

1 Prioritised substance group: Lead

Responsible author	Tamás Szigeti	E-mail	tszigeti.tamas@nnk.gov.hu
Short name of institution	NPHI	Phone	+36 30 9084346
Co-authors	/		

1.1 Background information

1.1.1 Hazardous properties

Lead, a silvery grey metal, has some unique properties, like soft softness, high malleability, low melting point, ductility and resistance to corrosion, which contributed to its widespread use. It exists in different forms (elemental, inorganic and organic) which have different chemical and toxicological properties.

Lead is found in concentrated and easily accessible lead ore deposits that are widely distributed throughout the world. Inorganic lead compounds exist in two oxidative states: +2 and +4. The former one is more common. Lead also forms stable organic compounds (e.g., as tetraethyl lead and tetramethyl lead). Water solubility of lead compounds varies widely: lead sulphides and lead oxides are purely soluble, while nitrate, chlorate and chloride salts are reasonably soluble in cold water. Organolead compounds are highly lipophilic and characterised by low water solubility.

Lead has been classified by the German Research Foundation (MAK Commission) in category 2, to be regarded as human carcinogen. IARC classified lead (in general) as possibly carcinogenic to humans (Group 2B) (IARC, 1987), inorganic lead compounds as probably carcinogenic to humans (Group 2A) (IARC, 2006); however, the evidence for organic lead compounds was considered to be inadequate in humans and animals (Group 3) (IARC, 2006).

1.1.1.1 Absorption, distribution, metabolism and excretion

Gastrointestinal absorption of ingested lead is influenced by physiological factors (e.g. age, fasting, nutritional calcium and iron status, pregnancy) and the physicochemical characteristics of particles (size, solubility, and lead species). The extent and rate of absorption are also influenced by the ingested dose (Jakubowski, 2012).

Deposition and absorption of inhaled lead-containing particles are influenced by their size and solubility. Large particles are transferred by mucociliary transport into the pharynx and then swallowed, with possible absorption from the gastrointestinal tract. Smaller particles can be deposited in the alveolar part of the lungs and almost completely absorbed after extracellular dissolution or ingestion by phagocytic cells (Bailey and Roy 1994).

Dermal absorption of inorganic lead compounds is generally considered to be much less than absorption by inhalation or oral routes of exposure. In contrast, animal studies have showed that organic lead compounds are rapidly and extensively absorbed through the skin (ATSDR, 2019).

The distribution of lead in the body is independent of the exposure route. Lead in blood is found primarily in the red blood cells (96-99%). The half-life of lead in blood is approximately 30 days in adult male humans but it varies depending on the level of exposure, sex and age (Jakubowski, 2012).

Half-life of lead in bones is approximately 10-30 years (EFSA, 2010), but it can be mobilised by certain physiological processes like pregnancy or other factors. Lead can be transferred from the mother to the fetus and also from the mother to infants via maternal milk (ATSDR, 2019).

Inorganic lead forms complexes with a variety of protein and nonprotein ligands (e.g., albumen, nonprotein sulfhydryls as extracellular ligands or ALAD as intracellular ligand), while alkyl lead compounds are actively metabolised in the liver by oxidative dealkylation catalysed by cytochrome P-450 (ATSDR, 2019).

Lead is excreted primarily in urine and feces independent of the route of exposure; sweat, saliva, hair and nails, breast milk and seminal fluids are minor routes of excretion (ATSDR, 2019).

1.1.1.2 Health effects

1.1.1.2.1 General overview of health effects

Based on the estimation of the Institute for Health Metrics and Evaluation (IHME), lead exposure accounted for 1.06 million deaths and 24.4 million years of healthy life lost (disability-adjusted life years (DALYs) worldwide in 2017 due to long-term effects on health. The highest burden was present in low- and middle-income countries. IHME also estimated that in 2016, lead exposure accounted for 63.2% of the global burden of idiopathic developmental intellectual disability, 10.3% of the global burden of hypertensive heart disease, 5.6% of the global burden of the ischaemic heart disease and 6.2% of the global burden of stroke (IHME, 2017). Lead is associated with a wide range of toxicity in children. These toxic effects extend from acute, clinically obvious, symptomatic poisoning at high levels of exposure down to subclinical (but still very damaging) effects at lower levels. Lead poisoning can affect virtually every organ system in the body. The principal organs affected are the **central and peripheral nervous system** and the cardiovascular, gastrointestinal, renal, endocrine, immune and haematological systems. (WHO, 2010).

1.1.1.2.1.2 Acute clinical toxicity

Intense, acute, high-dose exposure to lead can cause symptomatic poisoning in children. It is characterised by colic, constipation, fatigue, anaemia and neurological features that can vary from poor concentration to stupor. In the most severe cases, a potentially fatal acute encephalopathy with ataxia, coma and convulsions can occur. In many instances, children who survive acute lead poisoning go on to have permanent and clinically apparent deficits in their neurodevelopmental function (Byers & Lord, 1943, cit in WHO, 2010).

1.1.1.2.1.3 Subclinical (chronic) toxicity

The subclinical toxic effects of lead can be very damaging. The premise underlying the concept of subclinical toxicity is that there is a dose-related continuum of toxic effects in which clinically apparent effects have their asymptomatic (but still very real) counterparts (Landrigan, 1989).

Haematological toxicity

Due to blocking the enzymes involved in heme synthesis (δ -aminolevulinic acid dehydratase (δ -ALAD), ferrochelatase) and oxidative damage of erythrocyte membranes anaemia is the classic clinical manifestation of lead toxicity in erythrocytes (Schwartz et al., 1990; EHC, 1995). Therefore, ALAD is being used as a biomarker for testing Pb toxicity. The severity and prevalence of lead-induced anaemia correlate directly with the blood lead concentration. Younger and iron deficient children are at higher risk of lead-induced clinical anaemia.

The anaemia induced by lead is caused primarily by impairment of the haem biosynthesis, but an increased rate of erythrocyte destruction may also occur (Schwartz et al., 1990).

Reproductive toxicity

Lead exposure may damage fertility, may damage the unborn child (reduced foetal growth and disturbed maturation, pre-term delivery) and may cause harm to breast-fed children (Sun et al., 2019). Lead can easily cross the placental barrier, therefore can readily enter the bloodstream of

the foetus. Since lead can also pass the blood brain barrier, neurological development is of great concern when prenatal exposure to lead occurs (Baeyens et al., 2014).

Neurotoxicity

Neurodevelopmental effect of lead is the most important hazard of chronic lead exposure from public health point of view. In the central nervous system, lead causes asymptomatic impairment of neurobehavioural function in children at doses insufficient to produce clinical encephalopathy. The dose–response relationship between blood lead levels and loss of IQ was found to be stronger at blood lead levels lower than 10 µg/dl than at higher levels (Lanphear et al., 2000). An international pooled analysis of data from seven cohorts has confirmed these findings (Lanphear et al., 2005)

An increase in blood lead level from less than 1 µg/dL to 10 µg/dL was associated with a six IQ point decrement, which is considerably greater than the decrement associated with an increase in blood lead level from 10 µg/dL to 20 µg/dL. The findings of this pooled analysis – that there are adverse effects below 10 µg/dL and that the effects are steepest at the lowest levels of exposure – have been confirmed by numerous investigators (Emory et al., 1999, 2003; Bellinger & Needleman, 2003; Wasserman et al., 2003; Chiodo, Jacobson & Jacobson, 2004; Despres et al., 2005; Fraser, Muckle & Despres, 2006; Hu et al., 2006; Kordas et al., 2006; Schnaas et al., 2006; Tellez-Rojo et al., 2006; Chiodo et al., 2007; Surkan et al., 2007, all cit. in WHO, 2010). Recent studies confirmed previous data on long-term lead exposure caused reduction in intellectual functioning and hippocampal-dependent memory and learning dysfunction. School-age children with higher blood lead level have poor long-term memory ability (Zeng et al., 2019). In a recent pre-birth prospective cohort with maternal lead levels below 5 µg/dL, there have been found a trend of worse neurobehavioral scores with increasing prenatal lead concentrations, in particular for mid-childhood emotional problems and capacity to plan/organise and shift (Fruh et al., 2019). In a Polish cohort study, fetal exposure to very low lead levels (0.99 ± 0.15 µg/dL in maternal blood and 0.96 ± 0.16 µg/dL in the cord blood) was found to affect early cognitive function, with boys being more susceptible than girls (Polanska et al., 2018). The greater susceptibility of boys was also reported in a Canadian cohort, where prenatal blood lead concentrations below 5 µg/dL were still associated with a decline in cognitive function in, but only for boys (Desrochers-Couture, 2018).

When a population's exposure to lead is sufficiently widespread to cause a decrease in its mean IQ, there results a substantial increase in the number of children with diminished intelligence and mental retardation. At the same time, there is a substantial reduction in the number of children with truly superior intelligence. The consequences are: (a) a substantial increase in the number of children who do poorly in school, who may require special education and other remedial programmes, and who may not contribute fully to society when they become adults; (b) a reduction in a country's future leadership; and (c) a widening gap in socioeconomic attainment between countries with high and low levels of population exposed to lead (Needleman et al., 1979).

However, adverse effects of chronic lead exposure on cognitive function were observed not only in children. Sufficient evidence exists to conclude that there is an association between lead dose and decrements in cognitive function in adults, too. Overall, while the association between blood lead levels and cognitive function is more pronounced in occupational groups with high current lead exposures, associations between bone lead levels and cognitive function are more evident in studies of older subjects with lower current blood lead levels, particularly in longitudinal studies of cognitive decline. (Shih RA et al., 2007). A recent meta-analysis also concluded, that neurocognitive performance in adults with occupational or environmental lead exposure was significantly impaired. Based on a marginally significant ($p=.06$) effect of difference in exposure levels, a blood lead increase of 10 µg/dL translated into a decline in cognitive abilities of Hedges $g=.09$ (Vlasak et al., 2019).

Cardiovascular toxicity

An increasing body of evidence suggests an association between low-level lead exposure and clinical cardiovascular outcomes and cardiovascular mortality (Lanphear et al., 2018; Harari et al., 2019). There is a link between blood lead level and increase of blood pressure in pregnant women at low level exposure (Wells et al., 2011). Maternal prenatal toenail Pb was associated with statistically significant increases in child systemic blood pressure (Farzan et al., 2018). Bone lead was also associated with elevated systolic blood pressure in lead exposed workers (Barry et al., 2019). A previous systematic review evaluating the evidence on the associations between lead exposure and cardiovascular endpoints in human populations concluded that the evidence is sufficient to infer a causal relationship of lead exposure with hypertension (Navas-Acien et al., 2007).

Cancer risk

Epidemiological studies indicate higher risk of cancers of the stomach, lung, kidney, and brain in workers exposed to inorganic lead (Steenland, 2019, Barry et al, 2019). Several studies indicated its genotoxicity and ability to generate reactive oxygen species. (IARC, 2014). IARC classified inorganic lead compounds as probably carcinogenic to humans (Group 2A) (IARC, 2006).

1.1.1.2.1.4 Genetic and epigenetic factors influencing lead toxicity

Oxidative stress caused by lead exposure

Data from the literature show the involvement of oxidative stress in the mechanism of lead toxicity (Lopes et al., 2016). Lead causes oxidative stress of membranes and depletion of body antioxidants. Maternal blood Pb was associated with increased cord blood mtDNA content, a marker of oxidative stress (Sanchez-Guerra, 2019). Oxidative stress index was higher in workers with occupational exposure to lead (Qu et al., 2019).

Susceptibility to lead toxicity

Some polymorphic genes (are delta-aminolevulinic acid dehydratase (ALAD) gene, vitamin D receptor (VDR), glutathione S-transferase (GST), hemochromatosis gene) were identified to be able to potentially influence the bioaccumulation and toxicity of lead in humans (Mani et al., 2019).

Epigenetic alterations related to lead exposure

Prenatal low-level lead exposure was associated with DNA methylation changes in cord blood (Wu et al, 2017). Altered epigenetic regulation (DNA methylation at specific genes and also at the global genome level, histone modifications, miRNAs) can cause neurotoxic (cognitive dysfunction, memory loss, behavioral disorders, attention deficit hyperactivity disorder, autism spectrum disorder, Alzheimer's disease) and other toxic outcomes, such as metabolic disorder, cardiovascular disorders, hematopoietic disorder, and reproductive impairment (Khalid et al., 2019). In a recent work, genetic and epigenetic biomarkers of Pb exposure, susceptibility, and effect were reviewed (Mani et al, 2019). These data may help uncover the mechanism of action and in the identification of susceptible groups.

1.1.2 Exposure characteristics

1.1.2.1 Lead production and consumption

Lead is manufactured and/or imported in the European Economic Area in 1,000,000 – 10,000,000 tons per year (ECHA, 2018). About 50 nations mine lead in quantities ranging from a few hundred tons to more than half a million tons (U.S. Bureau of Mines, 1993). Roughly 20 nations produce only secondary (i.e., recycled) lead. Secondary smelting (recycling) of lead from lead-acid batteries from vehicles and industries has become increasingly important and by the end of the 20th century

accounted for almost half of world refined lead production. Other uses of lead include pigments and other compounds, rust inhibitors, rolled and extruded products, cable sheathing, alloys, radiation shielding, ceramic glazes, plastic stabilizers, jewellery making, soldering, crystal products, fishing weights, shot and ammunition, electronic waste, use in water pipes, and fuel additives (The Global Dimensions of Lead Poisoning: An Initial Analysis, 1994). Due to regulation in Europe on the use of lead in dyes and ceramics it is expected that exposure through these applications is decreasing. Global consumption of lead is increasing today, because of increasing demand for energy-efficient vehicles. The largest current use of lead is in storage batteries for cars and other vehicles. (WHO, 2010).

1.1.2.2 Lead exposure routes

Although some exposure to lead results from direct contact with lead containing products, human exposure more frequently occurs via environmental media such as air, water, and soil. Based on worldwide collection of results of airborne lead concentrations measured before 1994, it was concluded that lead levels in both air and soil were generally higher in urban areas and near industrial sources than in other areas (median values in urban areas were $1.075 \mu\text{g}/\text{m}^3$, in suburban ones $0.33 \mu\text{g}/\text{m}^3$ and in rural areas $0.1 \mu\text{g}/\text{m}^3$). In urban areas, air and soil levels were associated with use of leaded petrol. Lead concentrations in both air and soil increased with traffic density and proximity to roads, as well as with higher lead concentrations in petrol. (The Global Dimensions of Lead Poisoning: An Initial Analysis, 1994).

The ECHA (2018) is mentioning that releases of lead to the environment is likely to occur from:

- ▶ outdoor use in long-life materials with low release rate (e.g. metal, wooden and plastic construction and building materials)
- ▶ indoor use in long-life materials with low release rate (e.g. flooring, furniture, toys, construction materials, paints, curtains, foot-wear, leather products, paper and cardboard products, electronic equipments)
- ▶ indoor use in close systems with minimal release (e.g. cooling liquids in refrigerators, oil-based electric heaters)
- ▶ outdoor use in close systems with minimal release (e.g. hydraulic liquids in automotive suspension, lubricants in motor oil and break fluids)

Human exposure to lead from drinking water results primarily from lead leaching from leaded plumbing components, rather than contamination of source waters (i.e., lakes, rivers, and aquifers).

The following sources and products account for most cases of childhood exposure to lead and lead poisoning (WHO, 2010):

- ▶ lead from an active industry, such as mining (especially in soils),
- ▶ lead-based paints and pigments,
- ▶ lead solder in food cans,
- ▶ ceramic glazes,
- ▶ drinking-water systems with lead solder and lead pipes,
- ▶ lead in products, such as herbal and traditional medicines, folk remedies, cosmetics and toys,
- ▶ lead released by incineration of lead-containing waste,
- ▶ lead in electronic waste (e-waste),
- ▶ lead in the food chain, via contaminated soil,
- ▶ lead contamination as a legacy of historical contamination from former industrial sites.

Human exposure routes:

- ▶ **Inhalation:** inhalation of lead particles generated by burning materials containing lead (e.g. during smelting, recycling, stripping leaded paint, and using leaded petrol or leaded aviation fuel),
- ▶ **Oral:** ingestion of lead-contaminated dust, water (from leaded pipes), food from lead-glazed or lead-soldered containers, highly consumed food with low/medium lead content (e.g. grains) or food with known elevated lead content (e.g. mussels and lead-shot game meat),
- ▶ **Trans placental:** lead in bone is released into blood during pregnancy and becomes a source of exposure to the developing fetus. Moreover, lead is transmitted by maternal milk to infants.

1.1.2.3 Availability of HBM data

Surveys measuring blood lead levels in the general population have been conducted in several countries since the early 1980. After phasing out lead from petrol in most of the European countries interest in blood lead levels has been faded for a while. Results of blood lead level surveys conducted during the past two decades among the general population were found to be available in sixteen European countries (see Table 1), most of them covered children population, too. Decreasing trend in blood lead level of children could be observed with lowering lead content of petrol and finally phasing out leaded petrol in various countries. However, e.g. in Sweden it was found that after 2009 the decrease in the blood lead level discontinued (Wennberg et al., 2017) which means that there are still other existing lead exposure sources to be detected and eliminated.

Unfortunately, there are very few data on the present blood lead levels among the general population in the European countries. In an intensive literature search only 8 countries (Belgium, Germany, Denmark, Kosovo, Poland, Spain, Slovenia and Sweden) were found from where blood lead levels measured during the past 5 years were available.

Table 1-1: Summary of European blood lead surveys reported in the past 10 years

Country	Study	Population studied	N	Year of sampling	PbB (µg/L)	Reference
Armenia	3 towns adjacent to metal mining and smelting industries	4 – 6 years	159	2013	GM: 60.0 S.D.: ± 30.0	Grigoryan et al. (2016)
Belgium	FLEHS I	newborns	1,072	2002-2006	GM: 13.7; 95% C.I.:12.9-14.6	Schoeters et al. (2017)
		adolescents	1,650	2002-2006	GM: 22.5; 95% C.I.:21.8-23.3	
	FLEHS II	newborns	241	2007-2011	GM: 8.6; 95% C.I.:8.0-9.2	
		adolescents	207	2007-2011	GM: 14.6; 95% C.I.:13.8-15.5	
	FLEHS III	newborns	281	2012-2015	GM: 6.4; 95% C.I.:6.0-6.7	
		adolescents	204	2012-2015	GM: 9.5; 95% C.I.:9.0-10.0	
	Ath (Hainaut province)	2.5- 6 years	98	2009	GM: 16.6; 95% C.I.:14.8-18.2	Fierens et al. (2016)
		7-11 years	74	2009	GM: 14.8; 95% C.I.:13.2-16.6	
		40-60 years men	52	2009	GM: 31.7; 95% C.I.:27.9-36.1	
		40-60 years women	54	2009	GM: 21.4; 95% C.I.:18.1-25.3	
Croatia	Koprivnica	7-14 years	46	2007-2008	GM: 17.9; Range:10.0-42.0	Hrubá et al. (2012)
Czech Republic	Prague	7-14 years	8	2007-2008	GM: 15.5; Range:12.0-22.0	Hrubá et al. (2012)
	CZ-HBM	18-58 years	4,472	1994-2003 and 2005-2009	GM: 23.0	Cerna et al. (2012)
		8-10 years	3,798		GM: Boys: 22.0; Girls: 19.0	
		breastfeeding primipare	5,667		GM: 14.0	
Denmark	Snart Forældre/Milieu	18-40 years women	73	2011-2014	GM: 8.1 (95th% 15.8)	Rosofsky et al. (2017)
Finland	NFBC	31 years males	126	1997	GM: 17.06 S.D.:± 1.84	Abass et al. (2017)
		31 years females	123	1997	GM: 9.06; S.D.: ± 2.20	

Country	Study	Population studied	N	Year of sampling	PbB (µg/L)	Reference
France	ENNS 2006-2007	18-39 years	579	2006-2007	GM: 19; 95%C.I.: 44-62	Falq et al. (2008)
		40-59 years	947		GM: 29; 95%C.I.: 66-85	
		60-75 years	423		GM: 39; 95%C.I.: 86-115	
		Total 18-75 years	1,949		GM: 26; 95%C.I.: 68-77	
	hospital-based	1-6 years	3,831	2008-2009	GM: 14.9 (95% C.I.:14.5-15.4)	Etchevers et al. (2014)
Germany	GerES I	adults	2,731	1985-1986	GM: 61	Schulz et al. (2017)
	GerES II	adults	4,287	1990-1992	GM: 45	
		children	812	1990-1992	GM: 32	
	GerES III	adults	4,822	1997-1999	GM: 32	
	GerES IV	3-14 years	1,790	2003-2006	GM: 17	
	GerES V	3 – 17 years	2,500	2014-2017	not yet available	
Hungary	NKFP (past hot spots)	4 – 15 years	253	2006	GM: 30	Rudnai et al. (2009)
Italy	PROBE	18-65 years	1,423	2008-2011	GM: 19.9 (95% C.I.:19.2-20.5)	Bocca et al (2013)
Kosovo	Mitrovica	5-11 years	166	? 2012-2014	AM: 24 ±19 (Range: 5-163)	Kutllovci-Zogaj et al (2014)
	Shtime (control)	6-12 years	53	? 2012-2014	AM: 23 ±7 (Range: 12-52)	
	Mitrovica	kindergarten	31	? 2012-2014	AM: 38 ±13 (Range: 22-77)	
Poland	Upper Silesia	3-18 years	4,882	1999-2013	? (not available in abstract)	Pelc et al. (2016)
	REPRO_PL	pregnant women	594	2007-2011	GM: 11.0; Range: 3.0-57.0	Polanska et al (2014)
	Szczecin	2-18 year	78	? 2010-2011	AM: 19.7 ± 13.59	Szkup-Jabłońska et al. (2012)
	Piekary Śląskie (Silesia)	3 – 6 year	678	2013	GM: 24.7 ± 17.5	Kowalska et al (2018)
Slovakia	Banska Bystrica	7-14 years	57	2007-2008	GM: 19.4; Range: 8.0-47.0	Hruba et al. (2012)

Country	Study	Population studied	N	Year of sampling	PbB ($\mu\text{g/L}$)	Reference
Slovenia	Ljubljana	7-14 years	42	2007-2008	GM: 13.4; Range: 6.9-24.0	Hruba et al. (2012)
	National HBM Programme	6-11 years	174	2011 - 2014	GM: 16.1	Tratnik et al. (2013)
		men (20-35 years)	147		GM: 19.6	
		women (20-35 yrs)	127		GM: 17.3	
		women (50-60 yrs)	66		GM: 26.7	
Spain	BIOAMBIENT.ES	18-65 years	1,880	2007-2010	GM: 24 (95% CI:23.0-25.1)	Canas et al (2014)
	HEALS study	pregnant women	53	2016-2017	1 st trimester: 10, delivery: 12 cord blood: 7.9	Bocca et al (2019)
Sweden	Landskrona	7-14 years	41	2007-2008	GM: 14.0; Range: 6.0-25.0	Hruba et al. (2012)
	MONICA	adult men	619	2004-2014	25-35 yrs:11.1; 50-60 yrs:15.1	Wennberg et al (2017)
		adult women	926		25-35 yrs:9.69; 50-60 yrs:13.1	

1.1.2.4 Guidance values

Similar guidance values were considered safe for children and adults then CDC introduced an intervention level of **25 µg/dL** for children. After recognising the special susceptibility of children to lead's toxic effects CDC formulated **10 µg/dL** as the "**value of concern**" for children in 1991 (CDC, 1991), saying that there was enough information identifying harmful effects of lead in children at blood lead levels at least as low as 10 µg/dL. At that time CDC also stated that "as yet **no threshold has been identified** for the harmful effects of lead". In 2012 CDC threw away the "value of concern" expression and decided to use a childhood BLL **reference value** of **5 µg/dL** based on the 97.5th percentile of the population BLL in children aged 1-5 to identify *children and environments associated with lead-exposure hazards* (CDC, 2012)

Epidemiological studies have provided a lot of evidence that **there is no safe level of blood lead concentration**. In Germany the German HBM Commission concluded that any setting of an "effect threshold" for blood lead levels would be arbitrary and therefore unjustified, therefore it suspended the HBM-I and HBM-II guideline values for blood lead levels in children and adults (Wilhelm et al, 2010) .

The Panel on Contaminants in the Food Chain (CONTAM Panel) of the European Food Safety Authority (EFSA) identified developmental neurotoxicity in young children and cardiovascular effects and nephrotoxicity in adults as the critical effects for the risk assessment and derived Benchmark Dose Levels (BMDLs) from blood lead levels for these effects as follows: 12 µg/L in the case of developmental neurotoxicity, 15 µg/L for chronic kidney disease and 36 µg/dL for elevated systolic blood pressure (EFSA, 2010).

There is a need for a harmonised European biological guidance value !

1.1.3 Policy relevance

1.1.3.1 Existing regulations

The EU's Drinking Water Directive (98/83/EC) aims at protection of human health from adverse effects of any contamination of water intended for human consumption. It defines the health limit value of lead in drinking water as 10 µg/L.

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)

The 2013/39/EU Directive amending directives 2000/60/EC and 2008/1056EC as regards priority substances in the field of water policy, suggests to have lead concentration lowered to a limit of 1.2 µg/L in **inland surface water**, and 1.3 µg/L in outland surface water.

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/m³ per calendar year.

Regulatory **limit value of lead in soil**: 50 – 300 mg/kg, in sludge for agriculture: 750 – 1200 mg/kg ("EUR-Lex (86/278/EEC)")

1881/2006/EC set maximum levels for certain contaminants, including **lead in foodstuffs**.

However, the Panel on Contaminants in the Food Chain (CONTAM Panel) of the European Food Safety Authority (EFSA) concluded that the present PTWI of 25 µg/kg b.w. is no longer appropriate and noted that there was no evidence for a threshold for a number of critical endpoints including developmental neurotoxicity and renal effects in adults. Therefore, a margin of exposure approach was applied to risk characterisation (EFSA, 2010).

Occupational exposure is regulated by the Chemical Agents Directive 98/24/EC containing both a binding OEL and a Biological Limit Value for inorganic lead and its compounds, this latter being 70 µg/dL.

1.1.4 Technical aspects

To prevent false-positive results, stringent procedures are necessary to reduce environmental contamination of blood collection devices and supplies. Consequently, venous blood collected using evacuated tubes and needles certified as “lead-free” is considered the most appropriate specimen for blood lead measurements. However, collection of venous blood from paediatric subjects is sometimes difficult; thus, capillary blood from a finger puncture is used widely for screening purposes. Published studies have compared the quality of blood lead results for capillary and venous specimens drawn simultaneously (Schlenker et al., 1994; Schonfeld et al., 1994; Parsons et al., 1997). With stringent precautions, particularly rigorous hand washing, contamination errors can be held to <4% (Parsons et al. 1997). Therefore, although venous blood is preferable for epidemiologic studies of environmental lead exposure, use of capillary blood is acceptable if collected by staff specially trained in the technique using devices certified as “lead-free.” Data should be provided showing an acceptably low rate of contamination errors and low mean bias in the capillary BLLs as collected using the study protocol (CDC, 2005).

Acceptable analytic techniques include graphite furnace atomic absorption spectroscopy (GFAAS, also known as electrothermal AAS), anodic stripping voltammetry (ASV), inductively coupled plasma atomic emission spectroscopy (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS). Information on laboratory performance (i.e., accuracy and precision) from external and internal quality control data should be provided.

1.1.5 Societal concern

Blood lead levels vary widely from country to country and region to region. The highest blood lead levels and the largest burden of disease from exposures to lead are seen in low-income countries – in particular, in areas where there are industrial uses of lead (such as smelters, mines and refineries) and/or where leaded petrol is still used heavily.

Although lead can affect children from every socioeconomic stratum, socially and economically deprived children and children in low-income countries carry the greatest burden of disease due to lead. Poor people are more likely to be exposed to lead and to be at risk of exposure to multiple sources. They are more likely to dwell on marginal land (near landfills and polluted sites), to live in substandard housing with ageing and deteriorating lead-based paint, and to live near industry, sites where waste is burned and heavy traffic. Also, lead smelting is used by marginalised populations to generate resources (WHO,2010).

The economic costs associated with childhood exposure to lead are substantial (Landrigan et al., 2002). The costs of childhood lead poisoning may be divided into *direct* and *indirect* costs. The direct or medical costs include those costs associated with the provision of medical care to children with acute lead poisoning, as well as the costs of treating cardiovascular disease in adults who have developed hypertension following exposure to lead.

Analyses of the indirect (non-medical) costs of lead poisoning have focused mainly on the loss of intelligence that is caused by lead and on the lifelong decrements in economic productivity that result from this loss of intelligence. These costs are sometimes referred to as *lost opportunity costs*. Using a conservative estimate, the decrease in intelligence attributable to each 1 µg/dl increase in blood lead level is 0.25 IQ points, and the decrement in lifetime economic productivity associated with each lost IQ point is 2.4%. (WHO, 2010)

1.2 Categorisation of Substances

Table 1-2: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C,D,E substances (see general introduction)

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
A	Pb	Lead, Plumbane	7439-92-1	Regulation (EC) No 2006/1881 (food) EU 2017/738 (toys) 98/83/EC (drinking water) 2013/39/EU (surface water) 2008/50/EC (air) 86/278/EEC (soil) 98/24/EC (occupational exposure)

1.3 Policy-related questions

1. What is the concentration of lead in the human blood nowadays (after phasing out leaded petrol) in the countries of Europe?
2. Do blood lead levels of both adults and children still indicate permanent existence of lead exposure?
3. What are the sources of still existing lead exposure in different countries of Europe?
4. What kind of exposure sources are the most important for the children of various age groups and the younger or older adult population?
5. Taking the hazard from transplacental lead exposure of the unborn child into consideration, what are the blood lead levels of pregnant women?
6. Taking the presumably low concentration of lead in blood, is it feasible to measure blood lead levels in children from as small amount of blood as it can be gained from capillary samples? What criteria should be applied in order to avoid contamination from outside sources?
7. As it is difficult to connect later outcomes with exposures, which biomarkers of effects can be used in relation to effects caused by lead exposure?

1.4 Research Activities to be undertaken

While completing this table please think of data and gaps concerning toxicology (and exposure [in three dimensions: **location** (differences between the countries), **time** (trends) and **age** (data available for which age group)]). If no HBM method is available or the method has to be harmonised within partner countries, please indicate this too.

Table 1-3: Listing of research activities to be carried out to answer the policy questions

Policy question	Substance	Available knowledge	Knowledge gaps and activities needed
1, 2	Lead	After phasing out leaded petrol, blood lead levels significantly dropped but not at the same extent and not at the same time in different countries.	Collection of information on the time and extent of phasing out lead from petrol in the various countries. Collection, comparison and evaluation of existing data on current blood lead levels and their integration into IPCheM
3,4,5	Lead	Leaded petrol used to have dominant role in blood lead levels. After its phasing out, several possible lead sources earlier thought to be insignificant (e.g. drinking water from leaded pipes, lead-containing products, etc.) may have become important, because there is no safe level of lead exposure	In order to eliminate still existing lead sources in countries <u>showing interest in participation</u> , we have to identify their importance in the exposure of different population subgroups (e.g. children 1-3 years, 4-6 yrs, 7-14 yrs and 15-18 yrs, as well as adults (19-40 years; 41-65 years; > 65 years). Special attention should be paid to pregnant women, they should be a separate group in the survey.
6	Lead	It is unquestionable, that blood lead level is the most reliable marker of lead exposure, especially in children. (In adults, bone lead content can also be used to determine lead content accumulated in the organism). Taking venous blood samples from children lacking any clinical symptoms or environment suspicious for lead contamination, only for screening purposes raises ethical concerns. Therefore, more practicable way of sampling would be capillary blood collection. In principle it is possible to use not only venous but also capillary blood samples for the determination of blood lead level but there is a risk of contamination which may obscure the very low concentrations.	In order to demonstrate availability of appropriately trained personnel, parallel measurements of blood lead levels should be performed from capillary and venous blood samples <u>in small groups of children</u> . Detailed description of sampling circumstances should be provided..

Policy question	Substance	Available knowledge	Knowledge gaps and activities needed
7	Lead	Some biomarkers have already been identified as potential indicators for health effects associated with lead exposure; however, there are knowledge gaps.	Biomarkers of effect associated with lead exposure and health outcomes (e.g., neurodevelopment) should be reviewed to identify the most suitable indicators and to provide the baseline for further research directions.

1.5 References

1. Abass K et al (2017): Arsenic, cadmium, lead and mercury levels in blood of Finnish adults and their relation to diet, lifestyle habits and sociodemographic variables. *Environ Sci Pollut Res* 24:1347–1362
2. ATSDR (2019). Toxicological profile for lead. Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/toxprofiles/tp13.pdf>
3. Baeyens W. et al. (2014). Trace metals in blood and urine of newborn/mother pairs, adolescents and adults of the Flemish population (2007-2011). *Int J Hyg Environ Health* 217(8):878-90
4. Bailey M.R. and Roy M. (1994). Clearance of particles from the respiratory tract. In: Human respiratory tract model for radiological protection: A report of a task group of the International Commission on Radiological Protection. Oxford, UK: Pergamon Press, 301-413.
5. Barry V, Todd AC, Steenland K. (2019) Bone lead associations with blood lead, kidney function and blood pressure among US, lead-exposed workers in a surveillance programme. *Occup Environ Med.* 76(5):349-354.
6. Barry V, Steenland K. (2019). Lead exposure and mortality among U.S. workers in a surveillance program: Results from 10 additional years of follow-up. *Environ Res.*177:108625.
7. Bocca B. et al (2013). Metals as biomarkers of the environmental human exposure. E3S Web of Conferences DOI: 10.1051/ C
8. Bocca B, Ruggieri F, Pino A, et al. (2019). Human biomonitoring to evaluate exposure to toxic and essential trace elements during pregnancy. Part A. concentrations in maternal blood, urine and cord blood. *Environ Res.* 177:108599.
9. Canas, A.I. et al (2014) Blood lead levels in a representative sample of the Spanish population: the BIOAMBIENT.ES Projet. *International Journal of Hygiene and Environmental Health* 217(4): 452-459
10. CDC (1991). Preventing Lead Poisoning in Young Children. U.S. Department of Health and Human Services, Public Health service, Centers for Disease Control.
11. CDC (2012): CDC Response to Advisory Committee on Childhood Lead Poisoning Prevention Recommendations in “Low Level Lead Exposure Harms Children: A Renewed Call of Primary Prevention”) http://www.cdc.gov/nceh/lead/ACCLPP/CDC_Response_Lead_Exposure_Recs.pdf
12. Cerna M. et al. (2012). Human biomonitoring in the Czech Republic. An overview. *Int J Hyg Environ Health* 215(2), 109-119
13. Desrochers-Couture M, Oulhote Y, Arbuckle TE, et al. (2018). Prenatal, concurrent, and sex-specific associations between blood lead concentrations and IQ in preschool Canadian children. *Environ Int.*121(Pt 2):1235-1242.
14. ECHA (2018). Brief profile on lead, <https://echa.europa.eu/brief-profile/-/briefprofile/100.028.273>
15. EFSA (2010) Panel on Contaminants in the Food Chain (CONTAM). Scientific Opinion on Lead in Food. *EFSA Journal* 2010; 8(4):1570 [151 pp.], doi: 10.2903 /j.efsa.2010.1570. Available online: www.efsa.europa.eu
16. EHC (1995) Environmental Health Criteria vol. 165: Inorganic Lead, WHO, Geneva.
17. Etchevers A. et al (2014). Blood lead levels and risk factors in young children in France, 2008-2009. *Int J Hyg Environ Health.* 2014 Apr-May;217(4-5):528-37. doi: 10.1016/j.ijheh.2013.10.002.
18. EU (2017) http://ec.europa.eu/environment/water/water-drink/pdf/revised_drinking_water_directive.pdf
19. Falq, G et al. (2008). Exposition de la population adulte au plomb en France - Valeurs de référence. (étude nationale nutrition santé, ENNS 2006-2007), available at: http://invs.santepubliquefrance.fr/publications/2008/jvs_2008/47_poster_falq.pdf
20. Farzan SF, Howe CG, Chen Y, et al. (2018). Prenatal lead exposure and elevated blood pressure in children. *Environ Int.* 121(Pt 2):1289-1296.
21. Fierens S. et al. (2016). Human biomonitoring of heavy metals in the vicinity of non-ferrous metal plants in Ath, Belgium. *Archives of Public Health* 74:42
22. Fruh V, Rifas-Shiman SL, Amarasiriwardena C, et al. (2019). Prenatal lead exposure and childhood executive function and behavioral difficulties in project viva. *Neurotoxicology.* 75:105-115.
23. Garcia-Esquinas, E. et al. (2013). Lead, mercury and cadmium in umbilical cord blood and its association with parental epidemiological variables and birth factors. *BMC Public Health* 13:841. <http://www.biomedcentral.com/1471-2458/13/841>

24. Grigiryan, R. et al (2016) Risk factors for children's blood lead levels in metal mining and smelting communities in Armenia: a cross-sectional study. *BMC Public Health* 16:945
25. Harari F, Barregard L, Östling G, et al. (2019). Blood Lead Levels and Risk of Atherosclerosis in the Carotid Artery: Results from a Swedish Cohort. *Environ Health Perspect.* 127(12):127002.
26. Hrubá F. et al. (2012). Blood cadmium, mercury, and lead in children: an international comparison of cities in six European countries, and China, Ecuador, and Morocco. *Environ Int.* 2012 May;41:29-34. doi: 10.1016/j.envint.2011.12.001.
27. IARC (1987) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, IARC Lyon, France
28. IARC (2006). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 87: Inorganic and Organic Lead Compounds, IARC Lyon, France.
29. IARC (2014) <https://monographs.iarc.fr/wp-content/uploads/2018/08/14-002.pdf>
30. IHME (2017). Institute for Health Metrics and Evaluation (IHME). GBD Compare. Seattle, WA: IHME, University of Washington; 2017.
31. Jakubowski, M (2012). Lead In: Issues in Toxicology No.9. Biomarkers and Human Biomonitoring, Vol.1.: Ongoing Programs and Exposures, Eds: Knudsen L.E. and Merlo F., Royal Society of Chemistry.
32. Khalid M, Abdollahi M. (2019). Epigenetic modifications associated with pathophysiological effects of lead exposure. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 37(4):235-287.
33. Kutllovci-Zogaj, D et al (2014). Correlation between blood lead level and hemoglobin level in Mitrovica children. *Med Arh.* 2014 Oct; 68(5): 324-328
34. Landrigan, P.J. (1989). Toxicity of lead at low dose. *Brit J Ind Med* 46(9):593-596
35. Landrigan, P.J. et al (2002). Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environ Health Perspect*, 110(7):721-728
36. Lanphear BP et al. (2000). Cognitive deficits associated with blood lead concentrations <10µ/dL n US children and adolescents. *Public Health Reports* 115:521-529
37. Lanphear BP et al. (2005). Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect.* 113(7):894-899
38. Lanphear BP, Rauch S, Auinger P, Allen RW, Hornung RW. (2018). Low-level lead exposure and mortality in US adults: a population-based cohort study. *Lancet Public Health* 3(4):e177–e184,
39. Lopes AC, Peixe TS, Mesas AE, Paoliello MM. (2016) Lead Exposure and Oxidative Stress: A Systematic Review. *Rev Environ Contam Toxicol.* 236:193-238.
40. Mani MS, Kabekkodu SP, Joshi MB, Dsouza HS. (2019) Ecogenetics of lead toxicity and its influence on risk assessment. *Hum Exp Toxicol.* 38(9):1031-1059.
41. Navas-Acien A. et al. (2007). Lead exposure and cardiovascular disease – a systematic review. *Environ Health Perspect.* 115(3):472-482
42. Needleman H.L. et al. (1979). Deficit in psychologic and classroom performance of children with elevated dentine lead levels. *New England J Med*, 300(13):689-695
43. Oulhote, Y et al. (2013). Implications of different residential lead standards on children's blood lead levels in France: predictions based on a national cross-sectional survey. *Int J Hyg Environ Health.* 2013 Nov;216(6):743-50. doi: 10.1016/j.ijheh.2013.02.007.
44. Parsons, P.J., Reilly, A.A., Esernio-Jenssen, D.(1997) Screening children exposed to lead: an assessment of the capillary blood lead fingerstick test. *Clin Chem.* 43:302–311
45. Pelc W. et al. (2016). Environmental and socioeconomic factors contributing to elevated blood lead levels in children from an industrial area of Upper Silesia. *Environ Toxicol Chem* 2016;35:2597–2603.
46. Polanska K. et al (2014). Predictors of environmental lead exposure among pregnant women – a prospective cohort study in Poland. *Ann Agric Environ Med.* 21(1): 49–54.
47. Polanska, K.; Hanke, W.; Pawlas, N.; Wesolowska, E.; Jankowska, A.; Jagodic, M.; Mazej, D.; Dominowska, J.; Grzesiak, M.; Mirabella, F.; Chiarotti, F.; Calamandrei, G. (2018). Sex-Dependent Impact of Low-Level Lead Exposure during Prenatal Period on Child Psychomotor Functions. *Int. J. Environ. Res. Public Health.* 15, 2263.
48. Qu W, Du GL, Feng B, Shao H. (2019). Effects of oxidative stress on blood pressure and electrocardiogram findings in workers with occupational exposure to lead. *J Int Med Res.* 47(6):2461-2470.

49. Rosofsky A. et al (2017). Exposure to multiple chemicals in a cohort of reproductive –aged Danish women. *Environmental Research* 154 (Supplement C): 73-85
<https://doi.org/10.1016/envres.2016.12.011>.
50. Rudnai P, Varró M.J, Rudnai T, Náráy M, Schoket B, Anna L, Györffy E, Kovács K, Ürömi J, Herczegh T, Bodnár J (2009). Associations between the children's blood lead level and their health status. *Epidemiology* 20(6):S260
51. Sanchez-Guerra M, Peng C, Trevisi L, et al. (2019). Altered cord blood mitochondrial DNA content and pregnancy lead exposure in the PROGRESS cohort. *Environ Int.* 125:437-444.
52. Schlenker, T.L., Fritz, C.J., Mark, D., Layde, M., Linke, G., Murphy, A., et al.(1994) Screening for pediatric lead poisoning. Comparability of simultaneously drawn capillary and venous blood samples. *JAMA.*271:1346–1348.
53. Schonfeld, D.J., Cullen, M.R., Rainey, P.M., Berg, A.T., Brown, D.R., Hogan Jr., J.C., et al. (1994) Screening for lead poisoning in an urban pediatric clinic using samples obtained by fingerstick. *Pediatrics.* 94:174–179.
54. Schultz, C. et al. (2017). German Environmental Survey for Children and Adolescents 2014-2017 (GerES V) – the environmental module of KiGGS Wave 2. *Journal of Health Monitoring* ·2017 2(S3)DOI 10.17886/RKI-GBE-2017-108
55. Schwartz J et al. (1990). Lead-induced anemia: dose-response relationships and evidence for a threshold. *Amer J Publ Health*, 80(2):165-168
56. Shih RA et al.(2007). Cumulative Lead Dose and Cognitive Function in Adults: A Review of Studies That Measured Both Blood Lead and Bone Lead. *Environ Health Perspect.* 115:483–492
57. Steenland K, Barry V, Anttila A, et al. (2019). Cancer incidence among workers with blood lead measurements in two countries. *Occup Environ Med.* 76(9):603-610.
58. Sun X, Liu W, Zhang B, et al. (2019). Maternal Heavy Metal Exposure, Thyroid Hormones, and Birth Outcomes: A Prospective Cohort Study. *J Clin Endocrinol Metab.* 104(11):5043-5052.
59. Szkup-Jabłońska, M et al. (2012). Effects of blood lead and cadmium levels on the functioning of children with behaviour disorders in the family environment. *Annals of Agricultural and Environmental Medicine* 2012, Vol 19, No 2, 241-246
60. The Global Dimensions of Lead Poisoning: An Initial Analysis.(1994), Alliance to End Childhood Lead Poisoning, Environmental Defense Fund
61. Tratnik J.S. et al. (2013). Biomonitoring of selected trace elements in women, men and children from Slovenia. *E35 Web of conferences* 1: 26001. <https://doi.org/10.1051/e3sconf/20130126001>
62. U.S. Bureau of Mines (1993). Lead. Annual Report – 1991. US Department of the Interior, Washington, D.C.
63. Vlasak T, Jordakieva G, Gnambs T, et al. (2019). Blood lead levels and cognitive functioning: A meta-analysis. *Sci Total Environ.* 668:678-684.
64. Wells, E.M. et al. (2011). Low level lead exposure and elevations in blood pressure during pregnancy. *Environ Health Perspect.* 119(5):664-669
65. Wennberg M. et al (2017). Time trends and exposure determinants of lead and cadmium in the adult population of Northern Sweden 1990-2014. *Environmental Research* 159 (Supplement C): 111-117.
<https://doi.org/10.1016/j.envres.2017.07.029>
66. WHO (2010). Childhood lead poisoning, WHO, Geneva
67. Wilhelm, M. et al. (2010) Reassessment of critical lead effects by the German Human Biomonitoring Commission results in suspension of the Human Biomonitoring values (HBM I and HBM II) for lead in blood of children and adults. *Int J Hyg Environ Health* 213(4):265-69
68. Wu S, Hivert MF, Cardenas A, et al. (2017). Exposure to Low Levels of Lead in Utero and Umbilical Cord Blood DNA Methylation in Project Viva: An Epigenome-Wide Association Study. *Environ Health Perspect.* 2017;125(8):087019. Published 2017 Aug 25. doi:10.1289/EHP1246
69. Zeng H, Wang LQ, Xiang ML, et al. (2019). The Blood Lead Level and Its Relationship With Behavior in School-Age Children From Rural Areas of Chongqing. *Zhonghua Yu Fang Yi Xue Za Zhi.* 53(9):907-912.

