 0.81 (0.76 – 0.86) 0.85 (0.80 – 0.90) 1.02 (0.96 – 1.07)	p for trend < 0.0001 Adjusted for sex, birth year decade and country but not for smoking or other risk factors of ischaemic heart disease
Steenland continued			Mortality, stroke	µg/L < 200 200 – 299 300 – 399 ≥ 400 < 200 200 – 399 ≥ 400	 299 181 130 261 300 314 263	HR 1.00 ref 1.24 (1.03 – 1.50) 1.49 (1.20 – 1.85) 1.41 (1.16 – 1.72) SMR 0.82 (0.73 – 0.91) 0.99 (0.88 – 1.10) 0.99 (0.87 – 1.09)	p for trend 0.0002 Adjusted for sex, birth year decade and country but not for smoking or other risk factors of stroke
(Bertke et al., 2016)	Cohort of 1990 male US lead smelter workers. Only SMR results based on regional rates (Idaho) presented here as the authors state Idaho had lower	Cumulative exposure was estimated combining data based on personal and stationary air sampling data by department from 1973 to 1980 (the	Overall cardiovascular mortality	All Cumulative exposure mg/m^3 –days < 209 209 – 757 ≥ 757	703 241 264 276	SMR 1.22 (1.13 – 1.31) RR 1.00 ref 1.06 (0.89 – 1.26) 1.19 (1.00 – 1.42)	Adjusted for age but not for smoking or other known risk factors p for trend 0.04

	cancer rates than the US overall	smelter ceased munfacture in 1982)					
Bertke continued			Mortality from heart disase	All Cumulative exposure mg/m^3 –days < 209 209 – 757 ≥ 757	515 178 198 203	SMR 1.16 (1.06 – 1.26) RR 1.00 ref 1.08 (0.88 – 1.32) 1.20 (0.98 – 1.46)	Adjusted for age but not for smoking or other known risk factors p for trend 0.08
Bertke continued			Mortality from cerebrovascular disaese	All Cumulative exposure mg/m^3 –days < 209 209 – 757 ≥ 757	119 37 45 50	SMR 1.32 (1.10 – 1.58) RR 1.00 ref 1.13 (0.73 – 1.75) 1.38 (0.90 – 2.12)	Adjusted for age but not for smoking or other known risk factors p for trend 0.13
(McElvenny et al., 2015)	Cohort of 9 122 UK workers who had undergone PbB testing as part of their medical surveillanve due to their exposure	PbB level. Risks calculated both by mean and maximum PbB. Both internal comparison and external comparison to national rates	Mortality, Ischaemic heart disease	All Log mean PbB Lg maximum PbB	874	SMR 1.06 (0.99 – 1.13) HR 1.30 (1.17 – 1.43) 1.23 (1.11 – 1.34)	Adjusted for age and sex but not for smoking or other known risk factors p < 0.001 p < 0.001
McElvenny continued			Mortality, cerebrovascular disease	All Log mean PbB Lg maximum PbB	184	SMR 1.16 (1.00 – 1.34) HR 1.15 (0.83 – 1.28) 1.23 (0.98 – 1.48)	 p = 0.314 p = 0.103
(Kim et al., 2015)	Cohort of 81 067 South Korean workers who had undergone PbB testing as part of	PbB level. The median value in case several measuremnets	Mortality, all circulatory diseasee	µg/L Men < 100 100 - 200	 29 8	RR 1.00 ref 0.98 (0.45 – 2.16)	Adjusted for age and exposure to other carcinogenic metal ever/never (Cr, As, Ni and

	their health surveillanve due to their exposure			>200 Women < 100 100 - 200 >200	10 11 2 0	1.99 (0.95 – 4.15) 1.00 ref 1.26 (0.28 – 5.68) -	Cd), but not for smoking
Kim continued			Mortality, ischeamic heart disaese	µg/L Men < 100 100 - 200 >200 Women	 12 4 4 	RR 1.00 ref 0.98 (0.45 – 2.16) 1.74 (0.55 – 5.54) Not reported	Adjusted for age and exposure to other carcinogenic metal ever/never (Cr, As, Ni and Cd), but not for smoking
Kim continued			Mortality, cerebrovascular disase	µg/L Men < 100 100 - 200 >200 Women < 100 100 - 200 >200	 9 3 3 6 0 0	RR 1.00 ref 1.17 (0.31 – 4.36) 1.90 (0.50 – 7.28) 1.00 ref - -	Adjusted for age and exposure to other carcinogenic metal ever/never (Cr, As, Ni and Cd), but not for smoking
(Chowdhury et al., 2014)	Cohort of 58 368 US workers who had undergone PbB testing as part of their medidal surveillanve due to their exposure	PbB level. Highest value in case several measuremnets	Mortality, ischaemic heart disease	All µg/L 0 – 49 50 – 249 250 – 399 ≥ 400 0 – 49 50 – 249 250 – 399	569 21 95 230 223 21 95 230	SMR 0.61 (0.56 – 0.67) 0.44 (0.27 – 0.67) 0.49 (0.39 - 0.70) 0.62 (0.54 – 0.70) 0.72 (0.63 – 0.82) RR 1.00 ref 1.13 (0.78 – 1.66) 1.46 (1.02 – 2.10)	Adjusted for age, gender, race and calendar time at risk but not for smoking or other known risk factors p for trend < 0.0001

				≥ 400	223	1.77 (1.23 – 2.56)	
Chowdhury continued			Mortality, stroke	All µg/L 0 – 49 50 – 249 250 – 399 ≥ 400 0 – 49 50 – 249 250 – 399 ≥ 400	123 4 18 54 47 4 18 54 47	SMR 0.73 (0.60 – 0.87) 0.48 (0.13 – 1.23) 0.54 (0.32 - 0.86) 0.79 (0.59 – 1.03) 0.79 (0.58 – 1.05) RR 1.00 ref 1.12 (0.32 – 3.94) 1.76 (0.54 – 5.76) 1.88 (0.57 – 6.28)	 p for trend < 0.095
(Gwini et al., 2012)	Cohort of 4114 male Australian workers that underwent medical surveillanve and PbB tests. Geometric mean of PbB 196 µg/L.	High lead exposure occupations (all). Mandatory PbB tests for all but archived results for 2612 only and cardiovascular mortality not reported by PbB.	Mortality Ischaemic heart disease Stroke	All exposed	 75 24	SMR 0.95 (0.76 – 1.19) 1.25 (0.84 – 1.86)	Adjusted for age, but not for smoking or other known risk factors
(Min and Ahn, 2017)	Cohort of 54 788 Korean men who underwent lead-associated medical check-ups at least once in 2000-2004. Follow-up through hospital admissions in 2000-2005.	Median PbB of each individual. Mean number of PbB measurments per person was 2.7.	Hospital admission Hypertensive disaeses Ischemic heart diseases	PbB (µg/L) < 100 100 – 200 > 200 < 100 100 – 200 > 200 < 100 100 – 200 > 200	 150 55 33 89 20 30 70 33 21	HR 1.00 ref 1.20 (0.88 – 1.64) 1.12 (0.76 – 1.64) p for trend 0.36 1.00 ref 0.75 (0.46 – 1.21) 1.78 (1.17 – 2.72) p for trend 0.05 1.00 ref 1.52 (1.00 – 2.31) 1.53 (0.93 – 2.51)	Adjusted for age and dichotomous variable (Yes/No) for exposure to one or more heave metals. No adjustment for confounding by smoking or other risk factors.

			Cerebrovascular diseases			p for trend 0.04	

Table 52 Summary of the most relevant general population studies assessing the association between exposure to lead compounds and mortality or incidence of cardiovascular disease after the review of Navas-Acien et al. 2007. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
(Schober et al., 2006)	Cohort study of 9 757 participants (general population) aged 40 years or more of the NHANES II study. The median length of follow-up was 8.6 years. Mean age at baseline 58 years.	PbB at baseline	Motality All cardiovascular	PbB at baseline (µg/L) < 50 50 – 99 ≥ 100	 684 394 111	RR 1.00 ref 1.20 (0.93 – 1.55) 1.55 (1.16 – 2.07) p for trend < 0.01	Adjusted for sex, race/ethnicity, education, and smoking status
(Menke et al., 2006)	Cohort of 13 946 participants (general population) aged 20 years or more of the NHANES III study. Only participants with baseline PbB below 100 µg/L were included and the follow-up was up to 12 years. Mean age at baseline was 44.5 years	PbB at baseline	Mortality All cardiovascular Myocardial infarction Stroke	PbB at baseline (µg/L) < 19 19 – 36 ≥ 36 < 19 19 – 36 ≥ 36 < 19 19 – 36 ≥ 36	 104 219 443 50 83 234 22 56 63	HR 1.00 ref 1.03 (0.69–1.55) 1.55 (1.08–2.24) p trend = 0.003 1.00 ref 1.02 (0.55–1.89) 1.89 (1.04–3.43) p trend = 0.007 1.00 ref 2.19 (0.87–5.53) 2.51 (1.20–5.26) p trend = 0.017	Adjusted for age, race, sex, diabetes, body mass index, smoking, alcohol, physical activity, income, CRP, cholesterol, education, urban residence, postmenopausal status, hypertension, and level of kidney function

			Both Menke et al. (2006) and Schober et al. (2006) presented mortality curves that plot the hazard ratios against PbB level. Nonlinear associations were modeled for cardiovascular mortality by Schober et al (2006) and for myocardial infarction and stroke mortality by Menke et al (2006). The authors did not explain the shape of the PbB-mortality curves in detail. In the tails of the PbB distribution, hazard ratios decreased with increasing PbB level. However, HRs remained above 1 over most of the PbB distribution.				
(Weisskopf et al., 2009)	Cohort of 868 male participants (general population) in the Normative Aging Study (NAS) for mortality. The average follow-up time was 8.9 years. Mean age at baseline 67 years. The geometric mean of blood lead was 48 (inter quartile range 30–70) µg/L.	PbB and patella-Pb at baseline	Mortality All carciovascular Ischaemic heart disease Other cardiovascular All carciovascular Ischaemic hart disease Other cardiovascular	PbB (µg/L) < 40 40 – 60 >60 < 40 40 – 60 >60 < 40 40 – 60 >60 Patella-Pb (µg/g) <22 22–35 >35 <22 22–35 >35 <22 22–35 >35	 38 84 63 17 36 29 21 48 34 33 41 63 14 18 30 10 23 33	HR 1.00 ref 0.63 (0.29–1.38) 0.69 (0.33–1.47) p trend 0.44 1.00 ref 1.02 (0.32–3.21) 1.04 (0.33–3.22) p trend = 0.95 1.00 ref 0.30 (0.09–1.03) 0.39 (0.12–1.23) p trend = 0.23 1.00 ref 1.39 (0.61–3.19) 2.45 (1.07–5.60) p trend = 0.03 1.00 ref 2.99 (0.40–22.6) 8.37 (1.29–54.4) p trend = 0.01 1.00 ref 1.01 (0.38–2.70) 1.16 (0.40–3.39) p trend = 0.79	Adjusted for age, smoking, and education.
(Khalil et al., 2009b)	Cohort of 533 females aged 65-87 years in the	PbB at baseline	Mortality	PbB (µg/L) < 80	 41	HR 1.00 ref	

	Study of Osteoporotic Fractures (SOF) for mortality. The average duration of follow-up was 12 years.		All carciovascular Coronary heart disease Stroke	≥ 80 < 80 ≥ 80 < 80 ≥ 80	13 15 8 17 4	1.78 (0.92, 3.45) 1.0 ref 3.08 (1.23, 7.70) 1.00 ref 1.13 (0.34, 3.81)	
(Jain et al., 2007)	Cohort of 837 men in the Normative Aging Study (NAS) followed during 10 years. Mean age 66 years.	PbB and patella-Pb at baseline	Ischemic heart disease. Both fatal (from death certificates) and non-fatal (cardiologist confirmed myocardial infarction or angina pectoris) cases were identified. There were 83 cases (70 nonfatal and 13 fatal)	Risk estimates were for one standard deviation increase in PbB Patella-Pb		HR 1.27 (1.01–1.59) 1.29 (1.02–1.62).	The HRs are unadjusted, but the authors state HRs and their statistical significance for blood and bone lead were similar when confounders such as smoking, body mass index, alcohol, blood pressure, family history of hypertension, and total serum cholesterol were included in the models
(Eum et al., 2011)	Cohort of 600 men who were free of ECG abnormalities at the baseline assessment in the NAS study. The mean age at baseline was 66.7 years and mean interval between ECG rcordings 8.1 years.	PbB, tibia- and patella-Pb at baseline	Newly appearing ECG abnormalities,: pronlonged QT, pronlonged JT interval, intraventricular conduction defect (IVCD), atrioventricular conduction defect (AVCD) or arrhythmia	ORs were calculated by tertiles: Tibia-Pb (µg/g) < 16 16-23 >23 Patella-Pb (µg/g) <22 22-33 >33 PbB (µg/L) < 40 40-60 > 60	Tibia-Pb showed a significant trend of increasing OR for QT, JT and AVCD abnormalities, Patella-Pb for AVCD, while PbB showed no significant trend with any of the ECG abnormalities.		Adjusted for age and age squared, education, smoking, body mass index, albumin-adjusted serum calcium, and diabetes status at baseline, as well as years between ECG tests and QT-prolongation drugs (yes/no) at the time of ECG measurement.

Table 53. Summary of the most relevant recent general population cohort studies assessing the association between exposure to lead compounds and mortality from cardiovascular disease. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
(Lanphear et al., 2018)	Cohort of 14289 adult (> 20 years) participants of US NHANES III (1988-1994) followed until end of 2011	PbB at baseline by tertiles (µg/L) T1 < 20 T2 20 -37 T3 ≥ 38	Mortality, cardiovascular diseases Mortality, Ischaemic heart disease	Log transformed PbB as continuous variable, HRs for increase from 10th to 90th percentile (10 to 67 µg/L)	1801 988	HR 1.70 (1.30 – 2.22) 2.08 (1.52 – 2.85)	Adjusted for age, sex, income, race, BMI, smoking, hypertension, urinary Cd, alcohol, physical activity, healthy eating, cholesterol, glycated haemoglobin
(Aoki et al., 2016)	Cohort of 18602 US NHANES participants (1999-2010) aged 40 or more at baseline and followed until end of 2011	PbB at baseline (µg/L) Mean 17.3 < 50 (94%) 50 – 99 (5%) ≥ 100 (1%)	Mortality, Cardiovascular diseases	Log-transformed PbB as continuous variable, RRs for 10-fold increase in PbB (roughly from 2.5th to 97.5th percentile) PbB Haematocrit corrected – PbB Haemoglobin-corrected PbB	 985 985 985	RR 1.27 (0.91 – 1.78) 1.44 (1.05 – 1.98) 1.46 (1.06 – 2.01)	Adjusted for age, sex, race, blood Cd, serum Fe, Serum CRP, serum-Ca, smoking, alcohol and education

Appendix 6 Overview of recent epidemiological studies concerning exposure to lead and cancers of brain, kidney, stomach and lung

Abbreviations

PbB: Blood lead level

CI: confidencr interval

HR: Hazard ratio

OR: Odds ratio

Ref: reference group

RR: Risk ratio

SMR: Standardized mortality ratio

Table 54 Summary of the most relevant recent cohort studies and case-control studies assessing the association between exposure to lead compounds and brain cancer. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
(Steenland et al., 2017)	Cohort of 88 000 workers (US, Finland, UK) who had undergone PbB testing as part of their medidal surveillanve due to their exposure	PbB level. Highest value in case several measurements. Both internal comparison to lowest PbB category and external comparison to national rates	Mortality	µg/L < 200 200 – 299 300 – 399 ≥ 400 < 200 200 – 399 ≥ 400	 38 26 14 33 39 40 33	HR 1.00 ref 1.31 (0.79 – 2.17) 1.05 (0.55 – 1.99) 1.42 (0.83 – 2.43) SMR 0.78 (0.54 – 1.03) 0.84 (0.58 – 1.10) 0.93 (0.61 – 1.20)	p for trend = 0.09 Adjusted for sex, birth year decade and country
(Parent et al., 2017)	1800 incident cases and 5160 controls from Australia, Canda, France, Germany Israel, New Zealand and UK	Exposure to lead, cadmium, nickel, chromium, iron, welding fumes based on work histories and JEM. Ever/never exposure, life-time cumulative exposure and duration of exposure were used.		Glioma Never Ever Cumulative (µmol/L – yr) < 128.8 128.8 – 413.2 ≥ 414.2 Duration (yr) 1 – 4 5 – 9 ≥ 10 Glioblastoma Ever	 1419 159 45 47 67 58 32 69 85	OR 1.0 ref 0.8 (0.7 – 10) 0.8 (0.6 – 1.2) 0.7 (0.5 – 1.0) 1.0 (0.7 – 1.3) 1.0 (0.7 – 1.4) 0.7 (0.4 – 1.1) 0.8 (0.6 – 1.1) 0.9 (0.7 – 1.2)	5- year lagAdjusted for age, education, occupatioanal prestige scale, atopy and respondent status. Cumulative = probability*PbB level*duration
(Liao et al., 2016)	Cohorts of 73 363 women and 61 379 men from Shnaghai Health Survey	Job history and job exposure matrix (lead dust, lead fume and both). Those exposed were assigned to low exposure group when both lead	Incidence	Brain cancer (total Pb) Both sexes Never Ever Low High Women	 67 10 7 3	RR 1.0 ref 1.8 (0.7 – 4.8) 3.1 (1.0 – 9.1) 1.1 (0.3 – 3.2)	Adjusted for socio-economic factors and smoking.

		dust and fume estimates were below median and to high exposure when at least one of them was above median		Never Ever Low High Men Never Ever Low High Meningioma (Total Pb) Women Never Ever Low High Men Never Ever Low High	34 8 6 2 33 2 1 1 38 9 3 6 12 0 0 0	1.0 ref 2.6 (1.2 – 5.6) 4.2 (1.8 – 10) 1.2 (0.3 – 5.0) 1.0 ref 0.9 (0.2 – 3.8) 1.2 (0.2 – 8.5) 0.7 (0.1 – 5.4) 1.0 ref 2.4 (1.1 – 5.0) 1.7 (0.5 – 5.4) 3.1 (1.3 – 7.4) 1.0 ref - - -	
McElvenny et al (2015)	Cohort of 9 122 UK workers who had undergone PbB testing as part of their medical surveillanve due to their exposure	PbB level. Risks calculated both by mean and maximum PbB. Both internal comparison and external comparison to national rates	Mortality,	All Log mean PbB Lg maximum PbB	23	SMR 0.92 (0.61 – 1.38) HR 0.77 (0.37 – 1.62) 0.75 (0.38 – 1.46)	Adjusted for age, sex and exposure to As and Cd
(Chowdhury et al., 2014)	Cohort of 58 368 US workers who had undergone PbB testing as part of their health surveillanve due to their exposure	PbB level. Highest value in case several measuremnets	Mortality	All µg/L 0 – 49 50 – 249 250 – 399 ≥ 400	30 0 8 11 11	SMR 0.65 (0.44 – 0.93) 0.0 (0.0 – 1.26) 0.71 (0.31 – 1.40) 0.59 (0.30 – 1.06) 0.83 (0.41 – 1.49)	Adjusted for age, gender, race and calendar time at risk

(Gwini et al., 2012)	Cohort of 4114 male Australian workers that underwent medical surveillanve and PbB tests	High lead exspoure occupations (all). Mandatory PbB tests for all but archived results for 2612 only	Mortality and Incidence	All µg/L ≤ 300 > 300	6 2 0	SMR 1.05 (0.47 – 2.33) SIR 1.00 (0.25 – 4.02) - (expected N 1.0)	Not adjusted for factors other than age
(Ilychova and Zaridze, 2012)	Cohort of 1423 men and 3102 women employed at least 2 years in 27 printing industry facilities in Moscow.	Brain cancer reslts only for all exposed	Mortality	All men All women	3 3	SMR 1.24 (0.39 – 3.84) 0.71 (0.23 – 2.19)	Not adjusted for factors other than age
(Bhatti et al., 2011)	Case-control study of 355 glioma and 151 meningeoma patients and 505 controls in the US. Also effect modification of ALAD (aminolevulinate dehydratase) genotype on Pb exposure effect was studied	Based on questionnaire information on work history exposure to lead was assessed both with a job exposure matrix (JEM) by an expert of industrial hygiene	Glioma incidence	JEM Unexposed ≤ 80th percentile 80th – 95th percentile > 95th percentile Expert estimate Unexposed ≤ 80th percentile 80th – 95th percentile > 95th percentile	 253 15 53 22 196 77 48 21	OR 1.0 ref 0.6 (0.3 – 1.2) 0.8 (0.5 - 1.2) 0.9 (0.5 – 1.7) 1.0 ref 0.8 (0.5 – 1.1) 0.6 (0.4 – 0.9) 1.0 (0.5 - 2.0)	 p for trend 0.4 p for trend 0.1
Bhatti continued			Menigeoma incidence	JEM Unexposed ≤ 80th percentile 80th – 95th percentile > 95th percentile Expert estimate Unexposed ≤ 80th percentile 80th – 95th percentile > 95th percentile	 123 5 16 4 108 17 15 8	OR 1.0 ref 0.6 (0.2 – 1.8) 1.1 (0.5 - 2.1) 0.9 (0.3 – 2.8) 1.0 ref 0.7 (0.4 – 1.3) 1.0 (0.5 – 2.1) 2.7 (1.0 – 7.8)	 p for trend 0.9 p for trend 0.4 Adjusted for age, sex, race, hospital and residential proximity to the hospital

Bhatti continued			Menigeoma incidence, ALAD homozygotes ALAD2 carriers	Expert estimate Unexposed ≤ 80th percentile 80th – 95th percentile > 95th percentile Expert estimate Unexposed ≤ 80th percentile 80th – 95th percentile > 95th percentile	 86 15 9 3 52 17 13 3	OR 1.0 ref 0.7 (0.4 – 1.4) 0.7 (0.3 - 1.8) 1.2 (0.3 – 4.8) 1.0 ref 0.5 (0.1 – 2.5) 2.4 (0.7 – 8.8) 13 (2.4 – 73)	p for effect modification of Pb exposure by ALAD genotype = 0.04

Table 55 Summary of the most relevant recent cohort studies and case-control studies assessing the association between exposure to lead compounds and kidney cancer. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
(Michalek et al., 2019)	Nested case-control study of 59778 cases and 298890 controls from Finland, Iceland and Sweden. Cases identified from cancer registries for 1961-2005.	Job exposure matrix (JEM) applied to job title history of each case and control. JEM covered 29 substance. Cumulative exposure calculated as probability * level* time.	Incidence	PbB (µmol/l * years) All Unexposed < 370 370 – 1152 > 1152 Men Unexposed < 370 370 – 1152 > 1152 Women Unexposed < 370 370 – 1152 > 1152	 52154 3874 3040 710 27897 3427 2860 672 24257 447 180 38	OR 1.00 ref 1.09 (1.03 – 1.16) 1.06 (0.99 – 1.13) 0.95 (0.86 – 1.05) 1.00 ref 1.07 (1.00 – 1.15) 1.05 (0.98 – 1.13) 0.94 (0.85 – 1.04) 1.00 ref 1.17 (0.99 – 1.39) 0.99 (0.79 – 1.25) 0.83 (0.54 – 1.29)	 p for trend 0.58 p for trend 0.78 p for trend 0.87 Adjusted for various occupational exposures and age.
(Callahan et al., 2019)	1217 incident cases and 1235 controls from Detroit and Chicago	Job history was used to estimate duration, probability and intensity of exposure and was then converted to estimate average, maximum and cumulative exposure in terms of PbB	Incidence	PbB (µg/L) Average PbB Unexposed ≤ 12 13-29 30 – 66 ≥ 67 Maximum PbB Unexposed < 16 16-38 39 – 93 ≥ 94	 432 111 146 167 112 432 113 131 147 162	OR 1.0 ref 0.8 (0.6 – 1.2) 1.1 (0.8 – 1.5) 1.3 (0.9 – 1.7) 0.8 (0.6 – 1.1) 1.0 ref 0.8 (0.6 – 1.1) 1.1 (0.8 – 1.5) 1.2 (0.9 – 1.6) 1.0 (0.7 – 1.3)	 p for trend 0.32 p for trend 0.76 Similar null results also for duration and cumulative exposure. No effect modification by ALAD polymorphism. Adjusted for age, race,

							study centre, gender, education, smoking, BMI, history of hypertension
(Steenland et al., 2017)	Cohort of 88 000 workers (US, Finland, UK) who had undergone PbB testing as part of their medical surveillance due to their exposure	PbB level. Highest value in case several measurements. Both internal comparison to lowest PbB category and external comparison to national rates	Mortality	µg/L < 200 200 – 299 300 – 399 ≥ 400 < 200 200 – 399 ≥ 400	 53 24 9 42 47 31 28	HR 1.00 ref 0.89 (0.54 – 1.45) 0.50 (0.24 – 1.03) 1.21 (0.74 – 1.97) SMR 0.65 (0.46 – 0.83) 0.54 (0.35 – 0.72) 0.73 (0.46 – 0.97)	p for trend = 0.79 Adjusted for sex, birth year decade and country
(Bertke et al., 2016)	Cohort of 1990 amle US lead smelter workers. Only SMR results based on regional rates (Idaho) presented here as the authors state Idaho had lower cancer rates than the US overall	Cumulative exposure was estimated combining data based on personal and stationary air sampling data by department from 1973 to 1980 (the smelter ceased manufacture in 1982)		All Cumulative exposure mg/m^3 –days < 209 209 – 757 ≥ 757	11 5 6 3	SMR 1.56 (0.78 – 2.79) RR 1.00 ref 1.57 (0.48 – 5.20) 0.90 (0.21 – 3.82)	 p for trend 0.87 Not adjusted for factors other than age
(Liao et al., 2016)	Cohorts of 73 363 women and 61 379 men from Shnaghai Health Survey	Job history and job exposure matrix (lead dust, lead fume and both)	Incidence	Total Pb Both sexes Never Ever Low High Women Never Ever Low	 157 17 5 12 76 8 4	RR 1.0 ref 1.4 (0.9 – 2.3) 1.0 (0.4 – 2.5) 1.8 (1.0 – 3.3) 1.0 ref 1.3 (0.6 – 2.6) 1.3 (0.5 – 3.5)	Adjusted for socio-economic factors and smoking.

				High Men Never Ever Low High	4 81 9 1 8	1.2 (0.5 – 3.4) 1.0 ref 1.6 (0.8 – 3.1) 0.5 (0.1 – 3.2) 2.3 (1.1 – 4.7)	
McElvenny et al., 2015)	Cohort of 9 122 UK workers who had undergone PbB testing as part of their medical surveillanve due to their exposure	PbB level. Risks calculated both by mean and maximum PbB. Both internal comparison and external comparison to national rates	Mortality,	All Log mean PbB Lg maximum PbB	30	SMR 1.30 (0.91 – 1.86) HR 1.53 (0.70 – 3.36) 1.31 (0.67 – 2.56)	Adjusted for age and gender
(Chowdhury et al., 2014)	Cohort of 58 368 US workers who had undergone PbB testing as part of their health surveillance due to their exposure	PbB level. Highest value in case several measurements	Mortality	All µg/L 0 – 49 50 – 249 250 – 399 ≥ 400 0 – 49 50 – 249 250 – 399 ≥ 400	28 1 9 9 9 1 9 9 9	SMR 0.69 (0.46 – 1.00) 0.42 (0.01 – 2.35) 0.96 (0.44 – 1.83) 0.55 (0.25 – 1.05) 0.72 (0.33 – 1.37) RR 1.00 ref 2.41 (0.62 – 9.46) 1.31 (0.33 – 5.20) 1.70 (0.42 – 6.83)	 p for trend 0.62 Adjusted for age, gender, race and calendar time at risk
(Gwini et al., 2012)	Cohort of 4114 male Australian workers that underwent medical surveillance and PbB tests	High lead exposure occupations (all). Mandatory PbB tests for all but archived results for 2612 only	Mortality and Incidence	All µg/L ≤ 300 > 300	6 2 0	SMR 0.65 (0.29 – 1.46) SIR 0.67 (0.17 – 2.67) - (expected N 1.5)	Not adjusted for factors other than age

(Ilychova and Zaridze, 2012)	Cohort of 1423 men and 3102 women employed at least 2 years in 27 printing industry facilities in Moscow.	Cumulative exposure (low, medium, high) was estimated from duration of employment and histrorical measurement and other data.	Mortality	All men All women Cumulative, all Low Medium High	6 7 2 2 8	SMR 1.26 (0.46 – 2.75) 1.42 (0.57 – 2.93) 0.84 (0.21 – 3.36) 0.65 (0.16 - 2.61) 2.12 (1.10 – 4.07)	Not adjusted for factors other than age
(Southard et al., 2012)	Nested case-control study among Finnish male smokers participating in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. 154 case diagnosed at least 5 years after the onset of the study and 308 controls.	PgB level at start of the cancer prevention study	Incidence	µg/L < 25 25 – 33.1 33.1 – 46.6 ≥ 46.6		OR 1.00 ref 1.1 (0.6 – 2.0) 1.8 (1.0 – 3.6) 2.0 (1.0 – 3.9)	p for trend 0.022 Adjusted for age at randomization, smoking, systolic blood pressure, body mass index, alcohol, serum calcium, Calbindin D28K promoter (-366)(rs1800645) genotype
(Boffetta et al., 2011)	Hospital-based case-control study in Czech Republic, Poland, Romania and Russia. 1097 cases and 1476 controls	Exposure intensity (µg/m^3) and frequency (% of time) to As, Cd, Cr(III), Cr(VI), Pb and Ni estimated from questionnaire-based work history. Based on this, two exposure indices were constructed, duration and cumulative exposure	Incidence	Pb Never Ever exposed Duration (yrs) <10 10-19 >20 Cumulative Quartile 1 Quartile 2 Quartile 3 Quartile 4	 1017 80 27 25 28 22 12 19 27	OR 1.00 ref 1.55 (1.10 – 2.19) 1.43 (0.81 – 2.52) 2.06 (1.07 – 3.98) 1.38 (0.79 – 2.38) 1.71 (0.88 – 3.35) 0.89 (0.41 – 1.92) 1.38 (0.71 – 2.70) 2.25 (1.21 – 4.19)	Adjusted for age, gender, centre, residence, tobacco, body mass index, hypertension and the other metals

Table 56 Summary of the most relevant recent cohort studies and case-control studies assessing the association between exposure to lead compounds and stomach cancer. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
(Steenland et al., 2017)	Cohort of 88 000 workers (US, Finland, UK) who had undergone PbB testing as part of their medical surveillance due to their exposure	PbB level. Highest value in case several measurements. Both internal comparison to lowest PbB category and external comparison to national rates	Mortality	µg/L < 200 200 – 299 300 – 399 ≥ 400 < 200 200 – 399 ≥ 400	 67 57 18 53 67 75 54	HR 1.00 ref 1.62 (1.13 – 2.32) 0.84 (0.49 – 1.44) 1.09 (0.70 - 1.67) SMR 0.92 (0.70 – 1.14) 1.16 (0.90 – 1.43) 0.97 (0.73 – 1.17)	p for trend = 0.93 Adjusted for sex, birth year decade and country
(Bertke et al., 2016)	Cohort of 1990 male US lead smelter workers. Only SMR results based on regional rates (Idaho) presented here as the authors state Idaho had lower cancer rates than the US overall	Cumulative exposure was estimated combining data based on personal and stationary air sampling data by department from 1973 to 1980 (the smelter ceased manufacture in 1982)		All Cumulative exposure mg/m^3 –days < 209 209 – 757 ≥ 757	12 11 5 3	SMR 1.31 (0.67 – 2.28) RR 1.00 ref 0.65 (0.22 – 1.91) 0.44 (0.12 – 1.61)	Not adjusted for factors other than age p for trend 0.21
(Liao et al., 2016)	Cohorts of 73 363 women and 61 379 men from Shnaghai Health Survey	Job history and job exposure matrix (lead dust, lead fume and both)	Incidence	Total Pb Both sexes Never Ever Low High Women Never	 585 49 14 35 282	RR 1.0 ref 1.0 (0.5 – 1.9) 0.7 (0.4 – 1.2) 1.2 (0.6 – 2.2) 1.0 ref	Adjusted for socio-economic factors and smoking.

				Ever Low High Men Never Ever Low High	19 7 12 583 30 7 23	0.7 (0.4 – 1.1) 0.6 (0.3 – 1.2) 0.8 (0.5 – 1.5) 1.0 ref 1.4 (0.9 – 2.0) 0.9 (0.4 – 1.9) 1.6 (1.0 – 2.4)	
(McElvenny et al., 2015)	Cohort of 9 122 UK workers who had undergone PbB testing as part of their medical surveillanve due to their exposure	PbB level. Risks calculated both by mean and maximum PbB. Both internal comparison and external comparison to national rates	Mortality,	All Log mean PbB Lg maximum PbB	58	SMR 1.11 (0.86 – 1.43) HR 1.15 (0.70 – 1.89) 1.04 (0.67 – 1.61)	Adjusted for age and sex
(Kim et al., 2015)	Cohort of 81 067 South Korean workers who had undergone PbB testing as part of their health surveillance due to their exposure	PbB level. The median value in case several measurements	Mortality	µg/L Men < 100 100 - 200 > 200 Women < 100 100 - 200 >200	 22 4 3 4 1 0	RR 1.00 ref 0.66 (0.23 – 1.92) 0.80 (0.23 – 2.71) 1.00 ref 1.82 (0.95 – 4.20) 0.00	Adjusted for age and exposure to other carcinogenic metal ever/never (Cr, As, Ni and Cd),
(Chowdhury et al., 2014)	Cohort of 58 368 US workers who had undergone PbB testing as part oc their medidal surveillance due to their exposure	PbB level. Highest value in case several measurements	Mortality	All µg/L 0 – 49 50 – 249 250 – 399 ≥ 400	23 2 2 9 10	SMR 0.71 (0.45 – 1.07) 1.19 (0.14 – 4.32) 0.30 (0.04 - 1.08) 0.69 (0.31 – 1.30) 0.92 (0.44 – 1.69) RR	

				0 – 49 50 – 249 250 – 399 ≥ 400	2 2 9 10	1.00 ref 0.24 (0.04 – 1.34) 0.52 (0.13 – 2.04) 0.64 (0.16 – 2.60)	p for trend 0.49 Adjusted for age, gender, race and calendar time at risk
(Gwini et al., 2012)	Cohort of 4114 male Australian workers that underwent medical surveillance and PbB tests	High lead exposure occupations (all). Mandatory PbB tests for all but archived results for 2612 only	Mortality and Incidence	All µg/L ≤ 300 > 300	8 2 0	SMR 1.04 (0.52 – 2.07) SIR 0.91 (0.23 – 3.62) - (expected N 1.2)	Not adjusted for factors other than age
(Ilychova and Zaridze, 2012)	Cohort of 1423 men and 3102 women employed at least 2 years in 27 printing industry facilities in Moscow.	Stomach cancer reslts only for all exposed	Mortality	All men All women	24 34	SMR 0.82 (0.55 – 1.22) 0.96 (0.69 – 1.34)	Not adjusted for factors other than age

Table 57 Summary of the most relevant recent cohort studies and case-control studies assessing the association between exposure to lead compounds and lung cancer. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Relative risk (95% CI)	Comments
(Steenland et al., 2017)	Cohort of 88 000 workers (US, Finland, UK) who had undergone PbB testing as part of their medical surveillance due to their exposure	PbB level. Highest value in case several measurements. Both internal comparison to lowest PbB category and external comparison to national rates	Mortality	µg/L < 200 200 – 299 300 – 399 ≥ 400 < 200 200 – 399 ≥ 400	 348 271 214 500 350 490 506	HR 1.00 ref 1.39 (1.19 – 1.64) 1.54 (1.29 – 1.84) 1.78 (1.51 - 2.08) SMR 0.90 (0.81 – 1.00) 1.16 (1.06 – 1.26) 1.38 (1.26 – 1.48)	p for trend < 0.0001 Adjusted for sex, birth year decade and country
(Bertke et al., 2016)	Cohort of 1990 male US lead smelter workers. Only SMR results based on regional rates (Idaho) presented here as the authors state Idaho was lower cancer rates than the US overall	Cumulative exposure was estimated combining data based on personal and stationary air sampling data by department from 1973 to 1980 (the smelter ceased munfacture in 1982)		All Cumulative exposure mg/m^3 –days < 209 209 – 757 ≥ 757	154 70 49 43	SMR 1.94 (1.64 – 2.27) RR 1.00 ref 0.85 (0.59 – 1.22) 0.84 (0.58 – 1.23)	Not adjusted for factors other than age p for trend 0.39
(Liao et al., 2016)	Cohorts of 73 363 women and 61 379 men from Shnaghai Health Survey	Job history and job exposure matrix (lead dust, lead fume and both)	Incidence	Total Pb Both sexes Never Ever Low High Women Never Ever Low High	 900 74 22 52 440 19 7 12	RR 1.0 ref 0.9 (0.5 – 1.7) 0.7 (0.4 – 1.2) 1.1 (0.6 – 1.9) 1.0 ref 0.7 (0.5 – 1.0) 0.6 (0.3 – 1.1) 0.8 (0.5 – 1.3)	Adjusted for socio-economic factors and smoking

				Men Never Ever Low High	 460 30 7 23	 1.0 ref 1.2 (0.9 – 1.7) 1.0 (0.5 – 1.7) 1.4 (0.98 – 2.0)	
(McElvenny et al., 2015)	Cohort of 9 122 UK workers who had undergone PbB testing as part of their medical surveillanve due to their exposure	PbB level. Risks calculated both by mean and maximum PbB. Both internal comparison and external comparison to national rates	Mortality,	All Log mean PbB Lg maximum PbB	393	SMR 1.42 (1.29 – 1.57) HR 1.10 (0.89 – 1.37) 1.03 (0.85 – 1.24)	 Adjusted for age, sex and exposure to As, Cd, Cr VI, acids and chrystalline silica
(Kim et al., 2015)	Cohort of 81 067 South Korean workers who had undergone PbB testing as part of their health surveillanve due to their exposure	PbB level. The median value in case several measuremnets	Mortality	µg/L Men < 100 100 - 200 >200 Women < 100 100 - 200 >200	 19 5 2 2 3 1	RR 1.00 ref 0.79 (0.29 – 2.13) 0.46 (0.10 – 2.01) 1.00 ref 10.5 (1.74 – 62.9) 12.7 (1.69 – 148)	Adjusted for age and exposure to other carcinogenic metal ever/never (Cr, As, Ni and Cd)
(Chowdhury et al., 2014)	Cohort of 58 368 US workers who had undergone PbB testing as part of their medidal surveillanve due to their exposure	PbB level. Highest value in case several measuremnets	Mortality	All µg/L 0 – 49 50 – 249 250 – 399 ≥ 400 0 – 49 50 – 249	382 10 54 144 174 10 54	SMR 0.86 (0.78 – 0.95) 0.42 (0.20 – 0.77) 0.56 (0.42 - 0.74) 0.81 (0.68 – 0.95) 1.20 (1.03 – 1.39) RR 1.00 ref 1.34 (0.79 – 2.26)	 p for trend < 0.0001

				250 – 399 ≥ 400	144 174	1.88 (1.14 – 3.10) 2.79 (1.69 – 4.61)	Adjusted for age, gender, race and calendar time at risk
Wynant et al (2013)	Combination of two population based case-control studies in Montreal. 1593 male cases and 1426 male controls.	Expert evaluation of work history. Separetely for organic and inorganic lead. Risks calculated both by level and duration of exposure, only level shown here.	Incidence	Organic lead Never Ever Inorganic lead from engine emissions Never Ever Non-substantial Substantial Inorganic lead from other sources Never Ever Non-substantial Substantial	 895 41 895 487 430 57 895 267 236 31	OR 1.00 ref 1.39 (0.77 – 2.52) 1.00 ref 0.89 (0.72 – 1.09) 0.88 (0.71 – 1.08) 1.03 (0.62 – 1.69) 1.00 ref 0.99 (0.76 – 1.29) 0.96 (0.73 – 1.27) 1.22 (0.64 – 2.34)	Adjusted for smoking, age, education level, respondent type (proxy/self), ethnicity, asbestos, silica, As, Cr VI and Cd (ever/never)
(Gwini et al., 2012)	Cohort of 4114 male Australian workers that underwent medical surveillance and PbB tests	High lead exspoure occupations (all). Mandatory PbB tests for all but archived results for 2612 only	Mortality and Incidence	All µg/L ≤ 300 > 300	42 8 2	SMR 1.25 (0.92 – 1.69) SIR 0.86 (0.43 – 1.73) 0.39 (0.10 – 1.57)	Not adjusted for afctors other than age
(Ilychova and Zaridze, 2012)	Cohort of 1423 men and 3102 women employed at least 2 years in 27 printing industry facilities in Moscow.	Stomach cancer reslts only for all exposed	Mortality	All men All women	40 7	SMR 0.94 (0.69 – 1.28) 0.48 (0.23 – 0.99)	Not adjusted for afctors other than age