Substance report

June 2022

Mercury

HBM4EU
science and policy
for a healthy future

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

Table of contents

Authors and Acknowledgements

First version (March 2021) compiled by project team at Wood: Dr. Ian Keyte, Neil Patton and Dr. Robert Whiting based on scoping documents produced by the chemical group leader (CGL) and colleagues: Nina Weindel, Kristina Flexman, Caspar Corden. The EEA has since updated this document to reflect the work developed before the conclusion of HBM4EU, with the support of the CGL and other colleagues.

Lead authors

Andromachi Katsonouri (MOH-CY)

Contributors

Tommaso Filippini (University of Modena and Reggio Emilia, Italy), Flavia Ruggieri (Istituto Superiore di Sanità, ISS, Italy), Natasa Janev Holcer (Croatian National Institute of Public Health, Croatia), Marike Kolossa-Gehring, Rosa Lange and Ulrike Fiddicke (UBA, Germany), Susana Pedraza Diaz, Isabel Maya, Marta Esteban Lopez and Argelia Castaño (ISCIII, Spain), Marta Schuhmacher (IISPV, Spain), Milena Horvat (Jožef Stefan Institute, Slovenia), Stephan Böse-O'Reilly (UMIT), Denis Sarigiannis, Spyros Karakitsios (AUTH), Luděk Bláha, Christiana Neophytou (MOH-CY), Janja Snoj Tratnik (JSI), Thorallur Halldorsson (University of Iceland), Marieta Fernandez (University of Granada), Hanna Tolonen (THL), Andrea Springer (UBA), Joana Lobo Vicente, Ian Marnane and Petra Pontier (EEA).

Glossary

Abbreviations	
BLV	Biological Limit Values
C&L	Classification & Labelling
CAS	Chemical Abstracts Service
CLP	The 'Classification, Labelling, Packaging' Regulation Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures.
ECHA	European Chemicals Agency
EEA	European Environment Agency
HBM	Human Biomonitoring
IARC	International Agency for Research on Cancer
LED	Light-emitting diode
OEHHA	Office of Environmental Health Hazard Assessment
REACH	The 'Registration, Evaluation, Authorisation and Restriction of Chemicals' Regulation Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
UN	United Nations
UNEP	United Nations Environment Programme
WHO	World Health Organisation
WPL	Work Package Leader
C&L Classification Names	
Carc	Carcinogenicity
Acute Tox	Acute Toxicity
Repr	Reproductive Toxicity
Muta	Mutagenicity
STOT RE	Specific target organ toxicity - repeated exposure
STOT SE	Specific target organ toxicity- single exposure
Eye Dam/ Irrit.	Eye Damage / Eye Irritation
Resp Sens.	Respiratory Sensitivity
Skin Corr / Irrit.	Skin Corrosion/Irritation
Skin Sens.	Skin Sensitivity
Properties of concern	
R	Toxic to Reproduction
ED	Endocrine Disrupting
SS	Skin sensitising
PBT	Persistent, Bioaccumulative and Toxic

1 Key messages

- Human biomonitoring, completed as part of the HBM4EU-MOM study, has helped to increase our understanding of how we can best reduce prenatal exposure to mercury and prevent lifelong impacts from mercury exposure.
- Results from the HBM4EU-MOM study confirmed that the European pregnant women, whose diet includes specific fish and seafood, remain exposed to mercury and some cases their exposure exceeds EFSA's health-based guidance value. However, fish is an important component of a healthy diet and because the exposure can be controlled through suitable fish consumption, it is very important to communicate fish consumption advice to vulnerable populations.
- The provision of dietary advice through health care providers of vulnerable populations is important and suitable communication tools for these professionals are necessary.
- Long-term institutionalised EU-wide human biomonitoring activities are required to provide regular assessment of the risks posed by pollutants such as mercury, to our health and well-being.
- Based on engagements with citizens in the frame of Eurobarometers and HBM4EU Facebook live events, focus groups and citizen surveys, there is significant public concern in Europe, with regards to the risks posed by mercury in the environment.
- EU-policy in relation to control of mercury use and release to the environment, is well developed. However, because of its persistence in the environment and ongoing global emissions, the risks posed by mercury are unlikely to decrease for many decades. Further policy measures, aimed specifically at reducing human exposure to mercury in Europe, could be beneficial.
- The HBM4EU project has developed a new analytical method using Dry Blood Spots (DBS) in newborns, which can be systematically applied to assess and control Hg exposure.
- The HBM4EU project has developed a framework to provide a comprehensive mechanism to determine the impact of mercury exposure on the European population, including the development of harmonised assessment methods and HBM-based guidance values for mercury for the general population. This frame can be exploited for monitoring time-trends, in support of evaluations of the effectiveness of policy actions are European and global level.

2 Introduction

HBM4EU is a project funded under Horizon 2020 and runs from 2017 until 2022. It generates knowledge to inform about the safe management of chemicals, and hence protect human health in Europe. HBM4EU uses human biomonitoring (HBM) to monitor the actual human exposure to chemicals and resulting health impacts to build upon existing evidence bases and improve chemical risk assessment. HBM4EU compares data from across Europe which allows an understanding of regional differences and can help to identify vulnerable groups in order to inform targeted measures to reduce exposure. The results of the HBM4EU project are aimed at supporting policy development, by providing a key evidence base in the understanding of exposure and impacts to toxic chemicals.

If you would like to read more about the project itself, please visit the HBM4EU website.

2.1 How to use this document

This document provides a summary of the known and suspected adverse human health effects of mercury and describes the main exposure pathways for humans. It also indicates where HBM

could be of value in the development of EU policy, along with the remaining challenges in determining human mercury exposure. This substance report is intended to inform policy makers and relevant stakeholders on the value of HBM to establish the EU population's exposure to mercury.

This document is based largely on the HBM4EU scoping document for mercury, first draft produced in 2019 and updated regularly, as well as the accompanying reports on legislative mapping and policy questions. Where necessary, additional information has been used from the European Chemical Agency (ECHA) documents including the Classification and Labelling (C&L) Inventory, and legislative text for relevant EU policy areas, have also been used for this report.

2.2 Overview of Mercury

Mercury (chemical symbol Hg) is a naturally occurring heavy metal in the earth's crust (abundance in the Earth's crust is 0.03 parts per million/mg per kg) and can exist in three main forms: elemental (metallic), inorganic, and organic. Mercury is ubiquitous in the global environment and its sources of release to the environment can be both natural (e.g. weathering of rock, volcanic eruptions) and anthropogenic (e.g. from industrial/commercial uses and combustion of fossil fuels and waste).

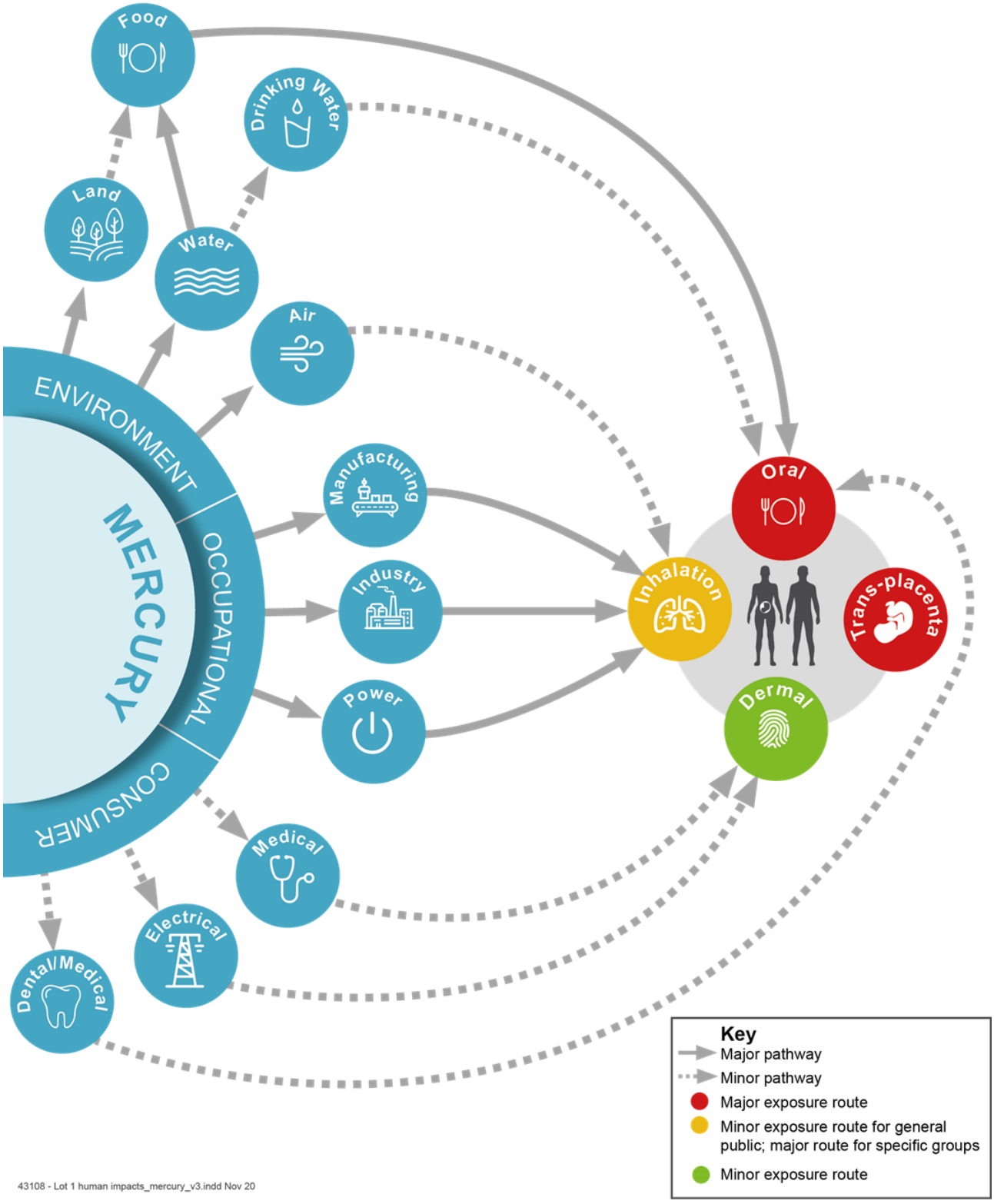
Elemental mercury has been commonly used in electrical equipment (e.g., thermostats and switches) and electrical lamps as well as medical and laboratory equipment (e.g. thermometers) and dental amalgams. Inorganic mercury compounds, such as mercuric oxide, are used in the production of batteries, polyvinylchloride, and pigments. Organic mercury compounds have historically been used in fungicides, antiseptics and disinfectants, but these uses have mostly been discontinued. Ethylmercury (thiomersal) is used in very small amounts in vaccines (as a preservative) and pharmaceuticals. Industrial uses of mercury have included the production of chlorine gas and caustic soda.

Despite extensive EU policy actions to control mercury (see Section 5), the European population is still exposed to legacy mercury and to mercury originating from sources outside the European Union (an estimated 40-80% of total mercury deposition in the EU originates from outside the Union). Mercury emissions to air and water are also still generated within the EU, primarily related to fossil fuel combustion for energy generation and in industrial processes. Therefore, mercury biomonitoring in the frame of HBM4EU is an important cornerstone to support EU and global actions to control mercury and to protect human health.

3 Human exposure to mercury

Human exposure to mercury is outlined in the sections below, broken down into environmental, occupational and consumer exposure routes. An overview of the key sources of exposure (environmental, occupational, and consumer) and exposure pathways (oral, inhalation, and/or dermal) is provided in **Error! Reference source not found.**. Additional explanations of these exposure sources and pathways are provided in Appendix 1.

Figure 1.1 Overview of exposure routes and pathways (from source to exposure) for mercury



3.1 Environmental exposure

Human activities, mainly industrial production processes and combustion of fossil fuel for energy and petroleum chemicals, can result in large quantities of mercury being released to the atmosphere or water.

Globally, the main sources of mercury to the environment are artisanal and small-scale gold mining (38%), stationary combustion of coal (21%), non-ferrous metal production (15%) and cement production (11%) (UNEP, 2019). In Europe emissions of mercury have been primarily associated with coal combustion (EEA, 2019). Emissions of mercury in Europe declined by about 30% between 1990 and 2017, which is attributed chiefly to changes in the industrial sector, fuel switching from coal to gas and renewable energy sources for generating power and heat, and the EU policies that mandate reductions in heavy metal emissions and prohibit its use in various products and processes (see Section 5).

Once released into the environment, mercury undergoes a series of complex transformations between the metallic, inorganic, and organic forms and can cycle between atmosphere, ocean, sediments, soil and living organisms (European Union, 2017).

The conversion of mercury into methylmercury in water by microorganisms is of particular importance for the safety of the food chain and consequently for public health (Gworek et al., 2016). The methylmercury form can then contaminate fish and bioaccumulates and biomagnifies through the food chain, concentrating at higher trophic levels, which represents a concern for higher predator species, and ultimately humans consuming predatory fish in their diet.

3.2 Occupational exposure

Mercury exposure from occupational settings may be a smaller but important exposure subset in Europe. For example, mercury has been used in a range of scientific and medical devices, it has also been used on a wide-scale within energy-efficient fluorescent light bulbs (although mercury-free LED technology is replacing these on a large-scale). There remains a risk that mercury can be released to the environment or within occupational settings (leading to exposure) if mercury-containing items are broken or handled inappropriately during the waste phase.

3.3 Consumer exposure

The main source of exposure of the general European population is from the diet due to contamination of the food chain by mercury released to the environment from anthropogenic activities.

The primary source of human exposure to mercury is through the consumption of fish and shellfish containing methylmercury, and to a lesser extent crops (e.g. rice) grown on land contaminated with methylmercury (Rothenberg et al., 2014; Sheehan et al., 2014; Tanner et al., 2016).

Transfer from mother to child is also an important route of exposure to mercury and its compounds, if the mother is exposed. Trans-placenta exposure is a significant route of human exposure since mercury crosses the placenta and results in foetal exposure. The most significant pathway of infant exposure is breast milk consumption (World Health Organization, 2010).

Use of mercury within consumer products (for example dental amalgams) may also represent a potential source for certain individuals or groups but can be considered less significant for the general public.

Overall, the extent and main routes of exposure to mercury will vary geographically, depending on factors such as diet (i.e. consumption of fish), occupation and proximity to mercury-polluted areas, for example populations living in regions with heavy industry. Artisanal mining sites may also be a key area where exposure is relatively high (UNEP, 2019), but this is of minor importance in Europe.

4 Health impacts of mercury

4.1 Overview of key health impacts from mercury

Mercury is a highly toxic heavy metal that poses a significant global threat to human health and the environment, and effects may be possible even at very low levels. For example, mercury causes potentially irreversible damage to the central nervous system through prolonged or repeated exposure. The most important organic form of mercury, with regards to human exposure and adverse effects on health, is methylmercury. This is because methylmercury has a higher membrane permeability than elemental mercury alone and greater capacity for tissue fixation.

Depending on a person's developmental stage, the chemical form, the dose, and the route, frequency and duration of exposure, mercury has been linked with several human health effects. Mercury has been shown to cause birth defects or other reproductive harm (The Office of Environmental Health Hazard Assessment (OEHHA), State of California, USA). 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).

Mercury and its compounds have also been suspected to cause cancer. 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).

An overview of current EU (ECHA C&L Inventory) and/or IARC classification of mercury and methylmercury is provided in Table 1.1 (see **Error! Reference source not found.** for full list of terms/classifications):

Table 1.1 Overview of CLP classifications for mercury

Substance	Properties of concern				Category according to CLP criteria										ECHA info card
	Toxic to Reproduction (R)	Endocrine Disrupting (ED)	Skin sensitising (SS)	Persistent,Bioaccumulative and Toxic (PBT)	Carcinogenicity	Acute Toxicity	Reproductive Toxicity	Mutagenicity	Specific target organ tox (repeated exposure)	Specific target organ tox (single exposure)	Eye Damage/ Eye Irritation	Respiratory Sensitivity	Skin Corrosion/ Irritation	Skin Sensitivity	
Mercury					3**	2*	1B*		1*						Link

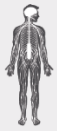
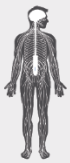
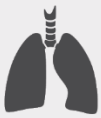
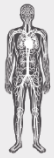
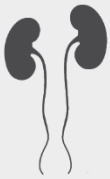
Methyl Mercury					2B**	1 & 2*			2*					Link

* Harmonised classification under the CLP Regulation. (Other classifications are those notified to the CLP inventory but without harmonised EU classification.); ** Based on IARC classification. Blank cells denote a lack of classification.

An overview of health effects associated with exposure to mercury is provided in **Error! Reference source not found.** below[1]. Further explanation on the categorisation of substances for different health effects is provided in Appendix 2.

[1] An explanation of the categorisation of the strength of evidence for the health effects presented in Figure 1.1 is provided in Appendix 2.

Figure 2.1 Overview of health effects associated with exposure to mercury

Target organ of the body	Effects	Relevant Substances	Adults (men)	Adults (women)	Infants / Foetuses
Brain/ neurological system 	Neurotoxic effects	Elemental mercury	●	●	○
	Developmental neurotoxicity and neurobehavioral effects	Methylmercury	○	○	●
Central nervous system 	Damage to organs through prolonged or repeated exposure	Elemental mercury and Methylmercury	◉	◉	○
Lung 	Cancer	Elemental mercury	●	●	○
		Methylmercury	◉	◉	○
Cardiovascular system 	Cardiovascular toxicity	Elemental mercury and Methylmercury	●	●	○
Liver 	Cancer	Elemental mercury	●	●	○
		Methylmercury	◉	◉	○
Kidney 	Cancer	Elemental mercury	●	●	○
		Methylmercury	◉	◉	○
DNA 	Birth defects and reproductive harm	Elemental mercury and Methylmercury	◉	◉	◉

Key: ● Strong evidence ◉ Suspected ● Evidence lacking ○ Not applicable

4.2 Vulnerable population groups

The high tendency of methylmercury to cross biological membranes in the body has important implications during pregnancy (due to possible transmission from the mother to the fetus through the placenta) and early childhood (due to possible transmission across the blood/brain barrier).

A particular concern is that foetuses, new-born babies and children are amongst the most vulnerable and sensitive to the adverse effects of exposure to mercury. Mercury and methylmercury are suspected neurotoxicants and methylmercury is suggested to be a developmental neurotoxicant (Grandjean and Landrigan, 2014).

Infants are at higher risk than older children and adults. This could be due to a higher rate of gastrointestinal absorption and less developed nervous system and detoxification mechanisms. Based on global level evidence, the most significant pathway of infant exposure is breast milk consumption, but also the use of specific mercury-containing products, such as teething powders and soaps (World Health Organization, 2010), though the latter two sources are not expected to be significant in Europe.

4.3 Societal concerns

Mercury is considered by the WHO[2] as one of the top ten chemicals or groups of chemicals of major public health concern.

European citizens consider environmental pollution as the top risk most likely to affect them personally, according to Special Eurobarometer Report 238 on risk issues. According to Special Eurobarometer 354 on food-related risks, one third of Europeans were 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 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. 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

[2] https://www.who.int/news-room/fact-sheets/detail/mercury-and-health

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.

5 EU policies on mercury

HBM4EU results have contributed to consultations for the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan, as well as the Secretariat of the UN Minamata Convention on Mercury. These are available in the HBM4EU Science to Policy section.

Several policy measures have been introduced in the EU to address human exposure to mercury and its compounds. These cover i) implementation of international actions and agreements, and wider chemicals legislation; ii) consumer products (including food); iii) occupational exposure, and iv) the environment (e.g. emissions to, and levels in air and water).

An overview of these regulatory measures at EU level are provided in Figure 3.1.

As illustrated in Figure 3.1, an important area of focus for EU policy concerning mercury is the protection of the public through the food chain. This includes regulating the acceptable levels of mercury in the aquatic environment, and in fish intended for human consumption, which is identified as the most important route of exposure for humans (see Section 3).

Figure 3.1 Overview of EU policy measures relating to mercury

General chemical

- The EU and most individual Member States are Parties to the **Minamata Convention on Mercury**, which came into force in 2017, and aims to protect human health and the environment from anthropogenic emissions and releases of mercury its compounds.
- The obligations under the Minamata Convention were transposed into EU law by Regulation (EU) 2017/852 on mercury.
- In 2005, the EU adopted a Community Strategy Concerning Mercury, setting out a plan to address mercury use and pollution.
- The manufacture, use and sale of mercury and its compounds are restricted for certain applications under Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).
- Mercury is subject to EU **harmonized classification and labelling** under Regulation (EC) No 1272/2008 on classification, labelling and packaging (the CLP Regulation) – see list of classifications above.
- **Human biomonitoring (HBM) values†** have been defined by the HBM German Commission, which include the HBM-I-value* for mercury of 7µg/L in urine and 5µg/L in blood ; and the HBM-II-value** for mercury of 25µg/L in urine and 15µg/L in blood.

Consumer

- **Food Safety** – The mercury content of fish for human consumption is regulated under European Regulation (EC) No 1881/2006 (updated as of 01/07/2022). This sets a maximum safe limit of 0.5 mg/kg for most fish species and 1 mg/kg for some predatory species (e.g. swordfish and tuna).
- **Medical and dental fields** – Regulation (EU) 2017/852 on mercury restricts the use of mercury in dental amalgam.
- **Cosmetic products** – Regulation (EC) No 1223/2009 on cosmetic products prohibits mercury and its compounds in cosmetic products, with limited exemptions (the maximum allowed concentration of Hg is 0,007%).
- **Toys** – Directive 2009/48/EC on the safety of toys sets migration limits for mercury from different types of toys (1.9-94 mg/kg).
- **Batteries** – Directive 2006/66/EC prohibits the use of mercury in all batteries or accumulators with more than 0,0005 % of Hg by weight.
- **Electrical equipment** – The Restriction of Hazardous Substances Directive (2002/95/EC) bans the use of mercury in electrical equipment, with some exemptions (e.g. fluorescent lamps with < 5 mg per lamp).

Environmental

Water

- Mercury and its compounds areincluded in the list of priority substances under the Water Framework Directive 2000/60/EC.
- Environmental Quality Standards for mercury are set (0.05 µg/L annual average and 0.07 µg/L maximum allowable).
- The Drinking Water Directive (98/83/EC) limits the concentration of mercury in water for public consumption to 1 µg/L.

Air

- The National Emissions Ceilings Directive ((EU) 2016/2284) sets reporting requirements on emissions and projections of mercury.

Industrial emissions

- Directive 2010/75/EU on industrial emissions sets emission limit values for mercury from waste incineration (mg/Nm^3) and for discharges of wastewater from the cleaning of waste gases (0.03 mg/L).

Occupational

- An occupational **exposure limit value (IOELV)** for mercury and divalent inorganic mercury compounds, including mercuric oxide and mercuric chloride (measured as mercury), of 0.02 mg/m^3 (8 hours exposure time) is defined under Directive 2009/161/EU, implementing Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at the workplace.

* The HBM-I-value represents the concentration of a substance in human biological material below which – according to the knowledge and judgement of the HBM Commission – there is no risk for adverse health effects and, consequently, no need for action.
** The HBM-II-value represents the concentration of a substance in a human biological material above which there is an increased risk for adverse health effects and, consequently, an acute need for exposure reduction measures and the provision of biomedical advice.

† Under WP5 of HBM4EU, these values were re-estimated based on currently available data in urine (inorganic, elemental mercury) and in blood (methylmercury).

6 Policy questions for mercury

6.1 Introduction

In line with HBM4EU's central aim to support policy decisions with current, quality-assured scientific knowledge, the policy-relevant knowledge gaps related to mercury, which could be addressed by HBM, were identified by the CGL with input from stakeholders and other internal experts. Activities were then elaborated under the different HBM4EU work packages, to fill in the gaps with new data.

The policy questions, proposed activities and detailed background information are presented in the scoping document on mercury and relevant input from stakeholders is provided in the report on stakeholder consultation and mapping of needs.

The relevant output of HBM4EU to each policy question on mercury is summarized below, based on information provided by the CGL, work package leaders (WPL) and other engaged experts.

6.2 How effective are policy actions to reduce human exposure to mercury in Europe?

HBM4EU results confirm an association between fish and seafood consumption with the body burden of mercury.The level of exposure to mercury through the fish/seafood consumption depends on the types of species (and portions / frequency) included in the diet.

Responsible fish consumption during pregnancy, can help to control exposure to mercury, while maintaining the nutritional benefits of fish.

Health-care providers of pregnant women are important stakeholders for awareness-raising and educational actions.

Harmonized, quality-assured HBM results can support the evaluation of the effectiveness of policy actions at European and international level.

6.3 How can harmonised, validated and comparable information be collected and transferred to support and evaluate current policies?

In the frame of HBM4EU WP7, strategies, Standard Operating Procedures (SOPs) and materials were developed. These can support the harmonised recruitment, sampling (including sample exchange), questionnaire implementation and communication with participants in HBM studies, in accordance with ethical and personal data protection requirements (AD7.1, D7.2, D7.3, D7.4, D7.7, AD7.2, D7.6).

Specifically, regarding mercury, questionnaires for adults, adolescents and children are available. Questionnaires for the 2nd occupational study on e-waste (incl. Mercury as a biomarker) have also been developed.

WP 7, 9 and 10 developed a frame to assure the quality of new collections of biomonitoring data and of existing samples and data, which are made available to the project.

WP9 elaborated criteria for the identification and selection of the best exposure biomarkers and matrices and for the evaluation of analytical methods, which can be used in European HBM surveys (see D9.1). Based on these criteria, a prioritised list of biomarkers, matrices and methods

for the assessment of human exposure to mercury and methylmercury was elaborated (see D9.5). The matrices of choice for both mercury and methylmercury were identified to be urine, whole blood and hair (with the latter being an easily available, non-invasive and inexpensive matrix for the estimation of methylmercury exposure). Dried blood spot samples and meconium are new matrices, which may prove valuable for the evaluation of internal exposure of new-borns, based on recent literature reports. The recommended analytical techniques for the determination of methylmercury are AAS (atomic absorption after generation of cold vapor of Hg) and ICP-MS. A list of 43 candidate laboratories for the determination of mercury was elaborated in D9.6.

WP10 elaborated a preliminary version of the final Data Management Plan (DMP) in AD10.1, which describes the data management life cycle for all datasets to be collected, processed and/or generated by HBM4EU (including criteria/methods and standards for data collection, data handling and sharing, data storage, data accessibility, while respecting ethics/legal requirements). This Plan includes the HBM4EU Data Policy. WP10 also developed a Statistical Analysis Plan (D10.5), which includes issues common to all HBM analyses, description of the statistical approach to look into time-trends, geographical comparisons, exposure determinants, exposure distributions and reference values, uncertainty analysis as well as a specific statistical analysis plan for the mercury priority substance group.

Targeted tools were developed specifically for the HBM4EU-MOM dietary intervention study for prenatal control of exposure to mercury through suitable fish consumption by pregnant women. These tools include targeted communication and intervention materials, questionnaires, and a statistical analysis plan for the MOM-study (D10.12), which includes data handling, descriptive statistics, approach to investigate association between hair Hg and seafood consumption patterns with an aim to discover effects of the intervention applied in the mom study. It also covers the plan to evaluate geographic patterns. The WP7 and WP10 materials, which have been developed to support harmonised practices, are publicly available to the whole consortium and any other interested party, via the HBM4EU online library.

6.4 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?

See Section 6.3 above. Harmonized, quality-controlled data on vulnerable populations collected at different time-points for time-trends are important for the assessment of the effectiveness evaluation of policies

The new, harmonized biomonitoring data of fish-consuming pregnant women in PT, ES, GR, CY, IS collected in the frame of the HBM4EU-MOM study, provide a basis to compare exposures in 2021 with exposures in 2011 (from DEMOCOPHES, which used a similar protocol to assess exposures of women of reproductive age. 3 countries participated in both studies).

Existing data coming from studies, which were implemented without a harmonized frame, hinder the risk assessment process.

Aggregated data, that is summary statistics (percentiles) for mercury exposure data available from existing HBM data collections are integrated in IPCHEM and the European HBM dashboard.

WP5, task 5.3 about the Risk Assessment (RA) of mercury and its organic compounds have identified high variability in the data from European HBM studies regarding Hg (blood and hair,

total Hg and/or MeHg) in the general population. This highlights the need for harmonized sampling protocols and chemical analysis to obtain comparable results between countries, to identify differences in European exposure.

WP10 achieved progress regarding the inclusion of existing European HBM data in the European commission's Information Platform for Chemical Monitoring (IPCHEM) and the European HBM dashboard was developed to interactively visualise the aggregated HBM data.

For total mercury, aggregated data from the following studies were made publicly available via the EU HBM dashboard from the 4 European regions (i.e. East, North, South and West).

6.5 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?

See answer in 6.3 above (questionnaires developed by WP7, that assist answering this question).

Stratification of available data by sex, educational level, degree of urbanisation, etc. showed that exposure to mercury is higher among participants of high educational status as compared to low educational status. The difference isn't pronounced for participants with middle educational status. The preliminary analysis of the MOM study results shows geographic variability of mercury exposures of pregnant European women, associated with fish consumption patterns. Though the GMs were lower than the current GVs (EFSA-2012, WHO/FAO-2006), some women exceeded these levels in early pregnancy. The highest exposures among the five countries were observed in PT, where also the provision of fish-consumption advice had the highest impact in protecting the foetus (as suggested by the mercury modelling).

The HBM4EU-MOM approach, which employed the central theme 'fish is good, eat good food' and the 'traffic-light system' to recommend fish to be preferred and fish to be avoided during pregnancy is a valuable way to communicate with pregnant women.

The health-care providers of pregnant women are important stakeholders, who should be aware, educated and provided with suitable, scientifically supported information to communicate with pregnant women regarding fish consumption during pregnancy

A lack of data from countries with high fish consumption was identified, which is the main exposure source. To protect these populations, it would be necessary to establish more awareness campaigns during pregnancy on the most suitable fish species for them and their children, which could be accompanied by regular sampling plans of methylmercury MeHg in these populations.

6.6 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?

The HBM4EU-MOM approach, which employed the central theme ‘fish is good, eat good food’ and the ‘traffic-light system’ to recommend fish to be preferred and fish to be avoided during pregnancy is a valuable way to communicate with pregnant women.

The health-care providers of pregnant women are important stakeholders, who should be aware, educated and provided with suitable, scientifically-supported information to communicate with pregnant women regarding fish consumption during pregnancy.

Actions to engage citizens (as participants in HBM studies, focus groups, surveys, etc) are very important for awareness-raising, assessing -addressing their needs.

6.7 At what level of exposure to different mercury species and to total mercury are health effects likely to occur? Current guidance values were based on 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.

In general, the European population does not exceed the daily average/intake dose for MeHg/Hg or the HBM-I value. Only countries with high fish consumption such as Spain and Portugal in some cases exceed these values. However, we have identified lack of data from other European countries with also high fish consumption such as France, Italy, Greece & Iceland. For this reason, further RA refinement is needed with harmonized and widespread HBM data to account for differences in European exposure.

The mercury species to be considered for deriving a HBM-GV_{GenPop} in urine are elemental mercury (dental amalgams, background exposure/air) and inorganic mercury compounds (non-fish food and drinking water consumption) covered by inhalation or oral studies measuring the mercury exposure level in urine.

In contrast, methylmercury (fish consumption) essentially contributes only to the blood mercury level so that a HBM-GV_{GenPop} in blood is needed to cover the methylmercury exposure in fish-consuming populations. Epidemiological studies in the respective populations are the most important data sources in this regard measuring methylmercury or total mercury exposure levels typically in blood or hair.

Nevertheless, the blood total mercury level is also triggered by the other mercury species, albeit negligible in fish-consuming populations, so that it is checked whether respective study data are available for a comparative analysis.

If not a more sensitive endpoint or point of departure (PoD) can be determined from current study data, the derivations of existing toxicological reference values are used as a source, e.g. tolerable weekly intakes (TWIs) for methylmercury and inorganic mercury by EFSA (2012) or occupational exposure levels converted to general population levels if the respective data are available.

Based on the EFSA TWI derivation for methylmercury using Seychelles and Faroe Islands cohort data, the HBM-GV blood value would result in 7.2 µg/L expressed as mercury under the use of uncertainty/assessment factor of in total 6.4. Whether a lower value would result from the comparative analyses covering different endpoints and exposure routes is yet to be determined.

Based on the EFSA TWI derivation for inorganic mercury using animal study data with effects on kidney weights, the PoD for the derivation of the HBM-GV in urine is proposed to be the benchmark dose lower confidence limit 10% BMDL10 of 0.06 mg/kg BW/d, expressed as mercury, if not a more sensitive PoD in urine will be determined for the inhalation route (ongoing work).

6.8 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?

New findings since 2012 do not provide robust evidence for adversity at or slightly above the current TWI.

Based on scoping reviews of published studies:

- association of mercury with Alzheimer's Disease is possible, but the results are inconsistent.
- mercury is only potentially associated with asthma, based on epidemiological studies
- Limited evidence exists for an association between ADHD and mercury
- Current evidence on environmental exposures and associations with metabolic disturbances and EDCs is still limited and heterogeneous, and mainly represent studies from North America and Asia, highlighting the need for well-conducted and harmonized HBM programmes among the European population.

Work Package 13 (WP13) carries out work to establish causal links between exposures and health. Tasks 13.1 and 13.2 jointly developed a WP13 Strategy on addressing the policy questions related to the 2nd list of priority compounds (see "AD13.1 Strategy on how to address policy questions related to the 2nd list of priority compounds"). A mercury-focus group was established and a leader for the substance group within WP13 was identified and actions on how to address the mercury policy questions were planned. In AD13.6 "Answers to exposure-health policy questions for the 2nd priority compounds", the ongoing work is summarised: Existing cohorts are used to assess Hg impact on neurobehavior taking into account co-exposures to other elements with neurotoxic potency (Pb,As,Mn) and OP pesticides and also beneficial elements (including Se, Zn) and to investigate the allele frequencies of related SNPs across Europe and how this may contribute to contradicting associations between exposure and health outcomes found so far. This is done in association with WP10. Currently, an extensive literature search is ongoing to obtain Europe-wide SNP frequencies for genes that are known to have potential impact on vulnerability and on the association between Hg exposure or/and neurodevelopmental effects. This will be assessed in terms of the reported adverse associations with prenatal Hg exposure across Europe.

Also, under the frame of WP13, a systematic literature review was carried out of all epidemiological studies on prenatal exposure to Hg in relation to neurodevelopmental outcomes in the offspring. This work was conducted with the aim to evaluate new evidence from the epidemiological literature since EFSA's 2012 opinion, to evaluate if new developments have occurred to address the

identified data gaps and if current knowledge supports or contradicts the EFSA's conclusions from eight years ago. The output of this work is now being written up for a peer-review publication and was communicated to task 5.2 for consideration for the derivation of HBM-GVs and to Task 5.3.

Work Package 14 (WP14) carries out work to identify the most suitable biomarkers of effect for mercury through a focused literature search of mercury-related human and animal studies and reported health endpoints (see D14.5 - Selection criteria and inventory of effect biomarkers for the 2nd set of substances). Comprehensive literature searches with defined search terms for mercury/methylmercury and selected health endpoints (reproduction, neurodevelopment, metabolic & cardiovascular, immune/allergy, endocrine, and cancer) were contacted conducted in the PubMed/MEDLINE database (D14.5). To focus the literature search on novel biomarkers and to reduce the number of articles, search terms related to OMICS, epigenetics or biomarker-related were included, while exclusion terms were used to eliminate articles with irrelevant focus. The most relevant effect biomarkers used in epidemiological settings are summarised, prioritised, and linked to the available experimental or AOP support (D14.6). BDNF, oxidative stress and many epigenetic and gene expression markers were found to be correlated with higher exposure to mercury in human studies. Given the wide amount of specifically deregulated genes and epigenetic effects identified, future efforts should prioritise the most interesting molecular targets based on mechanistic and AOP information. The output of this work on new epigenetic biomarkers of effects on multiple endpoints (neurodevelopment, metabolism, cancer, and reproduction) will be reported in a review article, which is under preparation (Tentative title: Novel effect biomarkers associated to mercury: a review of the epidemiological evidence for epigenetic modulation by mercury).

Good examples of biomarkers of effect of mercury exposure are the determination of TSH at birth in children in order to detect (and to mitigate early) congenital hypothyroidism, as well as the epigenetic biomarker PON1 (hypomethylation in newborns) or pSEPP1 (hypomethylation in adults) (reviewed by Couderq et al., 2022 submitted). Experimental validation had been conducted to test the impact of exposure to mercury on the expression of genes, including the BDNF gene, using a 3R-compliant model to identify specific mechanism pathways and to construct reliable AOPs.

7 HBM4EU outputs to date

7.1 Categorisation

Mercury and its compounds have been categorised depending on availability of HBM data (see Table 2.1):

Table 2.1 HBM4EU categorisation for mercury

Category		Priority substance(s)	Details
A	Sufficient HBM data exists with risk management measures implemented; focus is on policy-related research questions	Mercury	The health impact of mercury is well documented. 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.
B	HBM data exist but not for across Europe	Methyl-mercury	The health impact of methylmercury is well documented. Data on methylmercury exposure in Europe is not as common as for total mercury. 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.
C	HBM data are scarce or non-existent	n/a	n/a

7.2 Key outputs

In order to further support current and future HBM studies, HBM4EU has produced a variety of publicly available groundwork materials for a harmonised approach to study planning and conduct in Europe.

The “Mercury & Methylmercury” Chemical substance Group was prioritised for action within HBM4EU in the 2nd round of prioritisation, was approved in May 2018 and a Chemical Group Leader was appointed (D4.5). A scoping document was developed, which summarises the state of the art, identifies knowledge gaps, presents policy questions and suggests actions to be carried out in the frame of HBM4EU to address them (D4.6). The scoping document was updated yearly (D4.9).

The scoping document on mercury, developed under Work Package 4 (WP4), summarises a lot of available data related to the geographic spread of human exposure, reviews determining factors, provides some information on available relevant cohorts and identifies data gaps. The exposure is higher in coastal populations and correlates with high fish / seafood consumption. The formulation and provision of suitable dietary advice to vulnerable populations should consider both: the contamination levels in different species of fish, as well as the documented nutritional benefits of fish consumption.

Data on total mercury exposure from different countries across Europe are available and HBM4EU has produced a case study that assessed mercury exposure of pregnant women in five coastal European countries.

The HBM4EU-MOM study (“Methylmercury-control in European pregnant women through suitable dietary advice for pregnancy”) was implemented in Cyprus, Greece, Iceland, Spain and Portugal (10/2020-6/2022).

This is a randomized control trial of 654 pregnant women. Half of the participants of each national cohort received dietary advice for fish consumption during pregnancy. The central theme of the intervention was ”fish is good, eat good fish” and species to be consumed / species to be avoided were provided using the ‘traffic light system’. Mercury biomonitoring (using maternal hair and questionnaires) was done at early pregnancy and at ≤3 months after provision of advice to the intervention participants. The resulting harmonized European databases were used for statistical analyses and modelling.

However, several countries lack recent data or data on vulnerable populations, such as children. Also, in most instances, the sampling was not representative of the population.

The geographic spread of Hg exposure was therefore addressed in the HBM4EU-MOM study and provided detailed information about their diet related to types of fish/seafood species, portions and frequencies of consumption. In a randomized trial, half of the women received nationally tuned dietary advice for nutrition and mercury control and a second set of hair samples and personal information were collected from all participants after a minimum of 12 weeks.

Work Package 10 (WP10) collects, integrates and makes available existing HBM data on mercury into IPCHEM and the European HBM dashboard. The existing and available HBM data are analysed to assess the baseline exposure of Europeans to total and methyl mercury and the determinants of the exposure. In the European HBM dashboard, the available mercury data from European studies, provided to the project by the participating countries, were treated statistically in a harmonised way. Distribution plots were prepared, presenting the exposure data according to sex, European region, age group and educational level (as a measure of socioeconomic status) and other stratifying factors (more details in policy question 3).

For total mercury, aggregated data from the following studies were made publicly available via the EU HBM dashboard from the 4 European regions (i.e. East, North, South and West) :

Using urine: Eighteen studies on adults (>20y; East : 3, South: 2, West: 13) and 4 studies on children/teenagers (East : 3, West: 1).

Using Blood: Eleven available studies on adults (East: 4, South: 2, West: 4, North: 1), four studies on children/teenagers (East: 3 and West: 1) and one study in newborns (cord blood) (East: 1).

Using Breast Milk: One available study from Southern Europe (Freire et al, 2021) and one from Eastern Europe. ++

Fifteen available studies on adults (>20y; East: 5, South: 4, West:4, North:2), sixteen studies on children/teenagers (East: 6, South: 2, West: 6, North: 2).

Fewer studies were available with data on methylmercury (MeHg):

Using Blood: One study from Eastern Europe on newborns (cord blood);

Using Hair: Three studies on adults (>20y: East: 1, West: 2) and three on teenagers (12-19y, West: 3).

Using human placenta: One study from Southern Europe (Spain) (see Freire et al 2019)

Work Package 12 (WP12) prepared an integrated exposure modelling platform, which provides a web-based computational environment that brings together the different tools available from the HBM4EU consortium to address all the aspects of the full chain for aggregated exposure assessment in environmental and occupational settings (see "AD12.4 Conceptual design of the integrated computational platform"). The vertical modules include (a) the model run settings module, which serves to define some general settings for each platform run and the overall configuration of a specific platform simulation, (b) the multimedia model module, for the estimation of environmental media concentrations in different environmental matrixes, (c) the microenvironment module, for estimating chemical environmental concentration for indoor locations, (d) the exposure scenario definition module, which enables the development of an exposure scenario for the population group(s) selected, including all possible exposure routes and (e) the internal dosimetry module, which aims at estimating the internal doses of a chemical and its metabolites. The whole concept will be based on a suite of three different PBTK models according with their level of detail and complexity (the simpler PK model for data poor chemicals, the generic PBTK model and the life-stage changing mother-foetus generic PBTK model).

The integrated exposure modelling platform will be optimised by updating the exposure model parameterisation for mercury using available data and will be used to identify the internal exposure to total mercury and methylmercury for various population groups.

WP5, task 5.3 have developed the RA of MeHg related to neurodevelopmental diseases in vulnerable population groups (children and woman of childbearing age).

This was conducted based on earlier approaches by EFSA in 2012 and integrating data from European HBM surveys. Children/adolescents from 3 to 17 years old and, women of childbearing age, from 18 to 50 years old were identified as vulnerable population groups for this RA. Two types of MeHg HBM datasets were selected: HBM studies (n= 21) with Hg levels (blood and hair, total Hg and/or MeHg) in the general population in different EU countries and the DEMOCOPHES harmonised study as reference (urine and hair) (total Hg) in children/mothers in 17 EU countries. A total of 6 case-studies were suggested as strategies of RA for each group identified. These case-studies were based on estimations of the fraction of children/adolescents and women from the EU general population exceeding the TWI (or their equivalent to TDI) defined by EFSA in 2012 (case-studies 1 and 2, respectively); and based on estimations of the fraction of children/adolescent and women of childbearing age from the EU general population exceeding the HBM I value established by the German Human Biomonitoring Commission (Hazard Quotient-HQ) (case-studies 3 and 4). In addition, similar calculations but using the preliminary Human Biomonitoring Guidance Value defined for general population (HBM-GV_{GenPop}) provided by WP5 task 5.2 were conducted (case-studies 3b and 4b).

In HBM4EU, research protocols have been developed aimed at estimating internal Hg levels by using non-invasive matrices and factors affecting the predictive potential in the European population. The objective of this research protocol is to evaluate the current exposure of European residents to organic and inorganic Hg on a geographic and time scale, if possible, also with regards to effectiveness of policies different countries/regions are taking, and to evaluate the percentage of population currently exceeding the known health-based values.

An effort has been made to identify new biomarkers of mercury-associated effects by reviewing epidemiological studies with the hypothesis that the health effects of mercury exposure could be partly mediated by epigenetic mechanisms.

HBM4EU explored whether frequencies of relevant genetic variations between European regions could explain variability in Hg exposure. This helps to improve our understanding of the importance of these genetic variations on Hg exposure and health effects across Europe.

Regarding HBM4EU work on risk assessment, an update of the organic mercury risk assessment (methyl mercury-MeHg RA) has been carried out integrating data from Human Biomonitoring surveys conducted in European general population from 2012, specifically in children/adolescents from 3 to 17 years old and women of childbearing age in the range of 18 to 50 years.

HBM4EU-MOM study (Pillar 2: WPs 8,9,10,12) prepared and used harmonized targeted tools for the assessment of exposure, practices and attitudes of pregnant women related to mercury and diet. Tools were also developed for dietary intervention about fish/seafood consumption in pregnancy. The preliminary assessment from the use of these materials suggests that they were well suited for their indented purpose.

WP 7, 9 and 10 developed a frame to assure the quality of new collections of biomonitoring data and of existing samples and data, which are made available to the project.

WP9 elaborated criteria for the identification and selection of the best exposure biomarkers and matrices and for the evaluation of analytical methods, which can be used in European HBM surveys (see D9.1). Based on these criteria, a prioritised list of biomarkers, matrices and methods for the assessment of human exposure to mercury and methylmercury was elaborated (see D9.5). The matrices of choice for both mercury and methylmercury were identified to be urine, whole blood and hair (with the latter being an easily available, non-invasive and inexpensive matrix for the estimation of methylmercury exposure). Dried blood spot samples and meconium are new matrices, which may prove valuable for the evaluation of internal exposure of newborns based on

recent literature reports. The recommended analytical techniques for the determination of methylmercury are AAS (atomic absorption after generation of cold vapor of Hg) and ICP-MS. A list of 43 candidate laboratories for the determination of mercury was elaborated in D9.6.

WP10 elaborated a preliminary version of the final Data Management Plan (DMP) in AD10.1, which describes the data management life cycle for all datasets to be collected, processed and/or generated by HBM4EU (including criteria/methods and standards for data collection, data handling and sharing, data storage, data accessibility, while respecting ethics/legal requirements).

This Plan includes the HBM4EU Data Policy. WP10 also developed a Statistical Analysis Plan (D10.5), which includes issues common to all HBM analyses, description of the statistical approach to look into time-trends, geographical comparisons, exposure determinants, exposure distributions and reference values, uncertainty analysis as well as a specific statistical analysis plan for the mercury priority substance group.

Moreover, the statistical analysis plan for the MOM-study was elaborated in D10.12. It includes data handling, descriptive statistics, approach to investigate association between hair Hg and seafood consumption patterns with an aim to discover effects of the intervention applied in the mom study. It also covers the plan to evaluate geographic patterns All materials, which have been developed to support harmonised practices, are publicly available to the whole consortium and any other interested party, via the online library. Work Package 7 (WP7) developed strategies, Standard Operating Procedures (SOPs) and materials, which can support the harmonised recruitment, sampling (including sample exchange), questionnaire implementation and communication with participants in HBM studies, taking into account ethical and personal data protection requirements.

Work Package 13 (WP13) carries out work to establish causal links between exposures and health. Tasks 13.1 and 13.2 jointly developed a WP13 Strategy on addressing the policy questions related to the 2nd list of priority compounds (see "AD13.1 Strategy on how to address policy questions related to the 2nd list of priority compounds"). A mercury-focus group was established and a leader for the substance group within WP13 was identified and actions on how to address the mercury policy questions were planned. In AD13.6 "Answers to exposure-health policy questions for the 2nd priority compounds", the ongoing work is summarised: Existing cohorts are used to assess Hg impact on neurobehavior taking into account co-exposures to other elements with neurotoxic potency (Pb, As, Mn) and OP pesticides and also beneficial elements (including Se, Zn) and to investigate the allele frequencies of related SNPs across Europe and how this may contribute to contradicting associations between exposure and health outcomes found so far. This is done in association with WP10. Currently, an extensive literature search is ongoing to obtain Europe-wide SNP frequencies for genes that are known to have potential impact on vulnerability and on the association between Hg exposure or/and neurodevelopmental effects. This will be assessed in terms of the reported adverse associations with prenatal Hg exposure across Europe.

Under the frame of WP13, a systematic literature review was carried out of all epidemiological studies on prenatal exposure to Hg in relation to neurodevelopmental outcomes in the offspring. This work was conducted with the aim to evaluate new evidence from the epidemiological literature since EFSA's 2012 opinion, to evaluate if new developments have occurred to address the identified data gaps and if current knowledge supports or contradicts the EFSA's conclusions from eight years ago. The output of this work is now being written up for a peer-review publication and was communicated to task 5.2 for consideration for the derivation of HBM-GVs and to Task 5.3.

Work Package 14 (WP14) carries out work to identify the most suitable biomarkers of effect for mercury through a focused literature search of mercury-related human and animal studies and reported health endpoints (see D14.5 - Selection criteria and inventory of effect biomarkers for the 2nd set of substances). Comprehensive literature searches with defined search terms for

mercury/methylmercury and selected health endpoints (reproduction, neurodevelopment, metabolic & cardiovascular, immune/allergy, endocrine, and cancer) were conducted in the PubMed/MEDLINE database (D14.5). To focus the literature search on novel biomarkers and to reduce the number of articles, search terms related to OMICS, epigenetics or biomarker-related were included, while exclusion terms were used to eliminate articles with irrelevant focus. The most relevant effect biomarkers used in epidemiological settings are summarised, prioritised and linked to the available experimental or AOP support (D14.6). BDNF, oxidative stress and many epigenetic and gene expression markers were found to be correlated with higher exposure to mercury in human studies. Given the wide amount of specifically deregulated genes and epigenetic effects identified, future efforts should prioritise the most interesting molecular targets based on mechanistic and AOP information. The output of this work on new epigenetic biomarkers of effects on multiple endpoints (neurodevelopment, metabolism, cancer and reproduction) will be reported in a review article, which is under preparation (Tentative title: Novel effect biomarkers associated to mercury: a review of the epidemiological evidence for epigenetic modulation by mercury).

Good examples of biomarkers of effect of mercury exposure are the determination of TSH at birth in children in order to detect (and to mitigate early) congenital hypothyroidism, as well as the epigenetic biomarker PON1 (hypomethylation in newborns) or pSEPP1 (hypomethylation in adults) (reviewed by Couderq et al., 2022 submitted). Experimental validation had been conducted to test the impact of exposure to mercury on the expression of genes, including the BDNF gene, using a 3R-compliant model to identify specific mechanism pathways and to construct reliable AOPs.

Work Package 4 (WP4) organised Citizen Focus Groups in Austria, Portugal, Ireland and the United Kingdom with the aim to gain information on the interests, needs, and questions of European citizens regarding exposure to chemicals in their daily lives and their opinions about possible future actions on Human Biomonitoring. Mercury was among the top five environmental pollutants causing concern to the participating citizens, who regard it as a priority which should be addressed in Human Biomonitoring studies (see "AD4.2 Report of the citizen's focus groups" and AD4.4 for additional Focus groups in more HBM4EU countries).

Work Package 11 (WP11) reviewed known relations between substance (including mercury) exposures and health outcomes, based on the information from the scoping documents of WP4. Scientific review-manuscripts are in preparation for Metabolic syndrome, diabetes, osteoporosis and asthma, with the aim to raise awareness in health professionals regarding the health effects of environmental contaminants. Also, WP11 evaluated opportunities and obstacles related to linking HBM, health surveys and administrative data sources (Deliverable D11.3), generated an inventory of European health studies, which could be linked to HBM studies (D11.1) and provided SOPs/guidelines for combining HBM/health studies and for obtaining information regarding identified health effected related to mercury exposure.

To explore how HBM4EU might contribute at global level, the WPL2 and the CGL-Hg attended the 2nd Conference of the Parties (COP2) to the "UN Minamata Convention on Mercury", (Geneva, 11/2018). The work on Hg was presented, and ways in which HBM may contribute to the effectiveness evaluation of the convention were discussed. Possible collaborations with the World Health Organization to support global harmonisation of mercury biomonitoring were explored.

Work was presented in other international conferences, including Minamata Convention pre-COP4 side event. The event was promoted by the UN, the EEA and the CGL on social media and it took place on March 9, 2022 as a webinar hosted by the UN. Mercury in the context of HBM4EU was presented and the MOM study was featured.

A policy brief produced on mercury was being developed and will summarise toxicity, exposure, and policy status, any updates in legislation and relevant HBM4EU research results.

The main outputs from the HBM4EU to date include the following:

- The scoping document for mercury and its compounds presenting the currently available data, and identifies open policy questions and data gaps to fill in order to address them.
- A comprehensive summary of available human biomonitoring data from EU countries on mercury exposure has been compiled (Table 1.1 in the scoping document) This is based on a World Health Organization (WHO, 2015) report with additional data from by Ruggieri et al. (2017), also results were from the further review of the scientific literature, as well as additional inputs from within the HBM4EU consortium have been added.
- An overview of the European birth cohort studies, which included investigation of mercury, has been developed – based on Ruggieri et al. (2017).
- An overview of reference values for mercury in blood and urine for different countries, including those in Europe, as developed by Saravanabhavan et al. (2017).
- An overview of health-based guidance values available for HBM data on mercury – adopted from Ruggieri et al. (2017).
- An overview of recommended Biological Limit Values (BLV) for occupational exposure.

Specific work completed to date under the HMB4EU project for mercury is detailed on the HBM4EU website[3] and is summarised below.

7.3 Key data gaps

HBM4EU is a five-year project, that kicked off in 2017 and will run till June 2022. HBM4EU has helped to identify a number of specific data gaps that are needed to give policy makers relevant and strategic data to establish appropriate regulations and improve chemical risk management. However, some gaps and needs for action will remain after the end of HBM4EU which should be addressed in the future.

A number of specific data gaps have been identified in relation to the policy questions outlined in Section **Error! Reference source not found.**. 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. The identified gaps include:

- 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.
- The toxic effects of methylmercury at the levels of exposure found in the general population due to fish consumption are not fully understood.
- Exposure to mercury has been linked with Alzheimer's disease, but further research is required (Mutter et al., 2010).
- Exposure from dental amalgams is not fully understood (Bengtsson and Lars, 2017), (Bentung et al., 2016).

[3] See AD5.4 "Reporting for first and second set of substances"

- Mercury has possible endocrine disruptive effects, which have raised public concern, but further investigation is required (Rana, 2014; Iavicoliet et al., 2009; , Rahman et al., 2016).
- Further work is required for the investigation of the potential links of mercury to the metabolic syndrome, immunotoxicity and cardiovascular effects (Roy et al., 2017; Maqbool et al., 2017; Gardner and Nyland, 2016; Genchi et al., 2017).
- Biomarkers of susceptibility in European populations need to be better understood.
- The exposure level to which health effects may develop needs to be revisited.

Table 3.2 Summary of knowledge gaps and ongoing activities for mercury

#	Theme	Knowledge gaps and activities needed	HBM4EU WPs
1	**Impact of current policy actions**	• Overarching activity (links with activities in the other three thematic areas); • Development and update of inventories and evaluations of the best exposure biomarkers, matrices and analytical methods, and candidate laboratories for the analysis of biological samples for mercury biomonitoring.	2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14).
2	**Public Information**	• Mapping of the information needs of external bodies (e.g. understanding the perspectives of the public through focus groups). • Establishment of HBM-based guidance values for mercury for the general population.	4, 5
3	**Informing policy makers**	• Mapping of the information needs of external bodies • Support permanent European mercury biomonitoring as long-term support of global mercury policies (e.g. knowledge transfer with non-EU countries). • Collection, curation and provision of information relevant to the mercury chemical group (CG) to targeted audiences (e.g. public, health practitioners, scientists, policy makers) via the Knowledge Hub. • Development of a proposal on how to integrate HBM in risk assessment procedures and use of available mercury HBM data for risk assessment. • Construction of HBM-based indicators for mercury and development of associated information to facilitate their interpretation by stakeholders, including policy makers.	2, 4, 5
4	**Reducing public exposure and identifying vulnerable groups**	• Identification and systematic collection of relevant recent or ongoing European studies, identification of knowledge gaps, prioritisation of research needs. • Development of support materials for mercury biomonitoring surveys, including guidelines for the standardisation of measurements and comparability of collected data. • 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 policies.	5, 7, 8, 10, 11, 12

#	Theme	Knowledge gaps and activities needed	HBM4EU WPs
		• HBM4EU-mom, an intervention study carried out in five coastal European countries (Spain, Portugal, Iceland, Greece and Cyprus) is investigating ways to, i) reduce prenatal exposure to mercury in vulnerable European countries, ii) improve communication of fish consumption advice in the frame of clinical practice, and iii) support answers to open policy questions at European level about mercury, with new scientific data. • Analysis of HBM data to assess (a) baseline exposure of Europeans to 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).	

WP1: Programme management and coordination; WP2: Knowledge hub; WP4: Prioritisation and input to the annual work plan; WP5: Translation of results into policy; WP6: Sustainability and capacity building; WP7: Survey design and fieldwork preparation; WP8: Targeted field work surveys and alignment at EU level; WP9: Laboratory analysis and quality assurance; WP10: Data management and analysis; WP11: Linking HBM, health surveys and registers; WP12: From HBM to exposure; WP13: Establishing exposure health relationships; WP14: Effect biomarkers; WP15: Mixtures, HBM and human health risks; WP16: Emerging chemicals.

8 Future recommendations

- Continue HBM programs for Hg in Europe based on the methodology developed and established in HBM4EU in order to map and follow current exposure.
- Continue developing targeted consumer guidelines, dietary recommendations, with focus on vulnerable groups

9 References

Apel et al., 2020, Human biomonitoring initiative (HBM4EU) - Strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment, *International Journal of Hygiene and Environmental Health,* Vol. 230, September 2020, 113622, https://doi.org/10.1016/j.ijheh.2020.113622.

Bellanger, M., Pichery, C., Aerts, D. et al., 2013, Economic benefits of methylmercury exposure control in Europe: Monetary value of neurotoxicity prevention. Environ Health 12, 3 (2013). https://doi.org/10.1186/1476-069X-12-3.

HBM4EU, 2019, Scoping document for mercury and its organic compounds, part of the D4.9 scoping document set.

HBM4EU, 2019, prioritised substance group: mecury and its organic compounds – updated. Policy-related questions.

HBM4EU, 2020, Legislative mapping: mecury. Summary document prepared by RPA on behalf of the European Environment Agency.

Bengtsson, U.G. and Lars,H. D. (2017). Increased mercury emissions from modern dental amalgams, *Biometals*, 30, pp. 277-283.

Bentung Lygre, G., Haug, K., Skjærven, R. and Björkman L. (2016). Prenatal exposure to dental amalgam and pregnancy outcome, *Community Dentistry and Oral Epidemiology*, 44(5). pp. 442-449.

European Commission. (2018). RASFF — The Rapid Alert System for Food and Feed — 2017 annual report. Luxembourg: European Union. Retrieved October 14, 2018, from The Rapid Alert System for Food and Feed (RASFF) 2017 Annual Report: https://ec.europa.eu/food/sites/food/files/safety/docs/rasff_annual_report_2017.pdf

European Environment Agency (2019). Heavy metal emissions. Available at: https://www.eea.europa.eu/data-and-maps/indicators/eea32-heavy-metal-hm-emissions-1/assessment-10

European Environmental Bureau (EEB). (n.d.). Zero Mercury Campaign. Retrieved from http://eeb.org/work-areas/industry-health/zero-mercury-campaign/

European Union (2017). Tackling mercury pollution in the EU and worldwide. In-depth Report 15 produced for the European Commission, DG Environment by the Science Communication Unit, UWE, Bristol. Available at: https://ec.europa.eu/environment/chemicals/mercury/pdf/tackling_mercury_pollution_EU_and_worldwide_IR15_en.pdf

Gardner, R. M. and Nyland, J. F. (2016). “Immunotoxic Effects of Mercury", in Environmental Influences on the Immune System, C. Esser, Ed., Vienna, Springer, 2016.

Genchi, G., Sinicropi, M. S., Carocci, A., Lauria, G. and Catalano, A. (2017). Mercury Exposure and Heart Diseases, *International Journal of Environmental Research and Public Health*, 14(1), p.p 74.

Grandjean, P. and Landrigan, P.J. (2014). Neurobehavioural effects of developmental toxicity, *Lancet Neurol*, 13(3), p.p. 330–338.

Gworek, B., Bemowska-Kałabun, O., Kijeń, M. and Wrzosek-Jakubowska, J. (2016). Mercury in Marine and Oceanic Waters — a Review, *Water Air Soil Pollut*, . 227(10), p.p. 371.

Health and Environment Alliance. (n.d.). Halting the child brain drain: Why we need to tackle global mercury contamination. Retrieved from Health and Environment Alliance | Halting the child brain drain: Why we need to tackle global mercury contamination (env-health.org)

Iavicoli, I., Fontana, L. and Bergamaschi, A. (2009). The Effects of Metals as Endocrine Disruptors, *Journal of Toxicology and Environmental Health, Part B*, 12(3), p.p. 206-223.

IPEN. (n.d.). IPEN - Mercury-Free Campaign. Accessed 08/11/2021 Mercury | IPEN.

Maqbool, F., Niaz, K., Ismail Hassan, F., Khan, F. and Abdollahi, M. (2017). Immunotoxicity of mercury: Pathological and toxicological effects, *Journal of Environmental Science and Health, Part C. Environmental Carcinogenesis and Ecotoxicology Reviews*, 35(1) p.p. 29-46.

Mutter, J., Curth, A., Naumann, J., Deth, R. and Walach, H. (2010). Does inorganic mercury play a role in Alzheimer's disease? A systematic review and an integrated molecular mechanism., *Journal of Alzheimers Disease*, 22 (2), p.p. 357-374.

Rana, S. (2014). Perspectives in endocrine toxicity of heavy metals--a review. *Biological Trace Element Research*, 160(1), p.p. 1-14.

Rice, D. and Barone Jr, S. (2000). Critical Periods of Vulnerability for the Developing Nervous System: Evidence, *Environmental Health Perspectives*, 108(3), p.p. 511-533.

Rothenberg, S., Windham-Myers, E. L., and Creswell, J. E., (2014). Rice methylmercury exposure and mitigation: a comprehensive review. *Environmental Research,* 133, pp. 407 - 423.

Roy, C., Tremblay, P.-Y. and Ayotte, P. (2017). Is mercury exposure causing diabetes, metabolic syndrome and insulin resistance? A systematic review of the literature. *Environmental Research*, 156, p.p. 747-760.

Ruggieri, F., Majorani, C., Domanico, F. and Alimonti, A. (2017). Mercury in Children: Current State on Exposure. *International Journal of Environmental Research and Public Health*, 14(5), p. 519.

Saravanabhavan, G., Werry, K., Walker, M., Haines, D., Malowany, M. and Khoury, C. (2017). Human biomonitoring reference values for metals and trace elements in blood and urine derived from the Canadian Health Measures Survey 2007–2013, *International Journal of Hygiene and Environmental Health*, 220(2A) p.p. 189-200.

Sheehan, M.C., Burke, T.A., Navas-Acien, A., Breysse, P.N, McGready, J. and Fox, M.A. (2014). Global methylmercury exposure from seafood consumption and risk of developmental neurotoxicity: a systematic review. *Bulletin of the World Health Organization*, 92, 254-269F.

Tanner, K., Windham-Myers, L., Fleck, J. A., Tate, K. W., McCord, S. A. and Linquist, B. A. (2016). The Contribution of Rice Agriculture to Methylmercury in Surface Waters: A Review of Data from the Sacramento Valley, California. *Journal of Environmental Quality - Surface Water Quality*, 46(1), p.p. 133 – 142.

United Nations Environment Programme (2019). Global Mercury Assessment 2018. UN Environment Programme, Chemicals and Health Branch Geneva, Switzerland. Available at : https://www.unenvironment.org/resources/publication/global-mercury-assessment-2018

International Agency for Research on Cancer (1993). World Health Organization, IARC Monographs on the evaluation of carcinogenic risks to humans: Beryllium, Cadmium, Mercury and Exposures in the Glass Manufacturing Industry, vol. 58, Lyon: WHO - IARC, 1993

World Health Organization (2000). Air quality guidelines for Europe ; second edition, WHO Regional Publications, European Series, No. 91.

World Health Organization (2015). Human Biomonitoring - Facts and Figures. WHO Regional Office for Europe. https://apps.who.int/iris/handle/10665/164588

World Health Organization (2010). Children's exposure to mercury compounds. Available at:

https://www.who.int/ceh/publications/children_exposure/en/

World Health Organization (WHO). (n.d.). Ten chemicals of major public health concern. Retrieved September 14 , 2018, from: http://www.who.int/ipcs/assessment/public_health/chemicals_phc/en/

Zero Mercury Working Group (ZMWG) . (n.d.). Zero Mercury . Retrieved from http://www.zeromercury.org/

Appendix 1: Additional information on exposure routes

Source of exposure	References
Environmental • Natural sources (e.g. weathering of rock) – minor source. • Man-made sources (e.g. incineration, burning of fossil fuels, industrial processes) – major source. • Can be found in both the metallic form and in various inorganic and organic complexes – interconversion between different forms in the atmosphere). • Release to air – long atmospheric lifetime (0.8 – 2 years)– long-range transport, conversion to inorganic forms. • Release to water from surface run-off – conversion to organic form (methylmercury) by microorganisms – bioaccumulation in food chains – high levels in many fish species. • Deposition to land – sorption onto soil or sediment particles – accumulation of organic mercury in crops (especially rice).	Scoping report and references therein World Health Organization, 2000
Occupational • Used in industrial processes e.g. production of chlorine gas and caustic soda. • Used in production and manufacture (e.g. batteries, PVC, and pigments). • Possible issues for management and recycling of wastes, particularly electricals such as fluorescent light bulbs / strip lighting.	Scoping report and references therein World Health Organization, 2000
Consumer • Used in electrical equipment (e.g., thermostats and switches), electrical lamps. • Used in medical and laboratory equipment (e.g. thermometers, barometers) and dental amalgams. • Used in fungicides, antiseptics, and disinfectants, (mostly discontinued). • Ethylmercury (thiomersal), is used in very small amounts in vaccines (as preservative) and pharmaceuticals.	Scoping report and references therein World Health Organization, 2000

Route of exposure	
Oral • Primary source of human exposure to mercury is the diet. • The most important exposure route is through the consumption of fish and shellfish. • Other food sources include consumption of rice grown in soil/water contaminated with methylmercury. • Relatively minor public exposure through the use of mercury in dental amalgams.	Scoping report and references therein World Health Organization, 2000 World Health Organization, 2010 Rothenberg et al., 2014 Sheehan et al., 2014 Tanner et al., 2016
Dermal • Not significantly absorbed through the skin and so this is not a significant route.	Scoping report and references therein World Health Organization, 2000 World Health Organization, 2010
Inhalation • Inhalation of mercury vapours may occur in industrial processes. • For the general population this is not a significant risk since the levels of mercury in outdoor air are usually very low. Minor route of exposure for the general population but can be more significant in specific occupational settings. Particularly where elevated exposure is possible, i.e. waste handling.	Scoping report and references therein World Health Organization, 2000 World Health Organization, 2010
Trans-placenta Mercury, and in particular methyl mercury has the potential permeate across membranes, this is important for the placenta, and blood/brain barrier. Maternal exposure can in turn result in foetal exposure.	Scoping report and references therein Park & Zheng, 2012 World Health Organization, 2010

Appendix 2: Additional information on health effects

Human health effect	Category	Justification for category	References
Neurological effects	Mercury (suspected)	Based on a systematic review of the literature – as discussed in scoping report	Grandjean and Landrigan (2006 , 2014) in scoping report
Developmental neurotoxicity	Methylmercury (suspected)	Based on a systematic review of the literature – as discussed in scoping report	Rice & Barone Jr., 2000 in the scoping report
Damage to central nervous system	Strong (mercury) Suspected (methyl mercury)	Based on harmonised listing of STOT RE 1 (mercury) and STOT RE 2 (methyl mercury)	CLP harmonized classification and labelling- – CLP harmonized classification and labelling – see Table 4.1 in Section 4
Cancer (lung, liver, kidney)	Suspected (mercury) Evidence lacking (methyl mercury)	Listing under IARC classification for mercury (2B) and methyl mercury (3)	IARC classification (International Agency for Research on Cancer, World Health Organization, 1993) – CLP harmonized classification and labelling – see Table 4.1 in Section 4
Reproductive toxicity and birth defects	Strong (mercury) Evidence lacking (methyl mercury)	Based on harmonised listing of Repr.1B (mercury) and lack of classification (methylmercury) under CLP	CLP harmonized classification and labelling – see Table 4.1 in Section 4

For the categorisation of the strength of evidence for human health effects, the following criteria has been used:

- **Strong –** where the health effect is confirmed by either a harmonised classification indicating that there is a known effect (e.g. 1A or 1B for CMRs) (see Table 4.1), or where there is no applicable C&L classification, a statement in the Scoping Document that concludes there is strong evidence (or where a significant body of evidence is presented in the scoping document).
- **Suspected –** where there is either (a) a harmonised classification indicating that there is a suspected effect (e.g. category 2 CMRs or similar); (b) notified classification for that effect, or (c) where there is no applicable C&L classification, a statement in the Scoping Document (or other references presented in the Table above) that there is a suspected health impact.
- **Evidence lacking –** where a health effect is noted in the Scoping Document (or other evidence sources referenced in the Table above), but it is stated that evidence is currently lacking or there are uncertainties or inconsistencies in the available evidence.

- **Not applicable –** where a health effect does not apply to a specific group/gender