1 Prioritised substance group: Mercury and its organic compounds

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1.1 Background information

Mercury is a highly toxic heavy metal that poses a significant global threat to human health and the environment. Together with its various compounds, it can cause severe impacts on human health, including irreversible damage to the central nervous system. Effects can be seen even at very low levels. Fetuses, newborn babies and children are amongst the most vulnerable and sensitive to the adverse effects of mercury. Once released into the environment, mercury can move around the globe, impacting human health and environment even in remote locations, and can remain in circulation for thousands of years. Mercury in water bodies presents the greatest risk to humans since it gets converted by microorganisms into methylmercury, which is very toxic, easily absorbed by animals and bioaccumulates in the food chain. No country can control transboundary effects of mercury alone and therefore international cooperation necessary. The Minamata Convention on Mercury, which came into force in 2017, shows the global commitment to address mercury pollution. This international treaty was ratified by the European Union. Stringent European legislation is in place to restrict mercury pollution and human exposure. Although new releases to the environment in the European Union are on decline as a result of European policies, Europeans are still exposed primarily to legacy mercury and to mercury originating from sources outside the Union.

This scoping document focuses on mercury and methylmercury, the organic form of mercury, which poses the greatest risk for human health. It does not focus on inorganic forms of mercury, to which people may be exposed in the workplace.

1.1.1 Hazardous properties

1.1.1.1 Current understanding

Mercury is a naturally occurring metal in the earth's crust. It is ubiquitous in the global environment and occurs from both natural and anthropogenic sources. It exists in three main forms, which are not equally harmful: elemental (metallic), inorganic, and organic.

Elemental mercury (Hg, CAS number: 7439-97-6, EC number: 231-106-7) is a heavy, shiny, silver-white liquid. It is the only metal that is liquid at room temperature and for this reason, it is also known as "quicksilver" (European Environment Agency , 2018). It is obtained primarily from the refining of mercuric sulfide in cinnabar ore. If it is not contained, mercury vaporizes easily at room temperature to an invisible, odorless toxic gas referred to as elemental mercury vapor (Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services, Public Health Service, 1999). Elemental mercury is commonly used in human activities. It

has been used in electrical equipment (e.g., thermostats and switches), electrical lamps, medical and laboratory equipment (e.g. thermometers, sphygmomanometers, barometers) and dental amalgams. It has also been used industrially in the production of chlorine gas and caustic soda. The anthropogenic use of mercury results into the release of large amounts into the atmosphere and can travel long distances, presenting a significant risk to human health and environment. Elemental mercury can eventually react in the atmosphere to form inorganic mercury, which gets deposited in water bodies and on land.

Inorganic mercury compounds are formed when mercury combines with other elements such as chlorine, sulfur or oxygen. Inorganic mercury compounds exist in two oxidative states, mercurous (+1) and mercuric (+2). Mercury salts are highly toxic and corrosive. Inorganic mercury compounds, such as mercuric oxide, are used in the production of batteries, polyvinylchloride, and pigments (Agency for Toxic Substances and Disease Registry (ATSDR), U.S. Department of Health and Human Services, Public Health Service, 1999).

Organic mercury compounds are formed when inorganic mercury is methylated or combines with organic agents. Different forms of organic mercury have different properties and toxicities. The most important organic form of mercury, with regards to human exposure and adverse effects on health, is methylmercury. Methylmercury is formed by anaerobic methylation of inorganic mercury by microorganisms in sediments. In waterbodies, methylmercury accumulates in aquatic organisms and biomagnifies up the food chain. The primary source of human exposure to mercury is through the consumption of fish and shellfish containing methylmercury.

Other organic mercury compounds have been used in fungicides, antiseptics and disinfectants, but have mostly been discontinued. Ethylmercury (thiomersal), is used in very small amounts in vaccines (as preservative) and pharmaceuticals. Ethylmercury is broken down by the body quickly and does not accumulate. The World Health Organization monitors and evaluates scientific evidence on the use of thiomersal as a vaccine preservative, and consistently concludes that there is no evidence to date that the amount of thiomersal used in vaccines poses a health risk (World Health Organization, 2012). However, concerns are still raised in the scientific community regarding the safety of the use of ethylmercury in vaccines and the lack of precise regulations at EU level (Ruggieri, Majorani, Domanico, & Alimonti, 2017).

Mercury ranks 3rd and methylmercury 116th (out of a total of 275 substances) on the “ATSDR 2017 Substance Priority List” of the US Agency for Toxic Substances and Disease Registry (US Agency for Toxic Substances and Disease Registry (ATSDR), 2017).

According to the harmonised classification and labelling (ATP01) approved by the European Union, elemental mercury is a hazardous substance, which is fatal if inhaled (Acute Tox.2, “H330”), may damage the unborn child (Repr. 1B, “H360”), causes damage to organs through prolonged or repeated exposure (STOT RE 1, “H372” – Central Nervous System) and is very toxic to aquatic life (Aquatic Acute 1, “H400”) and with long-lasting effects (Aquatic Chronic 1, “H410”) (European Chemicals Agency, ECHA, n.d.).

Based on a systematic review of the literature, Grandjean and Landrigan suggested in 2006 that mercury and methylmercury are suspected neurotoxicants. The same authors updated their review of the existing data and noted that methylmercury is a developmental neurotoxicant, at much lower exposures than the concentrations that affect adult brain function. Genetic polymorphisms increase the vulnerability of the developing brain (Grandjean & Landrigan, Developmental neurotoxicity of industrial chemicals., 2006), (Grandjean & Landrigan, Neurobehavioural effects of developmental toxicity, 2014).

According to the International Agency for Research on Cancer (IARC), methylmercury compounds are possibly carcinogenic to humans (Group 2B). Metallic mercury and inorganic mercury compounds are classified in Group 3 (not classifiable as to their carcinogenicity to humans)

(International Agency for Research on Cancer, World Health Organization, 1993). The Commission for the Investigation of Health Hazards of Chemical Compounds of the Germany Research Foundation (DFG) placed organic and inorganic mercury compounds in Category 3B (substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data) (Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Germany Research Foundation, 2013). (Deutsche Forschungsgemeinschaft, 2020)

Mercury and mercury compounds are on the Proposition 65 list (Chemicals known to the State of California to Cause Cancer or Reproductive Toxicity) because they can cause birth defects or other reproductive harm. Methylmercury compounds are also on the Proposition 65 list because they can cause cancer (The Office of Environmental Health Hazard Assessment (OEHHA), State of California, USA).

According to the IRIS database, elemental mercury is not classifiable as to human carcinogenicity (Cat D) and methylmercury is a possible human carcinogen, for which human carcinogenicity data are inadequate (Cat C).

The Japanese GHS Classification classifies mercury as causing damage to organs through prolonged or repeated exposure (STOT RE 1 – nervous system, cardiovascular system, blood, liver, gingiva), as a reproductive toxicant (Category 1A), as Category 2 for mutagenicity, and does not classify it in terms of carcinogenicity.

1.1.1.2 Knowledge gaps

The toxic effects of methylmercury at the levels of exposure found in the general population due to fish consumption are not fully understood. New developments in epidemiological studies have indicated that n-3 long-chain polyunsaturated fatty acids in fish may counteract negative effects from methylmercury exposure that could impact the safety of the tolerable weekly intake (TWI) established by EFSA (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment, 2018). The risk associated with dental amalgams is not fully understood (Bengtsson & Lars, 2017), (Bentung Lygre , Haug , Skjærven , & Björkman, 2016). Exposure to mercury has been linked with Alzheimer's disease, but further research is required (Mutter, Curth, Naumann, Deth, & Walach, 2010). Mercury has possible endocrine disruptive effects, which have raised public concern, but further investigation is required (Rana, 2014), (Iavicoli, Fontana , & Bergamaschi, 2009), (Rahman, Kumarathasan, & Gomes, 2016).

Additional prospective studies, which will include speciation analysis of the different forms of mercury, are needed for the investigation of the potential links of mercury to the metabolic syndrome, immunotoxicity and cardiovascular effects (Roy, Tremblay, & Ayotte, 2017), (Maqbool, Niaz, Ismail Hassan, Khan, & Abdollahi, 2017), (Gardner & Nyland, 2016), (Genchi, Sinicropi, Carocci, Lauria, & Catalano, 2017). A recent review and meta-analysis of Environmental toxic metal contaminants and risk of cardiovascular disease was published by Chowdhury et al. (2018) found that mercury was not associated with any cardiovascular outcomes (Chowdhury, et al., 2018). In an accompanying editorial, the difficulties of taking into account fish consumption in the analyses were reported and the authors suggested that the previous findings had to be taken with caution (Tellez-Plaza, Guallar, & Navas-Acien, 2018).

1.1.2 Exposure characteristics

1.1.2.1 Environmental behaviour

Mercury is found in the environment in the metallic form and in various inorganic and organic complexes. The sources are both natural and anthropogenic.

The natural global bio-geochemical cycling of mercury is characterised by degassing of the element from soils and surface waters, atmospheric transport, deposition of mercury back to land and surface water, sorption onto soil or sediment particles and revolatilisation from land and surface water. This emission, deposition and revolatilisation creates difficulties in tracing the movement of mercury to its sources. Hg can be released into the air through weathering of rock containing Hg ore, or through human activities, such as incineration and burning of fossil fuels. The life-time of mercury in the atmosphere varies between 0.8 – 2 years (Gworek, Bemowska-Kałabun, Kijeń, & Wrzosek-Jakubowska, 2016). Hg released in atmosphere is a significant indirect risk to human health, since it is the main way in which it travels around the globe and gets deposited in water bodies and on land. For this reason, mercury is global pollutant. Once in the environment, interconversion between the different forms of Hg can occur. Particulate-bound Hg can be converted to insoluble Hg sulfide and can be precipitated or bioconverted into more volatile or soluble forms that re-enter the atmosphere or are bioaccumulated in aquatic and terrestrial food chains (National Research Council, Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology, 2000).

Water contamination can occur from run-off water, contaminated by either natural or anthropogenic sources or from air deposition. The biggest risk to human health is mercury in aquatic environments, because it stays there for a very long time (the lifetime of mercury in the upper oceans is 20 - 30 years and can be hundreds of years in the deep ocean) and it gets converted by microorganisms to the very toxic organic form, methylmercury (Gworek, Bemowska-Kałabun, Kijeń, & Wrzosek-Jakubowska, 2016).

Methylmercury bioaccumulates inside biological organisms, since its excretion is slower than its uptake and biomagnifies as predatory animals consume pray that already accumulated mercury (Hanna, Solomon, Poste, Buck, & Chapman, 2015), (Lavoie, Jardine, Chumchal, Kidd, & Campbell, 2013). The concentration of mercury in fish species is influenced by the position of the species in the food web (e.g. it is higher in predators, such as swordfish and lower in low-end species, such as sardines), but also on the region. In Europe, the highest concentrations are found in the Mediterranean Sea (Miklavčič Višnjevec, Kocman, & Horvat, Human mercury exposure and effects in Europe), which may be due to favourable conditions for the generation of methylmercury (European Environment Agency , 2018), (Cossa & Coquery, 2005).

Mercury deposited on land also enters the food-chain, as for example, in the case of rice grown on contaminated soil (Rothenberg, Windham-Myers, & Creswell, 2014). Because rice is grown in water, methylmercury may be formed and absorbed in the grain (Tanner, et al.).

1.1.2.2 Human exposure

Humans face exposure risks to all forms of mercury from numerous sources and routes of exposure. Human exposure to mercury may occur through the following routes:

- **Dermal**: Mercury is a suspected skin sensitiser and allergen, but it is not significantly absorbed through the skin and so this is not a significant route.
- **Inhalation**: Inhalation of mercury vapours may occur in industrial processes, but for the general population, this route is not a significant route.
- **Oral**: This is a significant route of exposure for the general population. Human exposure occurs mainly through the consumption of contaminated fish and shellfish, with methylmercury presenting the most significant risk. Elemental mercury from ingestion is poorly absorbed with a bioavailability of less than 0.01% (Park & Zheng, 2012).
- **Trans-placenta:** This is a significant route of human exposure, since mercury crosses the placenta and results in foetal exposure.

Sources and routes of exposure vary geographically in a significant way and this complicates the development of strategies able to protect populations in specific locations. In developing nations, exposure may result from occupational activities such as artisanal and small-scale mining, religious and cultural practices and diet based almost exclusively on fish consumption. The most significant source of human exposure to mercury in Europe is through the diet. Populations consuming a lot of fish, such as in coastal regions - the Mediterranean region of Europe or Arctic regions - are the most vulnerable. Exposure levels are influenced also by the type of fish consumed (eating predatory fish entails a higher risk). On the other hand, fish consumption provides omega-3 fatty acids, which have protective health effects. To balance the health benefits provided by seafood consumption with the negative effects from possible exposure to mercury, the European and many National Food Safety Authorities developed dietary advice. A recent study by Kirk et al. in Denmark, showed that providing dietary advice to pregnant women to consume preferably non-predatory fish, was effective in lowering their exposure to methylmercury as determined by mercury analysis in hair (Kirk, Jørgensen, Nielsen, & Grandjean, 2017), (European Environment Agency , 2018). Rise-based diets are an increasing risk factor (World Health Organization (WHO), 2010).

Mercury exposure from non-dietary sources is small for the general population. Inhaled mercury from ambient air is very efficiently absorbed, but for the general population this is not a significant risk since the levels of mercury in outdoor air are usually very low. Mercury amalgam used in dental fillings and broken mercury-containing products (e.g. thermometers) may also lead to minor exposures. Exposure to thimerosal, an ethylmercury-sulfidobenzoate used as preservative in several human vaccines, is now very limited in Europe. The European Centre for Disease Prevention and Control and the World Health Organization concluded that thimerosal is not harmful, based on assessment of the current scientific evidence (European Environment Agency , 2018).

Local communities living near mercury-polluted sites, such as the Almaden mining area in Spain, may face increased risk of becoming exposed. One example is the former mining town of Idrija, Slovenia, where locally produced foodstuffs (fish, mushrooms, chicory) have been found to contain increased mercury concentrations (Miklavčič, Mazej, Jaćimović, Dizdarevič, & Horvat, 2013).

Human exposure to mercury begins at the time of conception and continuous beyond the critical time of gestation throughout infancy, childhood and into adulthood. Prenatal exposures of the foetus relate to the sources of the mother’s exposure, with the diet being very important. Another source of exposure may be Hg vapours released from dental amalgams, which contain up to 50% elemental mercury (Bentung Lygre , Haug , Skjærven , & Björkman, 2016).

During pregnancy, maternal exposure to mercury can damage the neurodevelopment of the foetus, with noticeable effects on behaviour, cognition, motor skills and the immune and reproduction systems later in life (Rice & Barone Jr., 2000). Infants are at higher risk than older children and adults. This may relate to their highly efficient gastrointestinal absorption, physiological immaturity of homeostasis and detoxification mechanisms. The most significant pathway of infant exposure is breast milk consumption, but use of specific mercury-containing products, such as teething powders, soaps, may contribute (World Health Organization, 2010). Both organic and inorganic mercury occur in breast milk, but the physiology of the mammary gland causes preferential enrichment of inorganic mercury. Inorganic mercury rapidly enters the plasma and therefore, the breast milk. Methylmercury partitions preferentially to erythrocytes (Ask Björnberg, Vahter, & Petersson-Grawé, 2003).

Inorganic mercury salts are not lipid soluble; hence, they do not readily cross the blood-brain barrier or blood-placenta barrier (Dart & Sulliva, 2004). Inhalation is a major exposure route of elemental mercury in the form of mercury vapor. Inhaled mercury vapor is readily absorbed, at a

rate of approximately 80%, in the lungs, and quickly diffused into the blood and distributed into all of the organs of the body Elemental mercury can cross the blood-brain barrier and blood-placenta barrier as well as the lipid bilayers of cellular and intracellular organellar membranes (Park & Zheng, 2012). Elemental mercury is poorly absorbed in the gastrointestinal tract (less than 0.01%) (Von Burg, 1995).

1.1.2.3 Human Biomonitoring (HBM)

Recently, Basu et al. (2018) reviewed the state-of-the-science of mercury biomarkers in human populations worldwide between 2000-2018. A systematic search of the peer-reviewed literature resulted in collection of 424858 mercury biomarker measurements from 335991 individuals represented in 312 scientific articles from 75 countries. This assessment showed that general background populations with insignificant exposures have mercury levels that generally fall under 5 µg/L in blood, 2 µg/g in hair and 3 µg/L in urine. Four populations of concern were identified: a) Arctic populations, who consume fish and marine mammals; b) tropical riverine communities (especially Amazonian) who consume fish and, in some cases, may be exposed to mining; c) coastal and/or small-island communities who substantially depend on seafood; and d) individuals who either work or reside among artisanal and small-scale gold mining sites. The authors concluded that all populations worldwide are exposed to some amount of mercury and that there is great variability in exposures within and across countries and regions. Only limited data exist for many geographic regions and subpopulations, which hinders evidence-based decision making. This information-gap must be addressed, since it is critical in helping understand exposures, both at EU-level and globally, particularly in light of certain stipulations in the Minamata Convention on Mercury (Basu, et al., 2018).

Miklavčič Višnjevec et al. (2014) reviewed published studies from 2000 to 2014 on European populations. The exposure and effects studies were compared with known Hg levels in environmental compartments by mapping the various population groups studied and taking into account known sources of Hg. The spatial distribution trends confirmed that the highest exposure levels to Hg, mostly as methylmercury (MeHg), are found in coastal populations, which consume more fish than inland populations. Fewer studies addressed exposure to elemental Hg through inhalation of Hg in air and inorganic Hg in food, particularly in highly contaminated areas. Overall, at the currently low exposure levels of Hg prevalently found in Europe, further studies are needed to confirm the risk to European populations, taking into consideration exposure to various Hg compounds and mixtures of stressors with similar end-points, nutritional status, and a detailed understanding of Hg in fish present in European markets (Miklavčič Višnjevec, Kocman, & Horvat, Human mercury exposure and effects in Europe, 2014).

The United States (U.S.) Centers of Disease Control and and Prevention follows the exposure of the general U.S. population to mercury. Updated data on blood mercury species (inorganic, ethyl and methyl mercury) were published in 2019 (U.S. Centers for Disease Control and Prevention, 2019).

DEMOCOPHES, carried out in 2010-2012, was the first Europe-wide harmonised Human Biomonitoring study. It investigated the mercury exposure of children ages 6-11 and their mothers in 17 countries (BE, CH, CY, CZ, DE, DK, ES, HU, IE, LU, PL, PT, RO, SI, SK, SE, UK), using scalp-hair samples. The mercury concentrations found at European level, were Mean=0.14 µg/g, P_{90}=0.82 µg/g for children and Mean=0.22 µg/g, P_{90}=1.3 µg/g for mothers. The guidance value used for evaluation of the results, was the JECFA recommended Tolerable Daily Intake (TDI) = 2.3 µg/g (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2006). The results showed that Spain and Portugal had the highest exposures (7 and 5 times above the European mean), which was attributed to sea-food consumption (Den Hond, et al., 2015). Exposure was significantly lower (2 times above the European mean) in Cyprus, an island state with high sea-food consumption, which may be due to the consumption of primarily smaller non-piscivorous fish.

Based on the DEMOCOPHES results, it was estimated that nearly 1.9 million babies are born yearly in Europe with mercury levels above the recommended safe limit, with an estimated associated economic cost of at least EUR 9 billion (Bellanger , et al., 2013). In DEMOCOPHES, the sampling was not representative of the national populations. Further investigations are needed, using representative data, to assess the body burden of Europeans and the sources of exposure. It is also important to follow time trends, which will contribute to the effectiveness assessment of European policy actions and of the Minamata Convention.

A summary of available Human Biomonitoring from EU countries on mercury exposure are summarised in a report from the World Health Organization (2015) (World Health Organization (WHO), 2015) and are shown in the table below. Additional data are provided by Ruggieri et al. (2017) (Ruggieri, Majorani, Domanico, & Alimonti, 2017), who described current HBM studies on Hg exposure in children. Additional results were from further review of the scientific literature or provided by internal HBM4EU partners. In 2018, Steckling et al. reviewed available biomarkers of exposure, exposure determinants, reference and exposure limit values for mercury and other environmental stressors, in a review developed in the frame of the HEALS project (Steckling, et al., 2018). In 2019, the results on men and lactating women from the first Slovenian HBM study were reported (Snoj Tratnik, et al., 2019).

Table 1-1: Summary of European HBM studies on mercury exposure

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
Austria	2008-2010	Children Age: 6-11 y N=?? (A total of 104 samples from adults/children were analysed for MetHg. 50 children participated, but it is not specified if in how many hair samples were assessed for MetHg)	-	-	-	-	Median=0.006	(Hohenblum, et al., 2012)
		Adults (parents) Age: 25-50y N=?? (A total of 104 samples from adults/children were analysed for MetHg. 100 children participated, but it is not specified if in how many hair MetHg was assessed).	-	-	-	-	Median=0.064	
Belgium (Flanders)	FLESH (2007-2011)	Mothers Age: 20-40 y N = 242	-	-	-	GM=0.35 P_{90}=0.82	GM=0.26 P_{90}=0.65	(Schoeters, et al., 2012)
		Adolescents Age: 14-15 y N = 206	-	-	-	GM=0.19 P_{90}=0.47	GM=0.12 P_{90}=0.35	

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
	DEMOCOPHES-BE (2010-2012)	Children Age: 6-11y N=127	-	-	-	GM=0.204 (0.172,0.241)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=127	-	-	-	GM=0.368 (0.313,0.431)	-	
Croatia	PhD Thesis HBM survey in Croatian capital city 2008-2009	Mothers Age=25 to 35 (vegetarian and nonvegetarian) N=102	0.120-13.32 µg/l (Median= 1.840)	Creatinine concentrations 0,509 to 2,601 g/l (Median 1.176)	Concentrations of Hg in urine adjusted to creatinine 0.089 to 5.743 µg/g (Median= 0.689)	0.027-3.899 µg/g (Median= 0.418)		(Janev Holcer, 2010)
Cyprus	DEMOCOPHES-CY (2010-2012)	Children Age: 6-11y N=60	-	-	-	GM=0.326 (0.257,0.413)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=60	-	-	-	GM=0.462 (0.369,0.578)	-	
Czech Republic	CZ-HBM (2001-2003)	Children Age: 8-10y	GM=0.43 P95=1.44 N=333	GM=0.45 P95=4.18 N=619	-	-	-	(Batáriová, et al., 2006), (Černá, Krsková , Čejchanová , & Spěváčková, 2012)
		Adults Age: 18-58 y N=1188	GM=0.82 P95=3.45	GM=0.61 P95=6.8	-	-	-	
	CZ-HBM 2008	Children Age: 8-10y	GM=0.45 P95=1.39 N=382	-	GM=0.26 P95=2.19 N=364	GM=0.18 P95=0.61 N=316	-	
	CZ-HBM (2005-2009)	Adults Age: 18-58 y N=1227	GM=0.6 P95=0.75	-	-	-	-	

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
	DEMOCOPHES-CZ (2010-2012)	Children Age: 6-11y N=120	-	-	-	GM=0.098 (0.083, 0.116)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM=0.156 (0.133,0.183)	-	
Denmark	DEMOCOPHES-DK (2010-2012)	Children Age: 6-11y N=144	-	-	-	GM= 0.250 (0.211,0.295)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=144	-	-	-	GM= 0.391 (0.333,0.458)	-	
France	ENNS (2006-2007)	Adults 18–74 y N=365	-	-	GM=0.59 P95=1.90	-	-	(Fréry, Vandentorren, Etchevers, & Fillol, 2012)
		Children Age: 3–17 y N=1364	-	-	GM=0.37 P95=1.20	-	-	
Germany	Environmental Specimen Bank	Adults Age: 20-29 N= 480/ year from 4 sampling locations	Data available for time trends 1995-2017	Data available for time trends 1995-2017	Data available for time trends 1995-2017			www.umweltprobenbank.de
	GerES I (1985-86)	Adults Age: 25-69ar N=2519	-	-	-	-	-	(Kolossa-Gehring, et al.,

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
	GerES II (1990-92)	Adults Age: 18-79 y N=4287	GM=0.5 P_{95}=2.0	-	GM=0.53 P_{95}=3.7	-	-	2012), (Schulz, Wilhelm, Heudorf, & Kolossa-Gehring, Reprint of "Update of the reference and HBM values derived by the German Human Biomonitoring Commission", 2012)
		Children Age: 6-17 y N=812	GM=0.33 P_{95}=1.4	-	GM=0.54 P_{95}=3.9	-	-	
	GerES III (1998)	Adults Age: 18-69 y N=4822	GM=0.61 P_{95}=2.4	-	GM=0.4 P_{95}=3.0	-	-	
	GerES IV (2003-2006)	Children Age: 3-14 y N=1552	GM=0.23 P_{90}=0.3	-	GM<0.1 P_{90}=0.3	-	-	
	GerES V	Children and adolescens Age: 3- 17						Paper in preparation
	DEMOCOPHES-DE (2010-2012)	Children Age: 6-11y N=120	-	-	-	GM=0.055 (0.046, 0.065)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM=0.107 (0.092,0.126)	-	

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
Hungary	DEMOCOPHES-HU	Children Age: 6-11y N=119	-	-	-	GM=0.025 (0.021,0.029)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=119	-	-	-	GM=0.039 (0.033,0.045)	-	
Ireland	DEMOCOPHES-IE	Children Age: 6-11y N=120	-	-	-	GM=0.097 (0.082,0.114)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM=0.162 (0.139,0.190)	-	
Italy	PROBE (2008-2010)	Adolescents Age: 13–15 y N=252	GM=0.84 P95=3.55	-	-	-	-	(Pino, Amato, Alimonti, Mattei, & Bocca, 2012)
	2007-2009	Pregnant women	Median= 2.35 ng/g P_{75}= 3.98 ng/g N=606	-	-	Median=0.78 P_{75}=1.28 N=604	Median=1.38 P_{75}=1.85 N=220	(Valent, et al., 2013)
	PHIME Project Site A: North Italy - NACII	Children Age: 7y N=200	-	-	-	Median=0.596 P_{75}= 0.996 N=200	-	(Pino, et al., 2018)
	PHIME Project Site B: South Italy	Children Age: 6-11 y N=299	-	-	-	Median=0.477 P_{75}=0.747 N=299	-	

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
Luxembourg	DEMOCOPHES -LU	Children Age: 6-11y N=56	-	-	-	GM=0.181 (0.142,0.229)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=56	-	-	-	GM=0.387 (0.308,0.485)	-	
Poland	DEMOCOPHES-PL	Children Age: 6-11y N=120	-	-	-	GM=0.070 (0.060,0.083)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM=0.135 (0.116,0.159)	-	
Portugal	DEMOCOPHES-PT	Children Age: 6-11y N=120	-	-	-	GM=1.033 (0.873,1.222)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM=1.200 (1.023,1.406)	-	
Romania	DEMOCOPHES-RO	Children Age: 6-11y N=120	-	-	-	GM=0.085 (0.072,0.101)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM=0.100 (0.085,0.117)	-	
Slovakia	DEMOCOPHES-SK (2010-2012)	Children Age: 6-11y N=129	-	-	-	GM= 0.092 (0.078,0.109)	-	(Den Hond, et al., 2015)

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
		Mothers Age <45y N=129	-	-	-	GM=0.132 (0.112,0.154)	-	
Slovenia	National HBM Survey (2007-2009)	Adults Age: 20-40 y N=274	GM=1.07 P95=4.03	GM=0.50 P95=3.44	-	GM=0.23 P95=0.89	-	(Snoj Tratnik J, 2012)
	DEMOCOPHES-SI (2010-2012)	Children Age: 6-11y N=120	-	-	-	GM= 0.169 (0.142,0.200)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM= 0.255 (0.217,0.299)	-	
Spain	BIOVAL programme (2016)	Children Age: 6-11y N=611 (Valencia Region)	-	-	-	GM= 0.79 (Range 0.03-8.71) P75=1.57 P95=3.25	-	(Pérez, et al., 2019)
	ISCIII pilot study (2009 - 2010)	Adults Age: 23–66 y N=170	-	GM=1.23 P_{90}=2.72 P_{95}=3.30	-	-	-	(Castaño , et al., 2012)
	Yusà et. al. (2017)	Breastfeeding mothers Age: 20-45y N=120				GM=1.22 (Range= 0.07 to 6.87)		(Yusà , et al., 2017)
	Roca et. al (2016)	Children Age: 6-11y N=120 (Valencia)		GM= 0.730 P_{95}=2.64 Max= 6.21				(Roca, Sánchez, Pérez, Pardo, & Yusà, 2016)

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
	Batista et. al. (1996)	Children Age: 6-16y N= 233				GM=0.77		(Batista, Schuhmacher, Domingo, & Corbell, 1996)
	DEMOCOPHES-ES (2010-2012)	Children Age: 6-11y N=120	-	-	-	GM=0.884 (0.747,1.046)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM=1.486 (1.267,1.744)	-	
Sweden	DEMOCOPHES-SE (2010-2012)	Children Age: 6-11y N=100	-	-	-	GM= 0.181 (0.153,0.214)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=100	-	-	-	GM=0.252 (0.215,0.295)	-	
Switzerland	DEMOCOPHES-CH (2010-2012)	Children Age: 6-11y N=120	-	-	-	GM= 0.076 (0.065,0.090)	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=120	-	-	-	GM= 0.153 (0.131,0.180)	-	
United Kingdom	DEMOCOPHES-UK (2010-2012)	Children Age: 6-11y N=21	-	-	-	GM=0.192 (0.163,0.228)	-	(Den Hond, et al., 2015)

Country	Study	Population (N)	Total mercury				Methyl-mercury	Ref.
			Blood (ng/mL unless otherwise stated)	Urine		Hair (µg/g)	Hair (µg/g)	
				(µg/g creat)	(µg/L)			
		Mothers Age <45y N=21	-	-	-	GM=0.153 (0.130,0.180)	-	
Italy, Greece, Slovenia, and Croatia	PHIME project*	Mothers Age= 32 (median) N=1282	Median= 2.4 ng/g, P80=4.4 ng/g N=733	-	-	Median=0.70 P_{80}=1.46 N=1282	-	(Barbone , et al.)
17 EU countries	DEMO-COPHES (2010-2012)	Children Age: 6-11y N=1844	-	-	-	GM=0.15 P_{95}=0.80	-	(Den Hond, et al., 2015)
		Mothers Age <45y N=1844	-	-	-	GM=0.23 P_{95}=1.20	-	

**PHIME project results of total mercury in other matrices:*
Breast milk N=819, Median 0.2 ng/g, P80 0.4 ng/g;
Cord blood N=1078, Median 3.6 ng/g, P80 7.8 ng/g

HBM is generally a cross-sectional study (one time or over a short period sampling). Some national HBM cross-sectional surveys were complemented with longitudinal birth cohort studies that allowed to assess perinatal exposure (by biomarkers measured in specimens of the pregnant mother, in cord blood, or in breast milk) and, following up the children, to: (i) describe the degree of individual perinatal Hg exposure and the internal dose during pregnancy; (ii) monitor temporal and spatial patterns of exposure from birth; (iii) evaluate the health effects occurring on foetal and infant growth, and during childhood development; and (iv) link environmental factors and exposures to health, with the aim of informing and orienting public policy decision-making (Ruggieri, Majorani, Domanico, & Alimonti, 2017). The following table, reproduced from Ruggieri et al. (2017) (Ruggieri, Majorani, Domanico, & Alimonti, 2017), provides an overview of the European birth cohort studies, which included investigation of mercury (collected from the webpage www.birthcohorts.net) and some smaller scale longitudinal research.

Table 1-2: Overview of European birth national cohorts, which included investigation of mercury

Country	Birth Cohort	Metals	Enrollment Period	No. of Children at Birth	Ref.
Faroe Islands	Faroes: Children's Health and the Environment in the Faroes	Hg, Pb, Se	1986–2009	2351	(Grandjean, et al., 1997), (Grandjean, Murata, Budtz-Jørgensen, & Weihe, 2004)
United Kingdom	ALSPAC—The Avon Longitudinal Study of Parents and Children	As, Cd, Hg, Mn, Pb, Se	1991–1992	14,062	(Golding, et al., 2013)
Denmark	DNBC—Danish National Birth Cohort	Hg	1996–2002	96986	(Olsén, et al., 2001)
Spain	INMA—Environment and Childhood	Hg, Pb, TMS	1997–2008	3757	(Ramón, et al., 2011)
Norway	MoBa—Norwegian Mother and Child Cohort Study	Hg	1999–2008	100000	(Vejrup, et al., 2014)
Germany	Duisburg cohort	Cd, Hg, Pb, Se	2000–2003	234	(Wilhelm, et al., 2008)
Poland	Kraków cohort	Cd, Hg, Pb	2000–2003	505	(Jedrychowski, et al., 2007)
	REPRO_PL—Polish Mother and Child Cohort	Cd, Hg, Pb, Se, Zn, Cu	2007–2011	1800	(Polanska, et al., 2011)
Slovakia	PCB cohort—Early Childhood Development and PCB exposures in Slovakia	Hg, Pb	2001–2003	1134	(Sonneborn, et al., 2008)
Finland	LUKAS cohort: Finnish cohort	As, Cd, Hg, Pb, Se	2002–2005	442	(Leino, et al., 2013)
France	PÉLAGIE—Endocrine disruptors: longitudinal study on pregnancy abnormalities, infertility, and childhood	Hg	2002–2006	3421	(Guldner, Monfort, Rouget, Garlantezec, & Cordier, 2007)
	ELFE: French longitudinal study of children	Al, As, Cd, Hg, Pb	2011–2012	20000	(Vandentorren, et al., 2009)
Italy	Trieste Cohort: Trieste child development cohort	Hg, Pb, Se, Zn	2007–2009	900	(Valent, et al., 2013)

Country	Birth Cohort	Metals	Enrollment Period	No. of Children at Birth	Ref.
Greece	RHEA—Mother Child Cohort in Crete	As, Cd, Hg, Mn, Pb	2007–2008	1500	(Vardavas, et al., 2009)
Croatia	Implementation of Human Biomonitoring survey of prenatal exposure to mercury in two Croatian regions using the standardised WHO methodology – Mother Child study in Croatia	Hg	2015 - 2016	290	(Capak, et al., 2016)
Italy, Greece, Slovenia, and Croatia	NACII—Mediterranean cohort study, (within PHIME project)	Cd, Hg, Pb, Mn, Se, Zn	2006–2011	1700	(Valent, et al., 2013)

INMA: INfancia y Medio Ambiente (Spanish: Environment and Childhood); REPRO_PL: Polish Mother and Child Cohort; PCB: polychlorinated biphenyl; PÉLAGIE: Perturbateurs
Endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance (French: Endocrine Disruptors: Longitudinal Study on Disorders of Pregnancy, Infertility and
Children; ELFE: Etude Longitudinale Francaise depuis l'Enfance (French Longitudinal Study of Children); NACII: Northern Adriatic Cohort; PHIME: Public Health Impact of long-term low-level Mixed Element Exposure.

An overview of reference values for mercury in blood and urine are provided in Saravanabhavan et al. (2017) (Saravanabhavan, et al., 2017) and summarised in the tables below.

Table 1-3: Overview of reference values for mercury (total) in blood

Mercury (total)						
Country: Survey	Study period	Population (years)	N	Exclusion criteria	RV_{95} (µg/L)	Ref.
Brazil	2006	18–65	593		4	(Kuno, Roquetti, Becker, Seiwert, & Gouveia, 2013)
Czech Republic: HBM project	2005–2009	8–10	723		1.4	(Černá, Krsková , Čejchanová , & Spěváčková, 2012)
Czech Republic: HBM project	2005–2009	18–58	1221	A	2.6	(Černá, Krsková , Čejchanová , & Spěváčková, 2012)
Germany: GerES IV	2003–2006	3–14	891	B	0.8	(Schulz, Wilhelm, Heudorf, & Kolossa-Gehring, Reprint of "Update of the reference and HBM values derived by the German Human Biomonitoring Commission", 2012)
Germany: GerES III	1997–1999	18–69	2310	B	2.0	(Wilhelm, Ewers, & Schulz, 2004)
Italy: PROBE	2008–2010	18–65	1423		5.16	(Alimonti, Bocca, Mattei, & Pino, 2011)
Korea: KorSEP III	2008	≥20	1963	C	9.42	(Lee, et al., 2012)

A: average fish consumption of ≥1 time per week
B: average fish consumption of >3 times per month
C: fish consumption within 72 h of sample collection

Table 1-4: Overview of reference values for mercury (inorganic) in urine

Mercury (inorganic)						
Country: Survey	**Study period**	**Population (years)**	**N**	**Exclusion criteria**	**RV_{95} (µg/L)**	**Ref.**
Czech Republic: HBM project	2005–2009	8–10	723		3	(Černá, Krsková , Čejchanová , & Spěváčková, 2012)
Czech Republic: HBM project	2005–2009	18–58	1227		9	(Černá, Krsková , Čejchanová , & Spěváčková, 2012)
Germany: GerES IV	2003–2006	3–14	1612	A, C	0.4	(Schulz, Wilhelm, Heudorf, & Kolossa-Gehring, Reprint of "Update of the reference and HBM values derived by the German Human Biomonitoring Commission", 2012)
Germany: GerES III	1997–1999	18–69	1560	A, C	1.0	(Wilhelm, Ewers, & Schulz, 2004)
Belgium	2010–2011	>18	1001	B	1.88	(Hoet, Jacquerye, Deumer, Lison, & Haufroid, 2013)

A: creatinine levels <0.3 or >3.0 g/L, B: occupational exposure, C: presence of dental amalgam fillings

1.1.2.4 Health based guidance values available for HBM data

1.1.2.4.1.1 General population

The following table summarises the available public health risk-based values in terms of biomarker concentrations and has been adopted from Ruggieri et al. (2017) (Ruggieri, Majorani, Domanico, & Alimonti, 2017).

Table 1-5: Summary of available public health risk-based values for mercury

	Reference population	**HBM-I**	**HBM-II**	**NCR**	**JECFA**	**Bellanger et al. (2013) (Bellanger , et al., 2013)**
Mercury (total) in urine	Children, women of child-bearing age / adults	7 µg/L (5 µg/g creat.)	25 µg/L (20 µg/g creat.)			
Mercury (total) in blood	Children, women of child-bearing age / adults	5 µg/L	15 µg/L			
Mercury in hair (dry weight)	Children, women of child-bearing age			1 µg/g	2.3 µg/g	0.58 µg/g
Mercury (total) in cord blood	-			5.8 µg/L		
Mercury (total) in maternal blood	Pregnant women			3.5 µg/L		

HBM: Human Biomonitoring
NCR: National Research Council
JECFA: Joint FAO/WHO Expert Committee on Food Additives
FAO: Food and Agriculture Organization of the United Nations
creat.: creatinine

The German HBM Commission defined HBM-I and HBM-II values for total mercury in urine (HBM-I: 7 µg/L (5 µg/g creat.); HBM-II: 25 µg/L (20 µg/g creat.) and for total mercury in blood (HBM-I: 5 µg/L; HBM-II: 15 µg/L). The HBM-I value corresponds to the concentration of a substance in a human biological matrix below which no adverse health effects are expected.

The HBM-II value corresponds to the concentration above, which there is an increased risk of adverse health effects and is therefore an intervention or action threshold level.

No HBM values were set for hair by German HBM Commission (Schulz , Wilhelm , Heudorf, & Kolossa-Gehring, Update of the reference and HBM values derived by the German Human Biomonitoring Commission, 2011). The values derived for women of reproductive age are recommended for other groups of adults.

A guidance value for Hg in hair (2.3 µg/g dry weight) was defined by the Joint Food and Agriculture Organization of the United Nations and WHO (FAO/WHO) Expert Committee on Food Additives (JECFA), in order to protect foetus from neurotoxic effects. It is based on the provisional tolerable weekly intake (PTWI) limit of 1.6 µg/kg bw/week for MeHg and takes into in consideration the potential benefit of nutrients in fish (i.e., omega-3 fatty acids) against the MeHg toxicity (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2006).

The US EPA set a stricter RfD for chronic oral exposure to MeHg of 0.1 µg/kg bw/day for developmental neuropsychological impairment, which corresponds to 1 µg/g total Hg in hair for children and women in reproductive age (National Research Council, Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology, 2000), (Ruggieri, Majorani, Domanico, & Alimonti, 2017), but more recent calculations with data on developmental neurotoxicity at background exposure levels, resulted in the much lower biological limit in hair of 0.58 µg/g (Ruggieri, Majorani, Domanico, & Alimonti, 2017). Using the RfD value and assuming a ratio of MeHg in infant cord blood to maternal blood 1.7 : 1.1 (e.g., 70% higher in cord than maternal blood), a maternal total Hg blood safe-concentration was set at 3.5 µg/L and in cord blood at 5.8 µg/L (National Research Council, Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology, 2000), (Ruggieri, Majorani, Domanico, & Alimonti, 2017).

1.1.2.5 Occupational population

The following recommendations are available:

Table 1-6: Recommended Biological Limit Values (BLV) for occupational exposure

Organisation	Biological Limit Value (BLV)	Ref.
The Scientific Committee on Occupational Exposure Limits (SCOEL), European Commission, Employment, Social Affairs & Inclusion	Blood: 10 µg Hg/l Urine: 30 µg Hg/g creatinine	(The Scientific Committee on Occupational Exposure Limits (SCOEL), 2007)
Finland/FIOH	BAL Metallic mercury and inorganic mercury: Urine: 140 nmol/L (28 µg/L) BAL inorganic mercury: Blood: 50 nmol/L (10 µg/L)	(INRS) (INRS)
Germany/ Deutsche Forschungsgemeinschaft (DFG)	BAT Value Mercury and inorganic compounds: Urine: 30 µg/L or 25 µg/g creat.	(INRS), (Schaller, 2003), (Deutsche Forschungsgemeinschaft (DFG), Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, 2017), (Deutsche Forschungsgemeinschaft, 2020)
France/INRS	Organic mercury: Maintain blood methylmercury (for occupational exposure) below 100 µg/L	(INRS)
UK/HSL	Biological Biomonitoring Guidance Value (BMGV) for inorganic mercury Urine: 20 µmol /mol creat. (conversion: 1µmol/mol = 1.17µg/g)	(HSL)
USA/ ACGIH	BEI Inorganic mercury: Urine: 20 µg/g creat.	(INRS)
Spain	VLB: Elemental mercury and inorganic compounds (2013) Total inorganic mercury in urine: 30 µg/ g creatinine Total inorganic mercury in blood: 10 µg/l	(Instituto Nacional de Seguridad y Salud en el Trabajo, 2018)

1.1.3 Policy relevance

1.1.3.1 European Policies

The European Commission adopted in 2005 the Community Strategy Concerning Mercury (European Commission, 2005), which includes a comprehensive plan to address mercury use and pollution and has resulted in the enhancement of Union law on mercury, including restrictions on the inclusion of mercury or mercury compounds in products, ban of exports of mercury from the EU and inclusion of provisions on mercury emissions in EU legislation to protect people against exposure. European legislations concerning mercury are described below.

1.1.3.2 Food safety

Limits on the mercury content of fish for human consumption for protecting human health are defined in *European Regulation (EC) No 1881/2006* (European Commission, 2006) and amended on Regulation No 629/2008 (European Commission, 2008). The maximum safe limit for most fish species for human consumption is currently 0.5 mg/kg wet body weight and for some predatory

species such as swordfish and tuna, it is 1 mg/kg wet body weight. *Directive 2002/32/EC* sets limits in animal feedingstuff (European Commission, 2002) and *Regulation (EC) No 333/207* lays down sampling methods and methods of analysis for the official control of the levels of mercury and other restricted substances in foodstuffs (European Commisssion, 2007).

The European Food Safety Authority (EFSA) and national food safety authorities provide advice on fish consumption in an attempt to minimise mercury intake. According to EFSA's scientific opinion from 2015 (European Food Safety Authority (EFSA), 2015), limiting consumption of fish species with a high methylmercury content is the most effective way to achieve the health benefits of fish whilst minimising the risks posed by excessive exposure to methylmercury.

EFSA recommended that individual Member States, particularly those where fish/seafood species with a high mercury content – such as swordfish, pike, tuna and hake – are consumed regularly, consider their national patterns of fish consumption and assess the risk of different population groups exceeding safe levels of methylmercury while obtaining the health benefits of fish. Earlier EFSA scientific opinions (European Food Safety Authority (EFSA), 2014), (European Food Safety Authority (EFSA), 2012), (European Food Safety Authority (EFSA), 2004) looked respectively at the risks from mercury and methylmercury in food, and the health benefits of fish/seafood.

The first opinion established a TWI for methylmercury of 1.3 micrograms per kg of body weight; the second recommended weekly intakes of fish of between 1-2 servings and 3-4 servings in order to realise health benefits such as improved neurodevelopment in children and reduced risk of coronary heart disease in adults respectively, as was already proved in the DEMOCOPHES project (Castaño, et al., 2015).

In September 2018, the Standing Committee on Plants, Animals, Food and Feed of the European Commission, reported that for the time being, the review of the maximum levels (MLs) for mercury in fish will be discontinued. However, the Commission stressed the importance of consumption advice related to mercury in fish and encouraged Member States to:

- develop specific national consumption advice related to fish consumption, in order to fully achieve the beneficial effects of fish consumption, whilst limiting the risks of mercury toxicity. When developing this consumption advice, Member Sates shall especially include the frequency of fish consumption and the fish species consumed;
- communicate the specific national consumption advice to the consumers as well as to relevant health care workers, working with the consumer groups most at risk.

It further stated that possible data on the effectiveness of consumption advice can be sent to the Commission (European Commission Standing Committee on Plants, 2018).

Several Member States do not have national guidelines for fish/seafood consumption. Some Member States provide food safety advice on fish consumption by pregnant women and young children. Existing national guidelines exhibit great variation in their content, complexity and presentation style. According to a recent review, existing guidelines, are largely based on the mercury content of fish and far less consideration is given to the beneficial effects of nutrients provided by fish. Furthermore, the complexity of the guidelines may lead to pregnant women reducing or eliminating their fish intake, which can have negative consequences on the offspring (Taylor, Emmett, Emond, & Golding, 2018).

Two systematic literature reviews investigated the relationship between seafood consumption during pregnancy and childhood and neurocognitive development. They concluded that there is moderate and consistent evidence indicating that consumption of a wide range of amount amounts and types of commercially available seafood during pregnancy is associated with improved neurocognitive development of offspring as compared to eating no seafood. Although the data

were insufficient for a conclusive statement regarding neurocognitive effects from types of seafood or specific species, overall, the benefits to neurocognitive development provided by seafood appear to exceed the potential harms from mercury exposure (Hibbeln, et al., 2019). The effect of consumption of a specific species of fish (Atlantic cod, which generally has low levels of methylmercury contamination) on mercury exposure of pregnant women was investigated in a randomised controlled trial in Norway. The results showed that intervening to achieve 400g of cod fillets per week for 16 weeks, slightly increased the total hair mercury in the intervention group, but did not lead to an increase in the number of subjects exceeding the US EPA reference dose (Næss, et al., 2020).

1.1.3.3 Chemicals

Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) restricts specific uses of mercury under Annex XVII and was amended by *Commission Regulation (EC) No 552/2009* to also restrict mercury in measuring devices intended for use by the general public. Annex XVII was further amended by *Commission Regulation (EC) No 847/2012* to restrict mercury-containing measuring devices intended for industrial and professional uses. *Commission Regulation (EU) No. 848/2012* prohibited the manufacture, use and placement on the market of five phenylmercury compounds from 10 October 2017. To date, mercury has three active registrations under REACH (European Chemicals Agency, ECHA).

Mercury has been assigned a European Union harmonised classification and labelling according to *Regulation (EC) No 1272/2008* of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (CLP) (European Chemicals Authority (ECHA), n.d.) (see §1.1.1). Mercury and its compounds are included in the “Public Activities Coordination Tool” (PACT) list, which provides up-to-date-information on the activities planned, ongoing or completed by ECHA and or Member States Competent Authorities in the frame of the REACH and CLP regulations (European Chemicals Authority (ECHA), n.d.). Mercury is subject to the “Prior Informed Consent regulation” (PIC, *Regulation (EU) 649/2012*) and to export notification procedure (European Commission, 2012).

1.1.3.4 Environment

Regulation (EU) 2017/852 transposes in the European Union the obligations under the Minamata Convention on Mercury (see §1.1.3.7). It covers the full life cycle of mercury and complements existing EU environmental law on mercury and repeals regulation (EC) No 1102/2008 (European Commission, 2017).

It prohibits the export of mercury and mercury compounds, and the manufacture, export and import of a large range of mercury-added products, restricts all uses of mercury catalysts and large electrodes in industrial processes and future new uses of mercury in industry and in products and requires that all mercury waste is safely taken out of the economic sphere, stabilised in a less toxic form and stored permanently in environmentally sound conditions.

It also sets restrictions on the use of dental amalgam, which is the last large use of mercury in the EU, and sets out a process to assess the feasibility of a complete phase out of the use of mercury in dentistry. As from 1/7/2018, the use of dental amalgam is prohibited for dental treatment of (i) deciduous teeth, (ii) of children under 15 years and (iii) of pregnant or breastfeeding women, unless deemed strictly necessary by the dental practitioner on the ground of specific medical needs of the patient. By 1/7/2019, each Member State must set out and publish on the Internet a national plan on measures to phase down the use of dental amalgam. As from 1/1/2019, dental practitioners are no longer allowed to use dental amalgam in bulk, but only in pre-dosed encapsulated form and all dental facilities using amalgam and/or removing dental amalgam fillings must be equipped with amalgam separators ensuring the retention and collection of amalgam

particles with a view to preventing their release into wastewater systems. Dental practitioners must ensure that their amalgam waste is handled and collected by authorised waste management establishments or undertakings (no direct or indirect release into the environment).

The Commission shall report by 30/6/2020 on the feasibility of a phase out of the use of dental amalgam in the long term, and preferably by 2030, and present concomitantly, if deemed appropriate, a legislative proposal.

The EU Water Framework Directive ("WFD", *Directive 2000/60/EC*) requires EU Member States to ensure that water bodies achieve good chemical and ecological status. Directive 2013/39/EU sets environmental quality standards for mercury in surface waters and fish to protect higher level predators from secondary poisoning through bioaccumulation. The Groundwater *Directive 2006/118/EC*, the Environmental Quality Standards *Directive 2008/105/EC* and the Dangerous substances *Directive 2006/11/EC* complement the overall framework for integrated management. In particular *Decision 2455/2001/EC* (which forms Annex X of the Water Framework Directive) establishes the list of priority substances and priority hazardous substances for which measures must be adopted. *Directive 2006/118/EC* also complements the provisions preventing or limiting inputs of pollutants into groundwater already contained in the WFD. According to the European Environment Agency (European Environment Agency , 2018), ~41% of surface water bodies in the EU exceed the mercury concentration for protecting fish-eating birds and mammals.

Directive 2010/74/EU lays down rules on integrated prevention and control of pollution arising from industrial activities and rules designed to prevent or, where that is not practicable, to reduce emissions into air, water and land and to prevent the generation of waste, in order to achieve a high level of protection of the environment taken as a whole. This includes mercury and its compounds, expressed as mercury (Hg).

The Waste Incineration *Directive 2000/76/EC* aims to prevent or to limit pollution from the incineration and co-incineration of waste requiring operators of plants with a nominal capacity of 2 tonnes or more per hour to provide the competent authority with an annual report including emissions into air and water, but there is no specific requirement for an emission inventory. Member States provide reports to the Commission on implementation progress based on questionnaire sent by the Commission to Member States every three years. Periodic measurement is required but no obligation for an annual inventory is specified.

1.1.3.5 Consumer products

Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products prohibits mercury in cosmetic products (Annex II). Limited exemptions for mercury compounds used as preservatives in cosmetics are provided in Annex V.

The Restriction of Hazardous Substances *Directive 2002/95/EC* bans the use of mercury in Electrical and electronic equipment.

Directive 2008/12/EC in conjunction with *Directive 2006/66/EC* restricts mercury in batteries and accumulators.

1.1.3.6 Occupational health and safety

Chemical Agents *Directive 98/24/EC* lays down minimum requirements for the protection of workers from risks to their safety and health arising, or likely to arise, from the effects of chemical agents that are present at the workplace or as a result of any work activity involving chemical agents. *Directive 2009/161/EU26* established a third list of indicative occupational exposure limit values (IOELVs), which includes an IOELV for mercury and divalent inorganic mercury compounds for the protection of workers who may be exposed to mercury. Member States may have regulated the exposure limit value for alkyl compounds of mercury (e.g. Spain, 0.01 mg/m^3).

1.1.3.7 Global Policy

The Minamata Convention on Mercury

The *Minamata Convention on Mercury* is a global treaty, effective as of 16 August 2017, which aims to protect human health and the environment from anthropogenic emissions and releases of mercury and mercury compounds. It has been ratified by 99 parties, including the European Union. The obligations under the Convention are transposed in the EU by Regulation (EU) 2017/852 on mercury.

Some issues covered by the Convention, which relate to the scope of HBM4EU, are:

- Capacity-building, technical assistance and technology transfer
- It calls for cooperation between Parties for timely and appropriate capacity-building and technical assistance to developing country Parties.
- Health aspects
- It encourages Parties to promote the development and implementation of strategies and programmes to identify and protect populations at risk, to promote appropriate health-care services for prevention, treatment and care for populations affected by the exposure to mercury or mercury compounds and to establish and strengthen institutional and health professional capacities.
- Information exchange
- It calls for exchange of information concerning mercury and mercury compounds, including toxicological and safety information, and of epidemiological information concerning health impacts associated with exposure to mercury and mercury compounds, in close cooperation with the World Health Organization and other relevant organisations, as appropriate.
- Public information, awareness and education
- It calls for the provision to the public of available information, awareness and education about the effects of exposure to mercury/mercury compounds on human health/environment, about alternatives and about results from research & monitoring activities

Research, development and monitoring
It calls for Parties to cooperate to develop harmonised methodologies and to use them within their capacity, for modelling and geographically representative monitoring of levels of mercury and mercury compounds in vulnerable populations, for collaboration in the collection and exchange of relevant and appropriate samples and for assessments of the impact of mercury and mercury compounds on human health and the environment.

- Reporting
- Each Party shall report to the Conference of the Parties (COP) on the measures it has taken to implement the provisions of the Convention, on the effectiveness of such measures and of possible challenges in meeting the obligations of the Convention.
- Effectiveness evaluation
- The effectiveness of the Convention will be evaluated by COP within six years from the date of entry into force of the Convention and periodically thereafter, using comparable monitoring data on the presence and movement of mercury and mercury compounds in the environment as well as trends in levels of mercury and mercury compounds observed in biotic media and vulnerable populations.

1.1.4 Technical aspects

1.1.4.1 Availability of biomarkers and methods

Establishing a quantitative dose-response relationship is particularly challenging for mercury because it can exist in different forms (elemental mercury, mono- and divalent mercury and organic mercury), each having different kinetic properties (Ha, et al., 2017).

Mercury concentrations can be measured in different human matrices: hair, urine, blood, nails, breast milk, cord tissues, cord blood and the placenta. The choice of matrix depends on the time of sampling after exposure, if chronic or acute exposure will be investigated and the type of mercury compounds, which will be assessed (Miklavčič Višnjevec, Kocman, & Horvat, Human mercury exposure and effects in Europe, 2014). Other “unconventional” matrices may be used, depending on the study objectives and design.

- **Hair**: is a non-invasive matrix that is easy to sample and analyse and is very useful for monitoring long-term methylmercury exposure in the general population. Methylmercury analysis in other matrices requires complicated, time-consuming and expensive methods and so has very limited use in large Human Biomonitoring surveys. Both inorganic and organic forms of mercury bind to the hair structure, but there is a strong preference for MeHg. Methylmercury is incorporated into the follicle during hair formation. Once transported by the blood into follicular cells, it binds to cysteines of keratin proteins and it constitutes approximately 80% or more of the total mercury in hair for fish-consuming populations (National Research Council, Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology, 2000). The concentration of total mercury in scalp hair is proportional to the simultaneous concentration in blood, but in the case of exposure to methylmercury, it is ~250 times higher. Hair-to-blood concentration ratios of methylmercury can be highly variable among individuals. The error in blood Hg estimated from hair Hg using the WHO recommended hair-to-blood ratio of 250 was evaluated by Liberda et al. (2014) and it ranged -25% to +24%, with systematic underestimation for females and overestimation for males (Liberda, et al., 2014). Assuming a growth rate of 1.1 cm/month for scalp hair, an indication of temporal exposure is provided, but the uncertainty associated with this assumption must be considered (World Health Organization (WHO), 2010), (Sakamoto, et al., 2004). Hair mercury concentrations can be affected by several factors, including hair colour and variable growth rates, which can limit its usefulness as an indicator of Hg concentrations in the body (Miklavčič Višnjevec, Kocman, & Horvat, Human mercury exposure and effects in Europe, 2014). Quality assurance and control systems are required for accurate results (e.g. possible external contamination) (Grandjean, Jørgensen, & Weihe, Validity of mercury exposure biomarkers, 2002). QA/QC measures were already defined and tested in DEMOCOPHES with good results. These measures include sampling SOPs, training (including a video for hair sampling (ISCIII)) and ICI/EQUAS for mercury analysis in hair (Esteban, et al., 2015).

  Recently, the World Health Organization published standard operating procedures for the assessment of mercury in hair, cord blood and urine, with emphasis on quality control as a prerequisite for getting reliable results. This report also provides information on alternative methods that can be used for analysis of mercury (World Health Organization, 2018).
- **Blood**: in children and adults, can be used to assess short-term (~1 week) exposure. It involves invasive sampling and storage / transportation require attention. Speciation analysis is preferable for a comprehensive assessment of the type and magnitude of the exposure. Recently, dried blood spot (DBS) samples were demonstrated to be a useful matrix for assessment of mercury and methylmercury exposure. This development may be

especially useful for the assessment of the exposure of new-borns (Basu, et al., 2017), (Santa-Rios, Barst, & Basu, 2020).

- **Urine**: The predominant form in urine is inorganic mercury and so total urinary mercury reflects the internal dose of the inorganic form. Urine is a suitable biomarker of long-term low-exposure to both inorganic and elemental Hg, because it contains Hg which accumulated in the renal tissue (i.e., kidney is the target organ) during a chronic exposure (Ruggieri, Majorani, Domanico, & Alimonti, 2017), (Miklavčič Višnjevec, Kocman, & Horvat, Human mercury exposure and effects in Europe, 2014), (INRS).
- **Cord-blood**: is the most desirable biomarker for estimating pre-natal exposure. Total Hg in cord blood estimates foetal exposure over a longer period than that provided by maternal blood and provides a better indication of the risk for developmental neurotoxicity. However, it does not provide information on exposure variability during gestation and its storage and transportation are more complicated (Ruggieri, Majorani, Domanico, & Alimonti, 2017).
- **Umbilical cord tissue**: is a useful matrix for assessment of foetal middle-term exposure, sampling is simple and it is non-invasive. Total Hg represents exposure during the third trimester, but doesn't provide information on sensitive short-term variation. A dry weight-based total Hg concentration is more accurate, but more labor-intensive (Ruggieri, Majorani, Domanico, & Alimonti, 2017).
- **Nails**: Maternal mercury concentrations in nails at parturition have also been shown to have a strong correlation with mercury concentration in cord blood and can be used as biomarker (Ha, et al., 2017). Generally, this matrix assesses long-term (chronic) exposure. Sampling is simple, non-invasive and easy to preserve. Quality assurance/quality control systems are required for accurate results. Fingernails are sometimes contaminated (Ruggieri, Majorani, Domanico, & Alimonti, 2017).
- **Breast milk**: is useful for investigation of long-term exposure. Total Hg is suitable for estimating maternal exposure and for predicting the potential exposure for breast-feeding in infants (Ruggieri, Majorani, Domanico, & Alimonti, 2017).
- **Cerebrospinal fluid / Brain**: The use of such "unconventional" matrices, in combination with speciation analysis, can be useful for the investigation of the neurotoxic effects on the target system / organs. So far, there have been only few applications of this approach, due to limited access to cerebrospinal fluid and brain samples, analytical challenges caused by matrix interferences, low concentrations and limited stability of many trace element species of interest. Modern, powerful analytical techniques, which provide advanced validity and chemical information are necessary (Michalke, Willkommen, Drobyshev, & Solovyev, 2018), (Michalke, Halbach, & Nischwitz, JEM Spotlight: Metal speciation related to neurotoxicity in humans, 2009).
- **Meconium.** The earliest stool of new-borns (meconium), which is composed of materials ingested in utero, has been demonstrated to be a suitable matrix for prenatal mercury and methylmercury exposure assessment (Trdin, et al., 2019).

The determination of mercury in biological specimens requires sensitive analytical methods, performed under good quality control conditions. The DEMOCOPHES experience proved that is possible to study the exposure to mercury in a harmonised way if common Standard Operating Procedures (SOPs) are applied and under a Quality Assurance / Quality Control (QA/QC) scheme (Esteban, et al., 2015). Various methods exist that differ in sample preparation technique and/or the detections system. Determination of total Hg concentration can be done by (1) acid digestion followed by cold vapour atomic absorption technique (CV AAS), cold vapour atomic fluorescence (CV AFS) and/or ICP MS detection; (2) thermal combustion of a sample, gold amalgamation and AAS detection.

Speciation of mercury requires complex and lengthily analytical procedures and expensive reagents and equipment, which are not routinely available in analytical laboratories. Speciation analysis is necessary to differentiate between inorganic/elemental and methyl mercury exposure. It may be possible to obtain information without the need of speciation, by using a combination of different matrices, the choice of which should depend on the type of the hypothesised exposure.

1.1.4.2 Need for new approaches

Despite the plethora of data on exposure to mercury, the results are fragmented because different studies use different approaches, which limit their usefulness. It is important to harmonise the approaches used to investigate different study populations. The DEMO/COPHES (Esteban, et al., 2015) and the pilot UNEP/WHO project on mercury biomonitoring (World Health Organization, 2018) have laid the basis for harmonisation of exposure biomarkers, which needs to be further advanced (Ha, et al., 2017). HBM4EU provides a golden opportunity to improve on this basis, to test it in additional countries and to use to for answering specific policy questions.

The selection of best-suited matrices and biomarkers of exposure is crucial. For example, if hypotheses on the effects of MeHg exposure on child development will be tested, the best suited matrices and biomarkers of foetal exposure to MeHg should be selected.

The development of simple, robust and cost- effective methods for measuring total and organic mercury simultaneously is very important.

Development of suitable dietary advice for fish consumption for vulnerable groups, such as pregnant women and young children, is a major public health objective. At present, some countries have national guidelines, while many others do not. There is significant variability in existing guidelines, how they are developed and how they are communicated to stakeholders (Taylor, Emmett, Emond, & Golding, 2018). The formulation of dietary advice needs to be based on a benefit/risk analysis, considering the nutritional benefits of fish as a whole food vs. the risk of exposure to mercury and other contaminants. Further work is necessary to better understand the factors coming into play in this analysis (e.g. standardisation of outcome measures in cohorts involving assessment of exposure to mercury, the contribution of nutrients / mercury exposure of different fish species consumed, their origin and method of preparation, randomised controlled trials to better support causal interferences, genetic variants etc) (Hibbeln, et al., 2019).

Markers of susceptibility need to be validated (Karagas, et al., 2012). These are important for understanding the human health effects of low-level MeHg exposure as a basis for future research efforts, risk assessment, and exposure remediation policies worldwide (Karagas, et al., 2012). Hg speciation in biological matrices, particularly blood, would provide characterisation of species-specific exposure at levels relevant for European population. Individuals' inherited factors seem to play a role in determining toxic effects of environmental contaminants, including those of mercury. In recent years interest in gene-environment interaction has grown substantially, because of the progress in laboratory techniques, improved understanding of genetics and realisation of complex mechanisms between genetics and environment (Basu, Goodrich, & Head, Ecogenetics of mercury: from genetic polymorphisms and epigenetics to risk assessment and decision-making, 2014), (Andreoli & Sprovieri, 2017). Identification and validation of novel biomarkers of susceptibility is therefore an important part in investigation of exposure-health relationships.

Research on the elimination and enhancement of excretion of mercury is also needed and is important for risk management options.

1.1.5 Societal concern

Societal concern regarding mercury is very high.

Mercury is considered by WHO as one of the top ten chemicals or groups of chemicals of major public health concern (World Health Organization (WHO), n.d.).

European citizens consider environmental pollution as the top risk most likely to affect them personally, according to Special Eurobarometer 238 on risk issues. Although people do not differentiate greatly between the various types of risks, they are more likely to worry about risks caused by external factors over which they have no control. Mercury was reported as one of the top risks they are concerned about. In almost all Member States, at least one citizen in two is worried about pollutants like mercury or dioxins (European Commission, 2006). According to Special Eurobarometer 354 on food-related risks, one third of Europeans are very worried about mercury in fish (European Commission, 2010). This concern is validated by the fact that in 2017, mercury in fish was the second most notified hazard in RASFF for exceedance of the maximum limit set in EU legislation (European Commission, 2018).

Due to its classification as a substance toxic to reproduction ("CRM" according to Annex VI of Regulation 1272/2008) (Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures), mercury is included in the "SIN (Substitute It Now!) List", a comprehensive database of chemicals likely to be restricted or banned in the EU developed by the non-governmental organisation "International Chemical Secretariat" (ChemSec).

Mercury ranks 3rd and methylmercury 116th out of 275, on the "Substance Priority List" (SPL) prepared biannually by the ATSDR for substances most commonly found at facilities on the National Priorities List (NPL) and which are determined to pose the most significant potential threat to human health due to their known or suspected toxicity and potential for human exposure (US Agency for Toxic Substances and Disease Registry (ATSDR), 2017).

Mercury and its organic compounds are included in the "OSPAR List of Chemicals for Priority Action" of the OSPAR convention for the protection of the marine environment of the North-East Atlantic (OSPAR Convention for the protection of the marine environment of the North-East Atlantic, n.d.).

Several European and global non-governmental organisations recognise mercury pollution as a top priority, which must be addressed. Examples include:

- "Zero Mercury" campaign of the European Environmental Bureau (EEB) (European Environmental Bureau (EEB), n.d.).
- The EEB is the largest network of environmental citizens' organisations in Europe, with around 140 member-organisations in more than 30 countries (including all EU Member States) and representing 30 million individual members and supporters.
- "Mercury-Free" campaign of IPEN (IPEN, n.d.).
- IPEN is a global network of public-interest NGOs, comprising of over 500 participating organisations in more than 100 countries
- "Zero Mercury" campaign of the Zero Mercury Working Group (ZMWG) (Zero Mercury Working Group (ZMWG) , n.d.).
- The Zero Mercury Working Group (ZMWG) is an international coalition of over 95 public-interest environmental and health non-governmental organisations from more than 50 countries.
- "Stay Healthy, Stop Mercury" campaign, of the Health and Environment Alliance (HEAL) (Health and Environment Alliance).
- HEAL is a not-for-profit organisation addressing how the natural and built environments affect health in the European Union (EU).

Mercury and its compounds were voted by stakeholders who participated in the Stakeholder Workshop organised in the frame of HBM4EU in on November 20th 2017 as a “top substance of concern” and ranked in the 4th position. Stakeholders expressed concern regarding exposure from fish consumption (with pregnant women mentioned as an especially vulnerable group) and about the effects of lifelong exposures from multiple pathways. Mercury is a highly regulated substance but there is fragmentation into different pieces of legislation, which are not presently aligned. Stakeholders expressed the need for traceability, coordination, alignment and integration of data and policy. They also advocated that information on exposure levels should be made available and the exposure of the total population and specific exposure groups should be compared. Stakeholders would use the result of HBM4EU for a comparison of reference values for the general population to exposure of workers and for communication to citizens. They stated that within HBM4EU, information should be collected and made available in one single database. They also see a need for interpretation results for the purpose of generating and communicating useable advice for the public in an understandable manner.

1.2 Categorisation of Substances

The proposed category for Mercury is Category A.

The health impact of mercury is well documented and the European Commission introduced policies to manage the risk, e.g. restriction of use in industry, regulatory limit values in food. Data on total mercury exposure from different countries across Europe are available. However, several countries lack recent data or data on vulnerable populations, such as children. Also, in most instances, sampling is not representative of the population.

The proposed category for Methylmercury is Category B.

The health impact of methylmercury is well documented. Data on methylmercury exposure in Europe is not as common as for total mercury. Since hair mercury is mostly in the form of methylmercury, results on the concentration of mercury in hair provide a good indication of exposure to methylmercury. Representative data on the geographic spread of exposure and association with specific sources of exposure (e.g. associations with specific species of fish) are missing in Europe.

Some recommendations have been proposed by Food Safety Authorities in order to reduce methylmercury exposure through seafood in Europe, but a harmonised European global policy on this substance is lacking.

These recommendations have been based on studies of populations with unique diets. Further investigation is needed to understand the risks associated with typical diets in Europe.

The effects of chronic exposure to low levels and the factors of susceptibility have not been adequately investigated.

Table 1-7: 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	Abbrev./Acronym	Systematic name	CAS No.	Regulation
A	Hg	Mercury	7439-97-6	See §0*
B	MeHg, CH_3-Hg	Methylmercury	22967-92-6	See §0*

* *Section §0 provides an overview of relevant policies. Most policies refer to "mercury" or "mercury and its compounds" or "total mercury" and do not discriminate among the different forms of mercury.*

1.3 Policy-related questions

Section 15.1 presents an overview of current EU policies related to mercury, including the Minamata Convention, a global treaty to address mercury pollution, which was ratified by the EU.

The following policy-related questions relate to commitments under this frame:

1. How effective are policy actions to reduce human exposure to mercury in Europe? (including the EU's Strategy on Mercury and the Minamata Convention, which was ratified by the EU and Member States)?
2. How can harmonised, validated and comparable information be collected and transferred to support and evaluate current policies?
3. What biomonitoring and exposure data on mercury (and its species), relevant to the European population, are currently available and what new data are needed to address policy-related questions?
4. What is the geographic spread of the current exposure and how does it relate to different exposure sources (environmental; contaminated sites; dental amalgams; dietary, including different species of sea-food)? Ideally, this should capture the exposure of highly exposed populations (e.g. high seafood consumers with distinction of populations consuming predator fish from those with low/no consumption of such fish, such as Southern & Northern Europeans, European arctic populations), but also of low-exposure populations for comparison.
5. Which populations remain vulnerable to health impacts from mercury exposure and how can they be protected?
6. How can the public be informed and how can public awareness and education be raised regarding the effects of mercury on health and the environment and about management options?

   What advice should be given regarding dietary recommendations to vulnerable Europeans (e.g. pregnant women, infants, high sea-food consumers) and other stakeholders (e.g. health practitioners, policy makers) to reduce exposure to mercury while in keeping with nutritional requirements and cultural dietary preferences? Ideally, this should consider the different types of foodstuff (e.g. types of seafood) consumed in different parts of the EU, the toxicity and occurrence of the different mercury species in different foodstuff and the positive effects of n-3 long-chain polyunsaturated fatty acids in fish and of micro nutrients (e.g. selenium) in the diet.

   Related to this, how can HBM4EU results support policy decisions at EFSA and ECHA?

7. At what level of exposure to different mercury species and to total mercury are health effects likely to occur? Current guidance values were based studies of the Faroese people, who have a diet that is unique and does not relate to food consumption patterns in the EU. This important issue has not been given proper attention to date.
8. How does exposure relate to the manifestation of adverse health effects?

   What are possible health effects resulting from chronic low exposure to mercury and its organic compounds (such as from food consumption and dental amalgams)? This type of exposure is the most relevant for Europeans and can be addressed by speciation analysis of biobanked samples from existing cohorts and associations with adverse health effects.

   What factors make people more susceptible to the development of health effects due to mercury exposure?

1.4 Research Activities to be undertaken

Table 1-8: Listing of research activities to be carried out to answer the policy questions

Policy question (PQ)	Substance	Available knowledge	Knowledge gaps and activities needed
PQ1. How effective are policy actions to reduce human exposure to mercury in Europe? (including the EU's Strategy on Mercury and the Minamata Convention, which was ratified by the EU and Member States)?	Mercury and methylmercury	See chapter 0	**WP 2,4,5,6,7,8,9,10,11,12,13,14 - Overaching activity**: Support the establishment of permanent European mercury biomonitoring as long-term support of global mercury policies. Emphasis on transfer of knowledge to enable new, quality-assured, comparable data and their interpretation in countries which ratified the Minamata Convention through the established procedures at EU level. This is also relevant to PQs 2,3,4. Development of tools, collection of relevant data to assess the exposure of Europeans to mercury and methylmercury, harmonised analysis to assess exposure and its determinants and to facilitate assessment of time trends, making data and results available to policy makers and other stakeholders. **WP 2,7,8,9,10,12**: Implementation of an anligned intervention study aiming at controlling prenatal exposure to mercury in high fish-consuming countries (proposigtion under evaluation by the Management Board). Also relevant to PQ2,4,5.
PQ2. How can harmonised, validated and comparable information be collected and transferred to support and evaluate current policies?	Mercury and methylmercury	See chapters 1.1.4 and 1.1.2	**WP7**: Generation and distribution of survey via National Hubs, aiming to collect information on recent (past 5 years), ongoing and planned studies, which include mercury biomonitoring. Generation of tools for harmonised and quality-assured recruitment, sampling, sample storage and transfer, questionnaires, communication materials. **WP9**: Development and update (as information becomes available), of inventories and evaluations of the best exposure biomarkers, matrices and analytical methods relevant to mercury biomonitoring. Also relevant to PQs 1,3,4,5. Development and update (as information becomes available), of the inventories of candidate laboratories for the analysis of biological samples for mercury biomonitoring. Also relevant to PQ3. **WP10**: Development of guidelines and tools for harmonised data transfer, storage and statistical analysis. Making data accessible to policy managers and other stakeholders on IPChem to the extent possible. **WP11**: Development of guidelines to help standardisation of measurements and comparability of collected health data relevant to mercury, in future studies. Also relevant to PQ6.

Policy question (PQ)	Substance	Available knowledge	Knowledge gaps and activities needed
PQ3. What biomonitoring and exposure data on mercury (and its species), relevant to the European population, are currently available and what new data are needed to address policy-related questions?	Mercury and methylmercury	See chapter 15.1.2.3	**WP7 (and as relevant, WPs 8, 10,12,13,14)** Identification and systematic collection of relevant recent or ongoing European studies, identification of knowledge gaps, prioritisation of research needs. Review and analysis of existing epidemiological and toxicological data on mercury and its species as needed to address policy questions.
PQ4. What is the geographic spread of the current exposure and how does it relate to different exposure sources (environmental; contaminated sites; dental amalgams; dietary, including different species of sea-food)? Ideally, this should capture the exposure of highly exposed populations (e.g. high seafood consumers with distinction of populations consuming predator fish from those with low/no consumption of such fish, such as Southern & Northern Europeans, European arctic populations), but also of low-exposure populations for comparison. Which populations remain vulnerable to health impacts from mercury exposure and how can they be protected?	Mercury and methylmercury	See chapters 0, 1.1.5, 15.1.2.2 and 15.1.2.3	**WP10 (other WPs e.g. 5, 7, 8, 12 and possibly others, may also be involved as relevant)** Collection, integration and making available existing HBM data on mercury into IPChem. Also relevant to PQ1,2,3. Analysis to the extent possible of existing & available HBM data to assess (a) baseline exposure of Europeans to organic / total mercury and the associated risk and to facilitate the assessment of temporal trends with regards to the effectiveness of policies, (b) determinants of exposure, including geographic variations and their causes (e.g. environmental exposures, diet), (c) generation of European reference values for mercury exposure, (d) identification of groups at risk of exceeding health-based guidance values (e.g. by age, gender, highly exposed, hot-spots in Europe). This is a core activity. Also relevant to PQs1,2,3. **WP12:** Optimise the integrated exposure modelling platform by updating thof the exposure model parameterisatoin for mercury using available data; Characterisation of the toxicokinetic behavior differences in internal dose of mercury species.; identification of internal exposure to different mercury species and to tal mercury for various age groups; definition of optimised sampling schemes.

Policy question (PQ)	Substance	Available knowledge	Knowledge gaps and activities needed
PQ5. How can the public be informed and how can public awareness and education be raised regarding the effects of mercury on health and the environment and about management options? What advice should be given regarding dietary recommendations to vulnerable Europeans (e.g. pregnant women, infants, high sea-food consumers) and other stakeholders (e.g. health practitioners, policy makers) to reduce exposure to mercury while in keeping with nutritional requirements and cultural dietary preferences? Ideally, this should consider the different types of foodstuff (e.g. types of seafood) consumed in different parts of the EU, the toxicity and occurrence of the different mercury species in different foodstuff and the positive effects of n-3 long-chain polyunsaturated fatty acids in fish and of micro nutrients (e.g. selenium) in the diet. Related to this, how can HBM4EU results support policy decisions at EFSA and ECHA?	Mercury and methylmercury	See chapters 15.1.1.2, 1.1.3.2, 1.1.5 and 15.1.3.3	**WP2 and as relevant WP4,5,67,8,9,10,11,12,13,14** Collection, curation and provision of information relevant to the mercury chemical group (CG) as it becomes available (e.g. results, targeted communication products – including dietary advice to the extent feasible & relevant, common methods, protocols), to targeted audiences (e.g. public, health practitioners, scientists, policy makers) via the Knowledge Hub. **WP4**: Mapping of the information needs of external bodies related to mercury (e.g. understanding the perspectives of the public through focus groups). **WP5**: Reporting on progress achieved by HBM4EU for the mercury CG. Establishment of HBM-based guidance values for mercury for the general population provided that sufficient epidemiological / toxicological / toxicokintic data re available. If not, provide recommendations for data needed to fill the gap. Also relevant to PQ1,4. Development of a proposal on how to integrate HBM in risk assessment procedures and use of available mercury HBM data for risk assessment. Also relevant to PQ1,4. Based on the availability of aggregated data, construction of HBM-based indicators for mercury and development of associated information to facilitate their interpretation by stakeholders, including policy makers. Also relevant to PQ1,4. **WP11**: Development of scoping reviews for health professionals, on the association of environmental exposures to manifestation of specific non-communicables diseases. **WP13 and as relevant WP5**: Through a critical review of the literature published since EFSA's 2012 risk assessment, determine if recent findings on the health effects of mercury are consistent with the previously assessed evidence.
PQ6. At what level of exposure to different mercury species and to total mercury are health effects likely to occur? Current guidance values were based studies of the Faroese people, who have a diet that is unique and does not relate to food consumption patterns in the EU. This important issue has not been given proper attention to date.	Mercury and methylmercury	See sections § 1.1.2 (1.1.2.4), 0 (1.1.3.7)	**WP11**: Development of guidelines to help standardisation of measurements and comparability of collected health data relevant to mercury, in future studies. Also relevant to PQ1. **WP12**: Depending on data availability on total mercury and/or mercury species, use of exposure modelling to explore the linking of internal exposure to external sources for vulnerable population groups, investigation of substance toxicological behaviour, risk characterisation, support of the evaluation of the effectiveness of existing regulatory frames. This is also relevant to PQs 1,4,5,7

Policy question (PQ)	Substance	Available knowledge	Knowledge gaps and activities needed
PQ7. How does exposure relate to the manifestation of adverse health effects? - What are possible health effects resulting from chronic low exposure to mercury and its organic compounds (such as from food consumption and dental amalgams)? This type of exposure is the most relevant for Europeans and can be addressed by speciation analysis of biobanked samples from existing cohorts and associations with adverse health effects. - What factors make people more susceptible to the development of health effects due to mercury exposure?	Mercury and methylmercury	See chapters 15.1.1, 15.1.2.3 and 1.1.3.7	WP13, 10 Investigate allele frequencies of relevant Single Nucleotide Polymorphisms (SNPs) across Europe and how this might contradict exposure/health found so far, since inherited factors of individuals seem to play a role in determining toxic effects of mercury. Also relevant to PQ6. WP13 Use the available Mediterranean cohort to (a) examine the impact of mercury on neurobehavior while taking into account co-exposure to other neurotoxic contaminants and to beneficial elements and (b) explore relevant genetic polymorphisms. Also relevant to PQ6. Investigation of the causal pathways from exposure to mercury to health outcomes (Adverse Outcome Pathways) Apply automated text mining tools (e.g. AOP help-finder and systems biology approach to explore exposure/health associations and to promote broader use of mechanistic toxicology information and AOP among risk assessors. WP14 Identify the most suitable biomarkers of effect for mercury fthrough a focused literature search of mercury-related human studies and reported health endpoints. Also relevant to PQ2. By integrating all information obtained on effect biomarkers related to HBM4EU priority substances, (a) create maps of the most commonly affected physiological pathways affected (e.g. neurodevelopment), (b) establish a holistic framework for connecting epidemiological and toxicological data (focused on effect biomarkers and AOPs) for utility in a future sustainable European HBM agenda. Also relevant to PQ1, 2.

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