Human biomonitoring

Basics: educational course

World Health Organization
European Region

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Abstract

Human biomonitoring (HBM) is an instrument for measuring the internal dose of exogenous substances/chemicals that enter a body during a certain period of exposure from a range of sources. It contributes to reducing uncertainties in the assessment of health risks from chemicals and provides information for decision-making on the prevention of negative impacts of chemicals on human health and the environment. Promoting the use of HBM is a recognized priority of chemical safety globally and in the WHO European Region. Given the complexity of HBM, relevant capacities should be built at the national level to explore its benefits. This educational course on HBM, presented in the form of slides with accompanying notes and references, compiles scientific information on HBM as well as practical examples. It was developed to support the training of public-health and health-care professionals; students of medical, biological and other allied sciences; and professionals and decision-makers in the health, environment and other relevant sectors.

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Content

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Introduction

Exposure to chemicals is increasingly complex due to changes in the production, trade and use of chemicals; fast interventions and the promotion of different products; the prevalence of chemical mixtures; and growing awareness of chemicals among the public and policy-makers *(1)*. In this context, knowledge and information on humans' exposure to chemicals is important for RA and for the identification and implementation of risk-reduction measures.

Human biomonitoring (HBM) is an instrument for direct measurement of internal exposure to chemicals from different sources and by different pathways *(2,3*). Nowadays, everyone is exposed to hazardous chemicals. Alarming concentrations have been found in pregnant women, which can impact the health of the next generation *(4*), and high levels of persistent organic pollutants and heavy metals have been observed in certain population groups *(3,4,5)* within countries and globally *(6)*. To address these issues, carefully planned and conducted national HBM efforts are needed to identify critical exposures, derive effective measures, and ensure health and well-being.

Promoting the use of HBM is a recognized priority of chemical safety globally and in the WHO European Region, as set out in the WHO Chemicals Road Map in 2017 *(7)*, and in the Parma and Ostrava declarations on environment and health in 2010 and 2017, respectively *(8,9)*.

Planning and implementing HBM programmes is a complex task, requiring the involvement of broad expertise and proper planning in all stages. Despite the many benefits of HBM, due to methodological limitations it cannot answer all questions on exposure. Interpretation and communication of HBM results are challenging stages of HBM surveys. Much experience, knowledge and data are collected through national, multicountry and global HBM surveys; however, further developments are needed to widen the use of HBM for RA and decision-making. This educational course covers all of these aspects.

Sources

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Content and structure of the course

The information is presented in the following seven modules.

- **Module 1. Introduction**
  - Chemicals in the environment and consumer products
  - Environmental health paradigm
- **Module 2. Principles and objectives of HBM**
- **Module 3. Biomarkers**
  - Basics of toxicokinetics and toxicodynamics
  - Types of biomarkers
  - HBM in the exposome
- **Module 4. Planning and conducting HBM studies**
  - Selection of type of HBM study
  - Prioritization of chemicals
  - Selection of target population and biomarkers
  - HBM ethics
  - Sampling size
  - Community involvement and communication strategy
  - Field work
  - Phased approach to planning and conducting an HBM study
- **Module 5. Laboratory analysis, data management**
  - Quality assurance and quality control
  - Biobanking
  - Data management and analysis
- **Module 6. Interpretation and evaluation of results**
- **Module 7. HBM experience and initiatives**
  - Global: Stockholm Convention on Persistent Organic Pollutants (POPs), Minamata Convention on Mercury
  - Multicountry: European Human Biomonitoring Initiative (HBM4EU), Arctic Monitoring and Assessment Programme (AMAP)
  - National: examples from Belgium, Canada, Czechia, Germany, Japan, the Republic of Korea, Slovenia and the United States of America

The course includes 256 slides in PDF format accompanied by explanatory text, animation on toxicokinetics and toxicodynamics, and 7 interviews with leading scientists in the area. The PowerPoint version is available to interested users upon request. Please email euroeceh@who.int for more information.

MODULE 1

Introduction

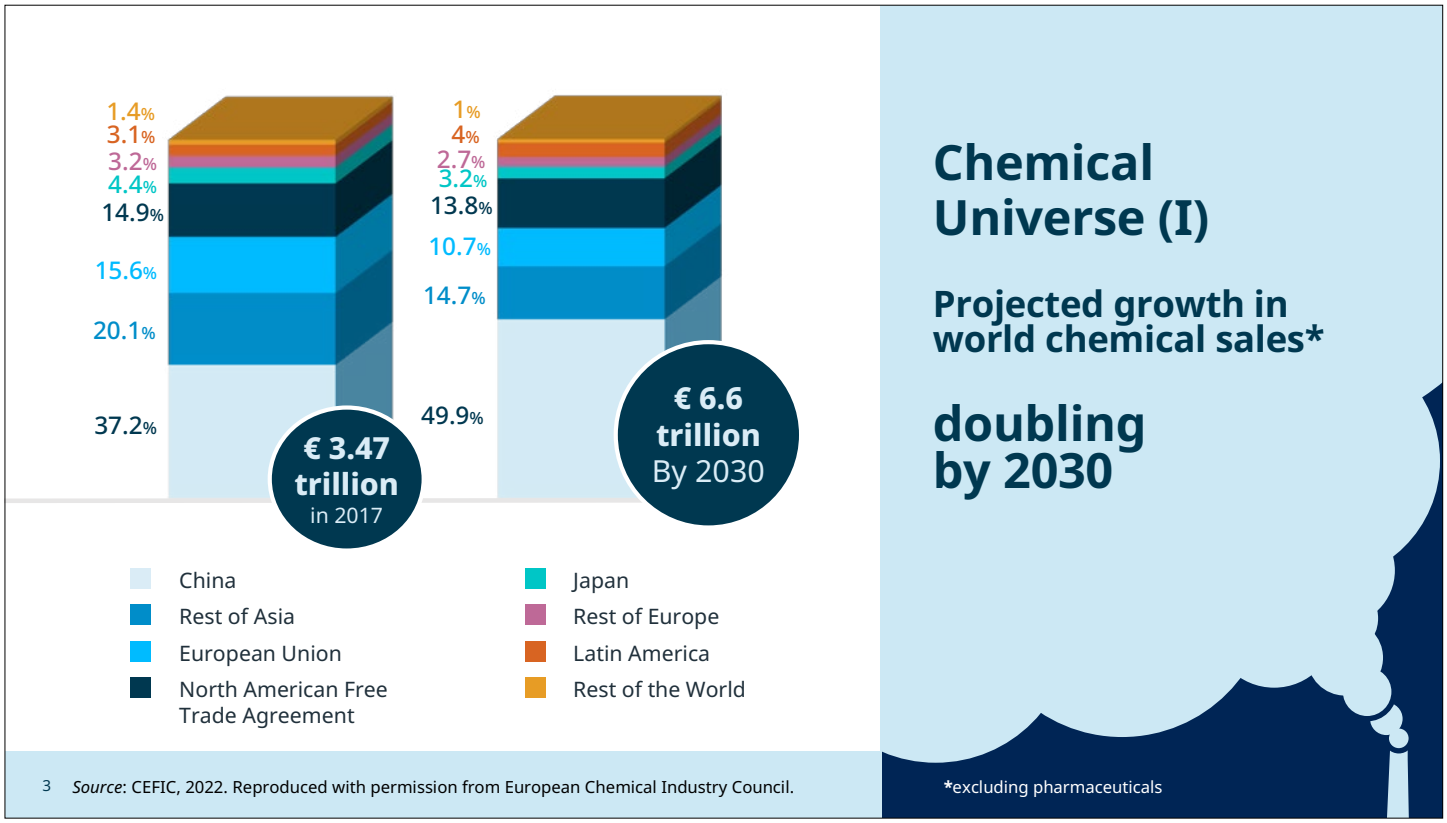
Chemicals in the environment and consumer products

Environmental health paradigm

World Health Organization

European Region

Chemicals in the environment and consumer products



3 *Source*: CEFIC, 2022. Reproduced with permission from European Chemical Industry Council.

Chemicals are essential for economic development and human well-being. According to the latest assessments, the size of the global chemical industry exceeded US$ 5 trillion in 2017. Between 2000 and 2017 the global chemical industry's production almost doubled, from about 1.2 billion tonnes to 2.3 billion tonnes. It is projected to double by 2030 and to triple by 2050. In 2017, the BRICS countries (Brazil, the Russian Federation, India, China and South Africa) accounted for around 44% of all sales of chemicals and Europe accounted for 16.9% of sales. Chemical manufacturing is the fourth largest industry in the European Union (EU) comprising 30 000 companies, 95% of which are small and medium-sized enterprises.

Notes: EU: European Union.

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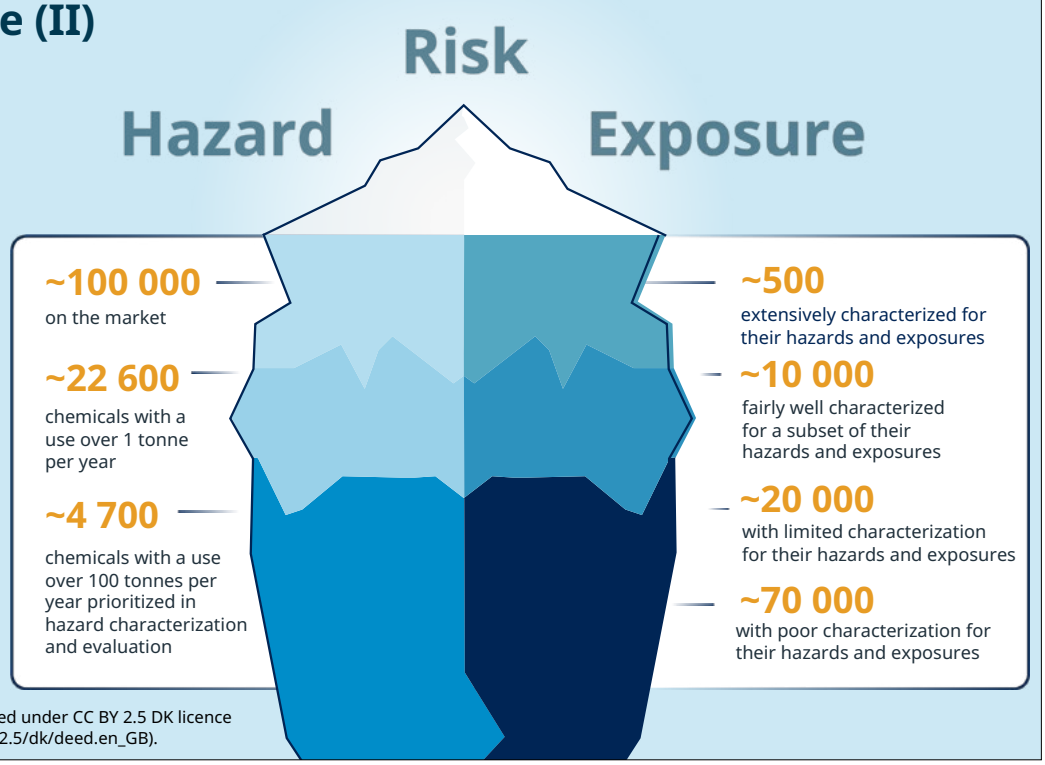
Chemical Universe (II)



4 *Source*: adapted from EEA, 2019. Reproduced under CC BY 2.5 DK licence (https://creativecommons.org/licenses/by/2.5/dk/deed.en_GB).

The number of chemicals on the market is growing rapidly. The 2019 report jointly developed by the UNEP and the ICCA estimated the total number of industrial chemicals in commerce globally at 40 000 to 60 000, with 6000 of these chemicals accounting for more than 99% of the total volume.

As of 2021, the CAS Registry contained over 250 million organic substances, alloys, minerals, mixtures, polymers, and salts disclosed in publications since the early 1900s, and around 70 million protein and nucleic acids sequences. By August 2019, under the EU's REACH 22 600 chemicals were registered.

Availability of information on chemicals hazards and exposure is as follows:

- ~ 500 chemicals are considered sufficiently regulated and monitored regularly;
- ~ 10 000 chemicals at the EU and national level are characterized for some but not for all known hazards, have specific limit values and are monitored quantitatively but irregularly across time, media or space;
- ~ 20 000 chemicals are characterized in term of hazards mainly by modelling, or where exposure data are based on qualitative screenings done occasionally and in few media; and
- ~ 70 000 chemicals – typically low-volume chemicals – usually have no or very few hazard characteristics available and information on uses and exposure is scarce, not characterized or measured in very few media.

Notes: CAS: Chemical Abstract Service; EEA: European Environmental Agency; EU: European Union; ICCA: International Council of Chemical Associations; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals; UNEP: United Nations Environment Programme.

Sources

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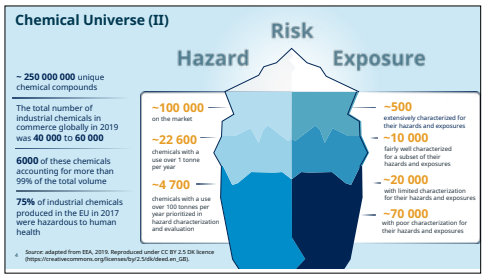

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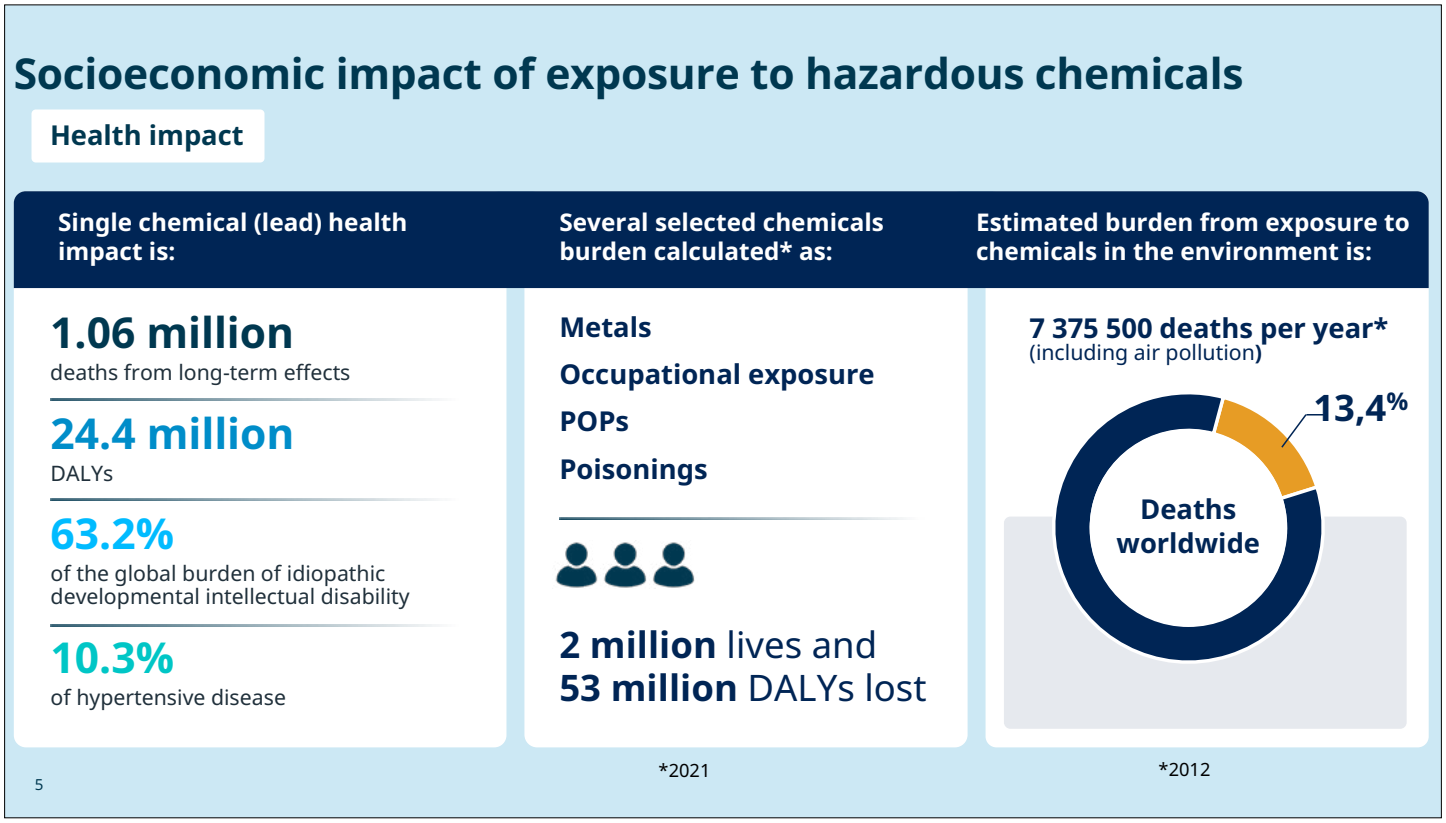

Exposure to hazardous chemicals can lead to health disorders and diseases. The 2021 WHO data addendum estimated that 2 million lives and 53 million disability-adjusted life-years were lost in 2019 through exposure to selected chemicals. This is higher than the estimate of the previous data addendum for 2016 of 1.6 million lives and 45 million disability-adjusted life-years lost. Even this latest calculation has been done for limited number of chemicals for which there are enough scientific data and is underestimated.

Notes: DALYs: disability-adjusted life years; POPs: persistent organic pollutants.

Sources

The public health impact of chemicals: knowns and unknowns. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/206553, accessed 10 November 2022).

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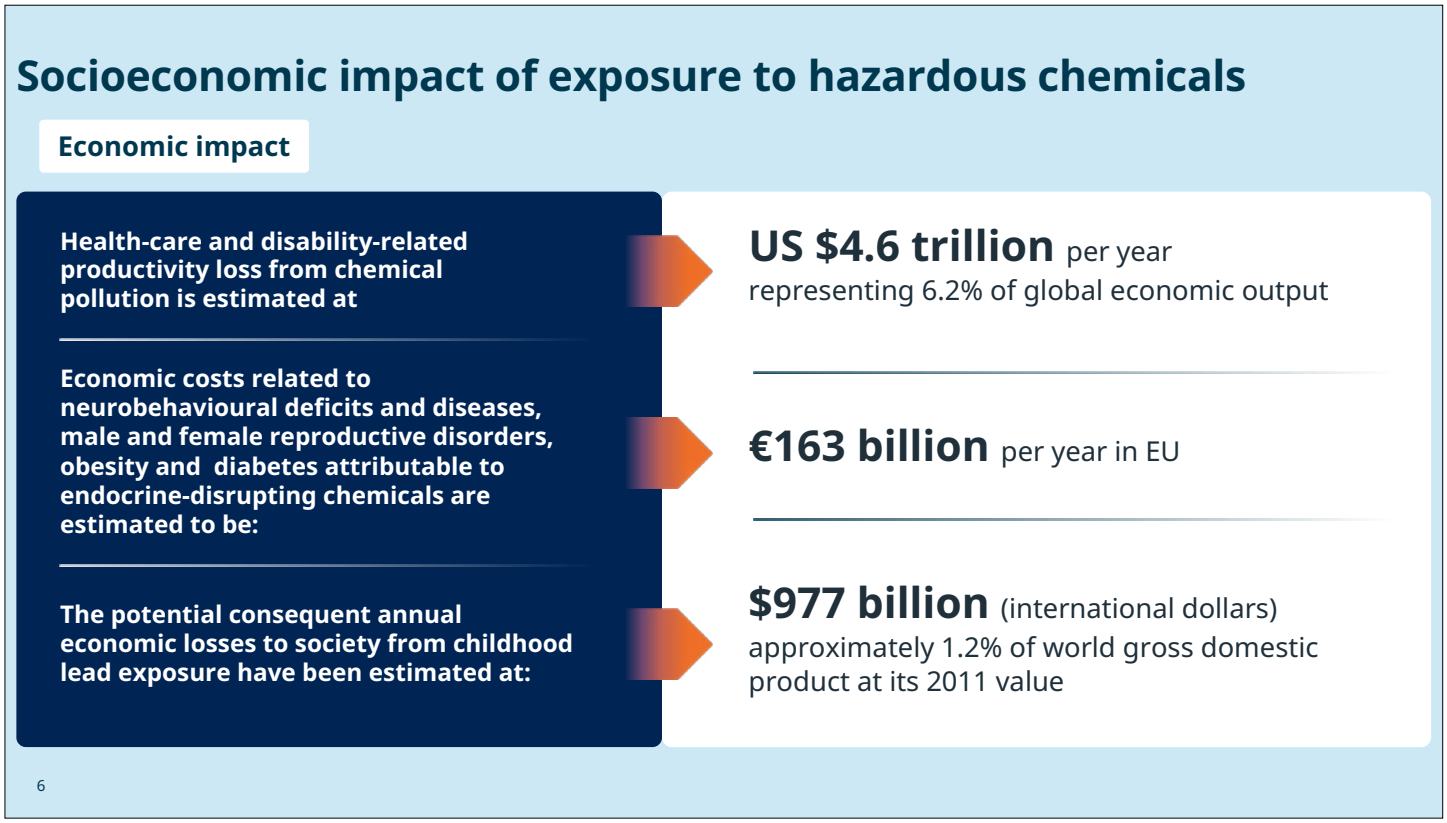

Economic costs from exposure to hazardous chemicals are large; for example, annual economic losses to society from childhood exposure to one chemical, lead, have been estimated at $ 977 billion international dollars: that is, 1.2% of world gross domestic product at its 2011 value. As per experts estimates for endocrine-disrupting chemicals, the substantial costs were related to loss of IQ and intellectual disability attributable to prenatal exposure to organophosphate. Base case estimates identified €146 billion in attributable costs, whereas sensitivity analyses suggested that costs might range from €46.8 billion to €195 billion annually. Phthalate-attributable adult obesity was the second largest driver of costs, at €15.6 billion per year. The total costs of all conditions probably attributable to endocrine-disrupting chemicals were €191 billion, with sensitivity analyses suggesting costs ranging from €81.3 billion to €269 billion annually.

Notes: EU: European Union.

Sources

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Mandate for actions: global policy (I)

SDGs

SDG target 3.9:
By 2030 substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water, and soil pollution and contamination.

SDG target 6.3:
By 2030, improve water quality by reducing pollution, eliminating dumping and minimizing release of hazardous chemicals and materials, halving the proportion of untreated wastewater and increasing recycling and safe reuse globally.

SDG target 12.4:
By 2020, achieve the environmentally sound management of chemicals and all wastes throughout their life cycle, in accordance with agreed international frameworks, and significantly reduce their release to air, water and soil in order to minimize their adverse impacts on human health and the environment.

7 *Source*: WHO, 2017.

Chemical and waste management plays increasingly significant role in every economic and social sector. Need for prevention of chemical pollution and implementing sound chemicals management is directly reflected in Targets 3.9, 6.4 and 12.4 of SDGs. Chemicals management is important for achieving many other goals, such as those related to poverty, agriculture, oceans, decent work and climate change; while less pronounced, their contribution is also important in areas such as education and gender equality. Actually, the sound management of chemicals and wastes can provide solutions to achieve practically all SDGs.

Notes: IHR: International Health Regulations (2005); SDG: sustainable development goal; UNECE: United Nations Economic Commission for Europe; WHA: World Health Assembly.

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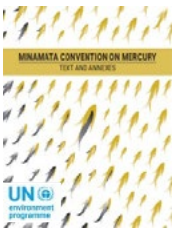
Mandate for actions: global policy (II)

Legally binding multilateral agreements

Stockholm Convention on persistent organic pollutants

Global monitoring plan



Minamata Convention on mercury

Monitoring of mercury and mercury compounds to support evaluation of human exposure to mercury

Voluntary policy frameworks

Strategic Approach to International Chemicals Management

Encourages Member States to take actions focused on filling gaps in knowledge and methodologies for RA, increasing biomonitoring and surveillance

8 *Source*: (top left) UNEP, 2020. Reproduced with permission from United Nations Environment Programme, Secretariat of the Stockholm Convention. (bottom left) UNEP, 2019. Reproduced with permission from United Nations Environment Programme, Secretariat of the Minamata Convention. (top right) UNEP, 2022. Reproduced with permission from SAICM Secretariat. (bottom right) WHO, 2017.

Assessment of exposure to chemicals and related health risks is a global priority, as stated in main strategic environment and health documents and policies: the multilateral environment agreements such as the Stockholm Convention on Persistent Organic Pollutants and the Minamata Convention on Mercury, SAICM as well as the WHO Chemical Roadmap.

Notes: RA: risk assessment; SAICM: Strategic Approach to International Chemicals Management; UNEP: United Nations Environment Programme.

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Mandate for actions: regional policy

Parma Declaration on Environment and Health (2010)	Ostrava Declaration on Environment and Health (2017)
Better monitoring exposure to hazardous chemicals and undertaking research to improve the understanding of human exposures to chemicals and the associated burden of diseases	Promote the use of HBM as a public health policy tool and support efforts to generate comparable data to allow international assessments
EU Chemicals Strategy for Sustainability towards a toxic-free environment	HBM is key to improve understanding of chemical impact and should be further promoted

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HBM is a chemical safety priority within the Parma and Ostrava Declarations on Environment and Health (2010, 2017), and other multicountry agreements in the WHO European Region (e.g. the EU Chemical Strategy for Sustainability).

Notes: EU: European Union; HBM: human biomonitoring.

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Hazardous chemicals may present in air, surface and groundwater, soils and sediments, food, products/ article, and living organisms (including people) that is a growing public concern. According to the 2019 EU survey of 27 000 citizens regarding their attitudes towards chemicals, 84% of Europeans are worried about the impact of chemicals present in everyday products on their health, and 90% are worried about their impact on the environment.

Notes: EU: European Union.

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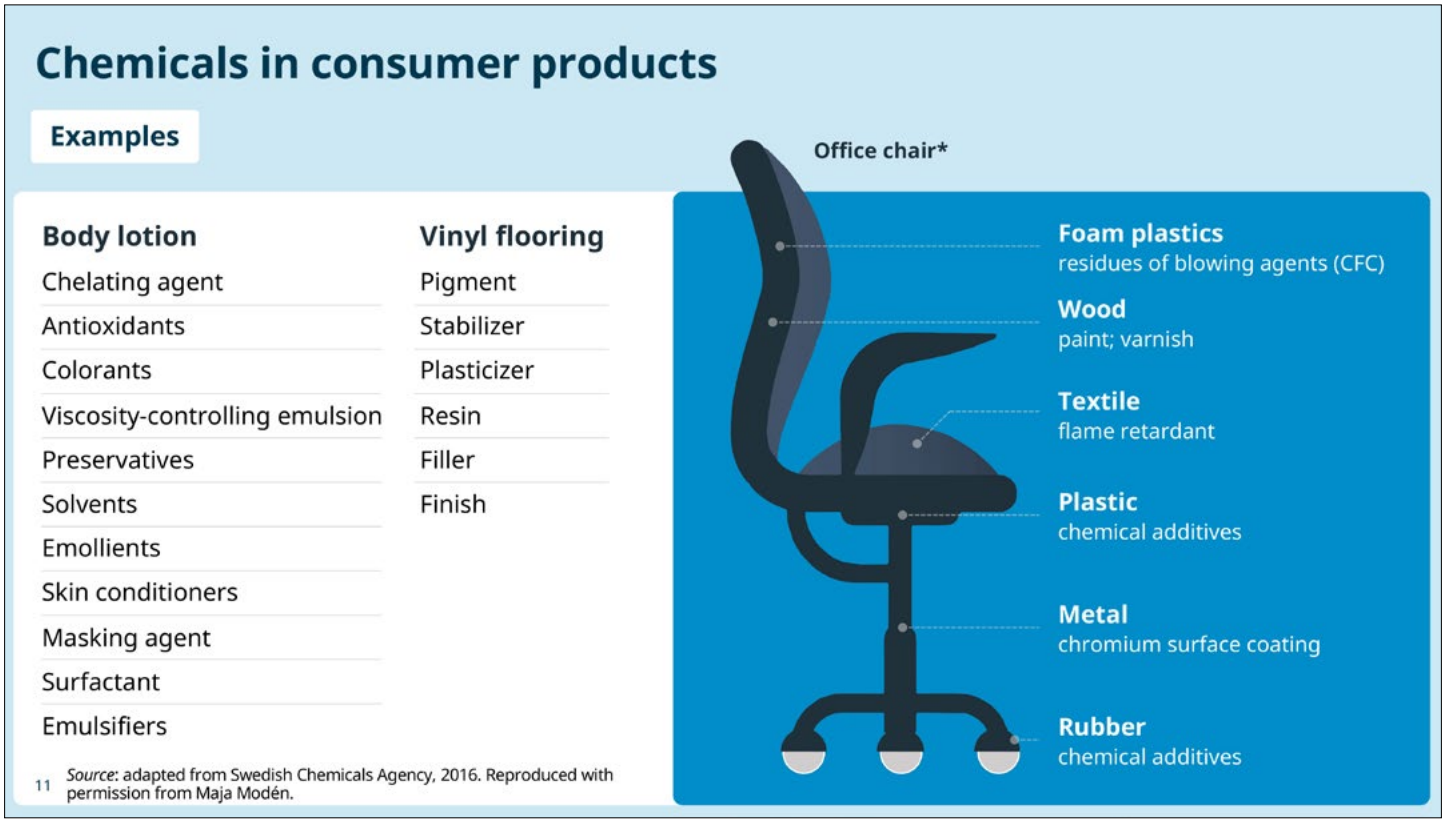

Chemical substances provide important functionality in a wide range of products. The majority are used with a high degree of safety. However, the use of toxic chemicals in articles is not decreasing, and they are a growing concern.

People are rarely exposed to single chemicals. Commonly, it is a mixture of chemicals from various sources and at different stages of a product life-cycle: during manufacturing, use or manipulation, and disposal.

Notes: CFC: Chlorofluorocarbons; UNEP: United Nations Environment Programme.

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Grouping of chemicals

Examples

According to chemical nature:	organic, inorganic
According to persistence/timespan in the environment and human body:	persistent versus not persistent/short life bioaccumulating versus not accumulating
According to solubility:	lipophilic water soluble
According to toxicity:	carcinogenic toxic for reproduction endocrine disruptor, etc.
According to physical state:	liquid solid gaseous
According to use:	pesticides, cosmetics, industrial chemicals, household chemicals, food additives, preservatives, pharmaceuticals, etc.

12

Chemicals can be grouped according to different criteria, such as nature, use, toxicity, physicochemical characteristics, etc. In the context of HBM, chemicals characteristics such as structure and type or persistence, bioaccumulation ability, toxicokinetics and toxicodynamics have a critical role. Planning of HBM studies guided by scientific information on the specific characteristics or chemical properties, such as toxicokinetic.

The purpose of chemicals use is also important for prioritizing chemicals for HBM. Pesticides are used all over the world, and dietary uptake is considered as the main source of human exposure to pesticides in the general population. Other commonly monitored substances include metals, organic compounds including PAHs, polychlorinated biphenyls, phthalates, dioxins, aromatic amines, per- and polyfluorinated chemicals. Metals (particularly cadmium, lead and mercury) are the most studied chemicals among the investigated HBM programmes. They are toxic, can cause a serious health impact and are still widely used.

Notes: HBM: human biomonitoring; PAHs: polyaromatic hydrocarbons.

Sources

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Angeler J, Ewers E, Wilhelm M. Human biomonitoring: state of the art. Int Journal Hygiene Environ Health. 2007;210(3-4):201-28. doi: 10.1016/j.ijheh.2007.01.024.

Chemical form: how it influences HBM

A chemical's nature determines its fate in the environment, toxicology, human health and environment impacts

The same chemical in different forms can differ in characteristics that are important for HBM

Pathways of exposure depend on the chemical's physical state (liquid, solid, gaseous)

Example demonstrating how the form of mercury influences the planning and conducting of a HBM survey

Mercury form	Sources into environment	Exposure pathways	Main excretion pathways	Preferred matrix for HBM	Heath endpoints
Elemental (metallic) mercury (**Hg^0**)	Natural and anthropogenic	Inhalation	Urine Feces	Blood	Central and peripheral nervous system, kidneys, lungs
Inorganic mercury **Hg^{2+}**	Natural and anthropogenic	Ingestion Dermal	Urine	Urine	Central nervous system, kidneys, gastrointestinal tract, immune system, skin (acrodynia in children)
Organic mercury **MeHg** (methylmercury)	Environmental conversion	Ingestion Parenteral Transplacental	Feces	Hair Blood	Central nervous system, cardiovascular system

13 *Source*: WHO, 2021.

Toxicity of chemical compounds, fate in the environment, exposure pathways, human health and environmental impacts depend on chemical nature. Mercury is an example of how the chemical form and nature influences HBM of mercury.

Notes: HBM: human biomonitoring.

Sources

Human biomonitoring: facts and figures. Copenhagen: WHO Regional Office for Europe; 2015 (https://apps.who.int/iris/handle/10665/164588, accessed 10 November 2022).

Mercury and human health: educational course. Copenhagen: WHO Regional Office for Europe; 2021 (https://apps.who.int/iris/handle/10665/345443, accessed 10 November 2022).

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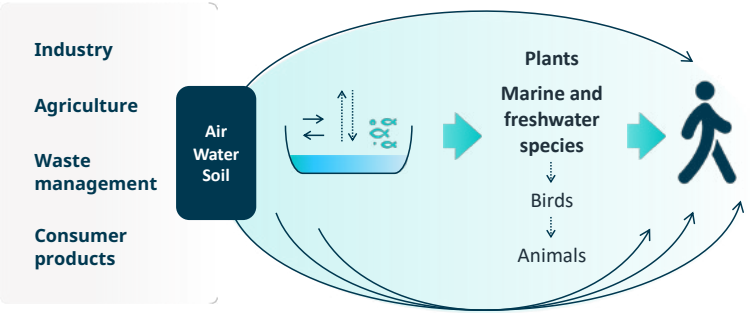
Persistence in the environment and bioaccumulation

Persistent and bioaccumulating

- Resistance to degradation in the environment; once in the environment the chemical stays for months and years
- Often lipid soluble
- Many have high mobility and ability for transfer over long distances
- Bioaccumulating in human bodies

Not persistent and not accumulating

- Half-life in the environment and human body is short (hours to days)
- Mostly water soluble
- Quickly metabolized; not only parental compound but also, their metabolites can be considered for HBM



Persistence:

the length of time a chemical stays in the environment, once introduced. Persistent chemicals do not break down easily in the environment or in the body

Bioaccumulation:

the process by which a chemical toxicant builds up in an individual organism

14

There are chemicals known as persistent in the environment and bioaccumulating in the human body. They can be transported long distances, persist in the environment, have an ability to biomagnify and bioaccumulate in ecosystems. Their negative effects on human health can be significant. HBM of these chemicals is of particular interest. The most encountered POPs are pesticides and some industrial chemicals. The most typical representatives are metals, polychlorinated bisphenols, perfluorinated compounds, unintentional by-products of many industrial processes, especially PCDD and PCDF. PBTs are mostly lipophilic and accumulate in adipose tissue. They have very long period of elimination from a human body and can be measured in biomatrix with a high lipids concentration: such as blood or breastmilk.

Examples of non-persistent chemicals are bisphenols and phthalates, which are mostly water soluble and, often, urine is the best matrix to assess exposure.

Individual exposure to persistent and bioaccumulative compounds can be characterized using a single sample. This is because they are partitioned into and stored in certain tissues (e.g. adipose tissue) and they are eliminated slowly. This results in low sample-to-sample variability in biomarker values during a short time interval. By comparison, biomarkers for rapidly eliminated compounds can vary substantially over time, depending on recent exposure episodes. Here repetitive sampling may be required in order to characterize individual exposure levels in populations and individuals.

Notes: HBM: human biomonitoring; PBTs: persistent bioaccumulative toxic chemicals; PCDD: polychlorinated dibenzo-*p*-dioxins; PCDF: polychlorinated dibenzofurans; POPs: persistent organic pollutants.

Sources

Stockholm convention on persistent organic pollutants [website]. Geneva: Secretariat of the Stockholm Convention; 2022 (http://www.pops.int/, accessed 10 November 2022).

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Ougier E, Zeman F, Antignac JP, Rousselle C, lange R, Kolossa-Gehring M, Apel P. Human biomonitoring initiative (HBM4EU): Human biomonitoring guidance values (HBM-GVs) derived for bisphenol A. Environ Int. 2021;154. doi: 10.1016/j.envint.2021.106563.

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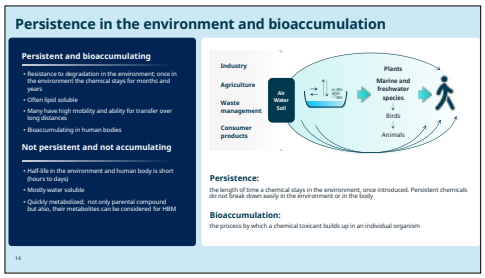
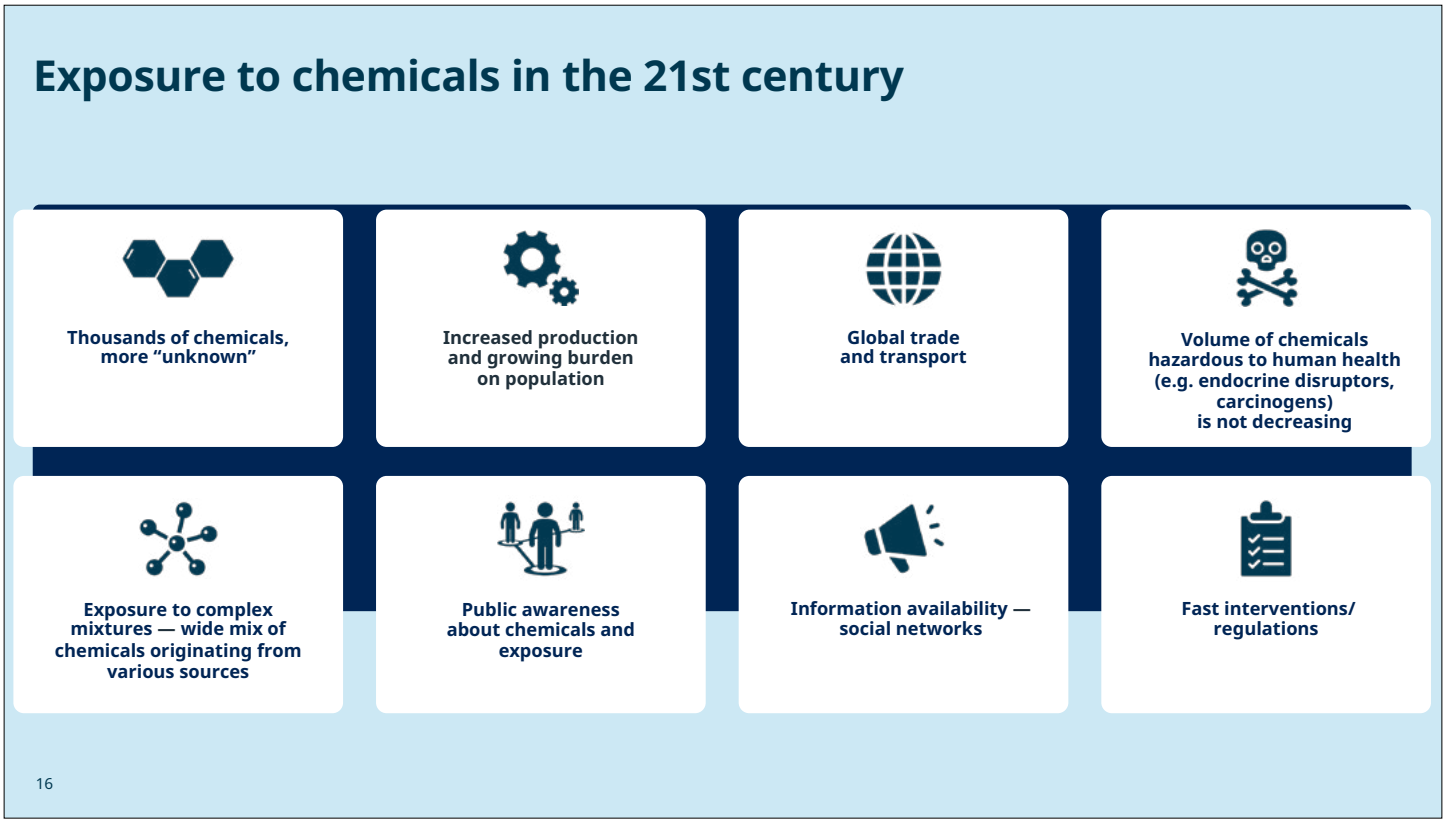


Lange R, Apel P, Rousselle C, Charles S, Sissoko, Kolossa-Gehring M, Ougier E. The European Human Biomonitoring Initiative (HBM4EU): Human biomonitoring guidance values for selected phthalates and a substitute plasticizer. Int J Hyg Environ Health. 2021;234:113722. doi: 0.1016/j.ijheh.2021.113722.

Human biomonitoring: facts and figures. Copenhagen: WHO Regional Office for Europe; 2015 (https://apps.who.int/iris/handle/10665/164588, accessed 10 November 2022).

Environmental health paradigm

Notes: Throughout the course the term “environment” includes the ambient environment, consumer products and food.



Exposure* to chemicals is getting more complex because of changes in production, trade and use of chemicals. The rate of chemical production is growing and exposure within a population is, consequently, also growing. Fast interventions and promotion of different products, and exposure to mixtures, raise awareness in public and policy-makers. Regulatory decisions on chemicals require more scientific information, including on exposure, as a priority.

*WHO defines exposure as the concentration or amount of a particular agent that reaches a target organism, system or (sub)population in a specific frequency for a defined duration. The exposure concentration is the concentration of a chemical in a medium (air, water or soil in outdoor and indoor locations, food and products) with which a person is in contact.

Sources

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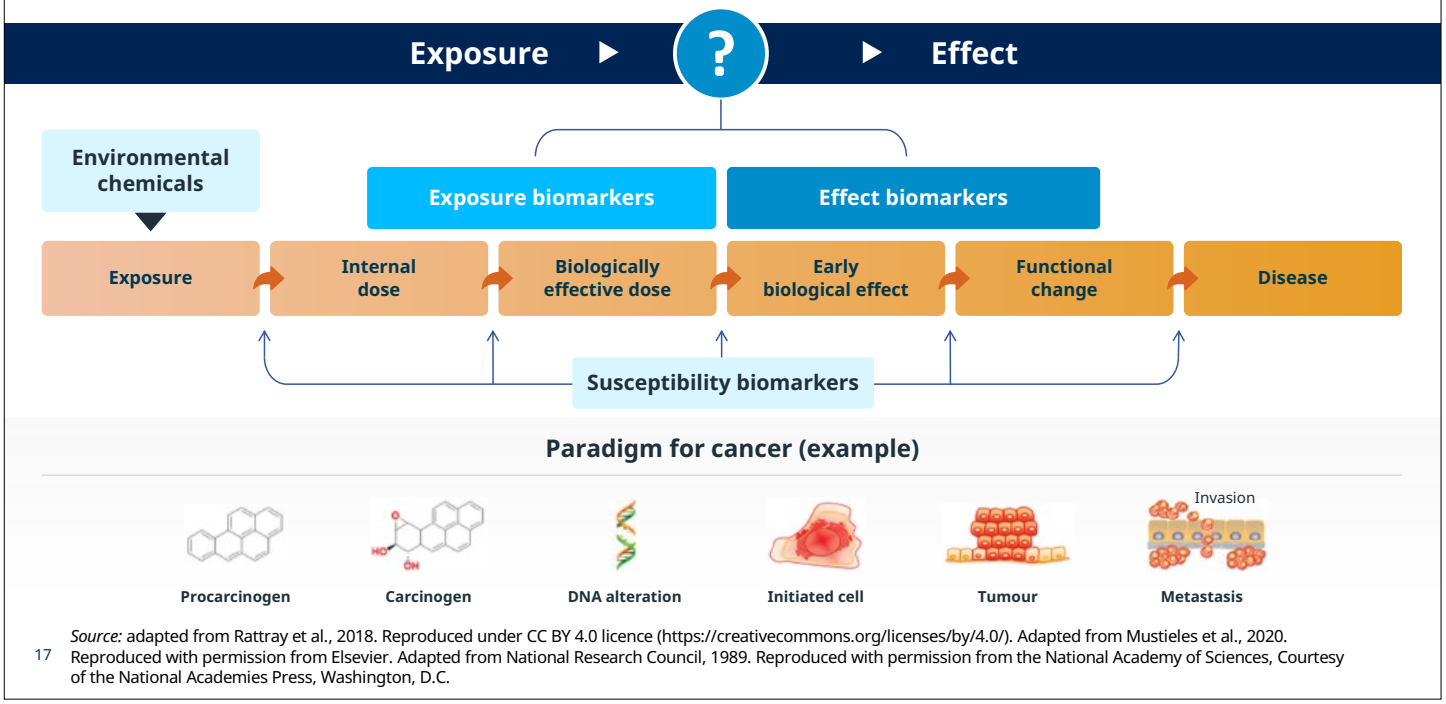
Environmental health paradigm



17 *Source:* adapted from Rattray et al., 2018. Reproduced under CC BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/). Adapted from Mustieles et al., 2020. Reproduced with permission from Elsevier. Adapted from National Research Council, 1989. Reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.

Humans are exposed to a complex mixture of chemicals, from multiple sources and varying durations, and these exposures can impact people health depending on the route of exposure, the internal dose at the target organ, the critical window of exposure, timing of exposure, individual susceptibility, lifestyle, and so on.

This slide shows in detail the conceptual pathway representing the continuum between environmental chemical exposure and the potential onset of clinical disease – the environmental exposure–health paradigm – identifying concrete stages in the sequence and the biomarkers used to track each phase.

Sources

National Research Council. Biologic Markers in Reproductive Toxicology. Washington (DC): National Academies Press; 1989. doi.org/10.17226/774.

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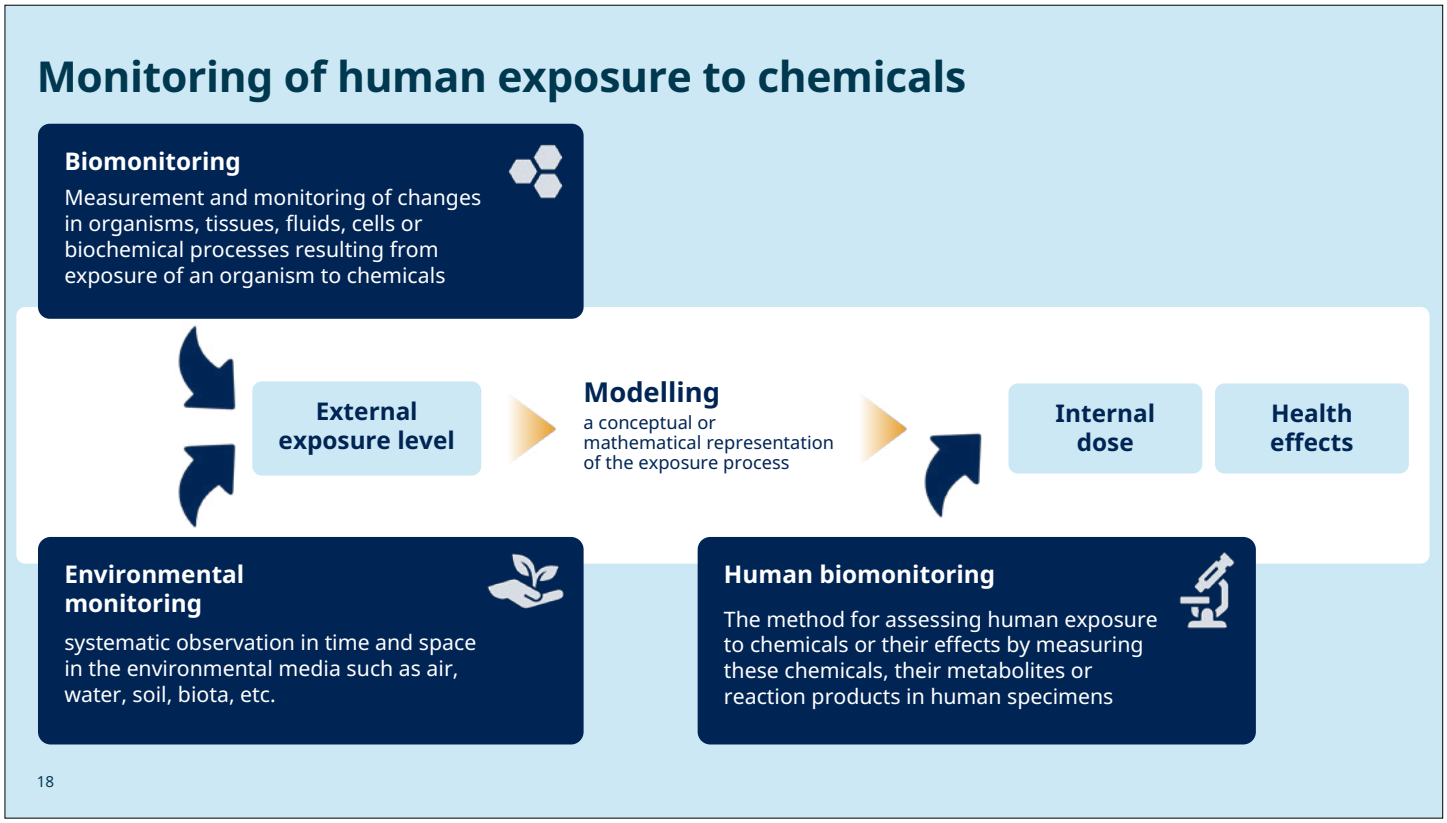

There are different approaches to assessment of exposure that can complement each other.

- Environmental monitoring as the measurement of concentration of chemicals in a medium (air, water, soil, and food): external exposure. In practice, exposure often includes estimates of intake (e.g. amount of chemical inhaled or ingested) and the amount of a chemical that is absorbed into the body.
- Monitoring of biota, species other than humans, for example measuring mercury in fish; from these data ingested dose can be estimated.
- HBM is a method for assessing human exposure to chemicals by measuring the chemicals, their metabolites or reaction products in a biological matrix (internal exposure).

Modelling is needed to calculate internal dose from external exposure data; HBM allows the direct measure of internal dose.

Notes: HBM: human biomonitoring.

Sources

Sexton K, Needham LL, Pirkle JL. Human biomonitoring of environmental chemicals: measuring chemicals in human tissue is the "gold standard" for assessing the people's exposure to pollution. Am Sci. 2004;92(1):38–45.

Human Biomonitoring Commission (HBM Commission): about [website]. Dessau-Roßlau: German Environment Agency; 2020 (https://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/human-biomonitoring-commission-hbm-commission, accessed 10 November 2022).

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International Programme on Chemical Safety, Organisation for Economic Co-operation and Development. IPCS glossary of key exposure assessment terminology. In: IPCS risk assessment terminology. Geneva: World Health Organization; 2004 (https://apps.who.int/iris/handle/10665/42908, accessed 10 November 2022).

Principles of characterizing and applying human exposure models. Geneva: World Health Organization; 2005 (https://apps.who.int/iris/handle/10665/43370, accessed 10 November 2022).

Use of chemicals: examples of pathways and routes of exposure

Chemical(s)	Type of use	Source/pathway of exposure	Route of exposure (main)
Solvents	Building materials	Indoor air, dust	Inhalation, dermal
Plasticizers	Children toys	Object-to-mouth behaviour (in children)	Ingestion
Dyers	Textile	Skin contact	Dermal
PFAS	Bakery bags and other food contacting products	Food contamination	Ingestion
Insecticides	Insect control in home	Indoor air and sediments on surfaces	Inhalation, dermal

Pathway of exposure:
link between environmental releases and intake of the environmental chemicals in local populations that might come into contact with, or be exposed to, environmental contaminants

Dermal exposure:
the process by which chemical come in contact with the skin surface and penetrate through the skin and are taken up in the body

Ingestion:
oral intake of chemicals

Inhalation:
intake of chemicals through the respiratory system

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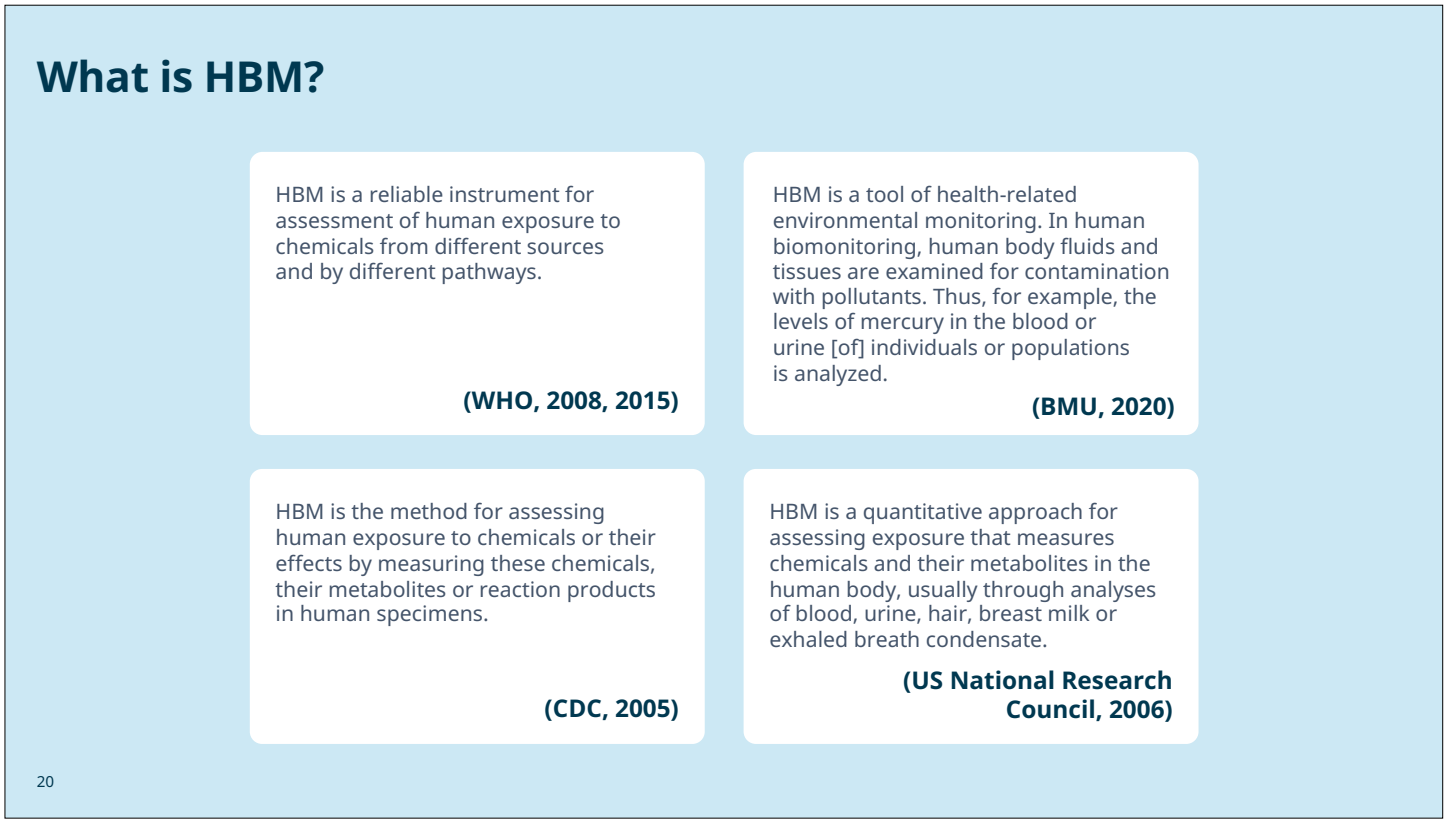
Chemicals are used for different purposes: pesticides in agricultural production, industrial chemicals for production of solvents, plastics, building materials, textile, children's toys, cosmetics, pharmaceuticals, and so on.

The purpose/area of chemical use often determines a chemical of concern and exposure pathways that is important to be considered in planning of HBM surveys.

Notes: HBM: human biomonitoring; PFAS: per- and polyfluoroalkyl substances.

Sources

Human health risk assessment toolkit. chemical hazards, second edition. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/handle/10665/44458, accessed 10 November 2022).



There is no one definition of HBM agreed at a global level. However, the understanding of HBM is common.

In fact, HBM is a powerful tool for tracing the uptake of chemicals in the human body, allowing the assessment of internal concentrations of chemicals or their metabolites in human biological samples such as urine or blood. It aggregates exposure from different sources and by different exposure routes, hence providing a more accurate estimate of the body burden. Therefore, assessment of human exposure provides important information on exposure for health RA and provides data to improve it.

Notes: BMU: Bundesministerium für Umwelt, Naturschutz und nukleare Sicherheit [German Environment Agency]; CDC: United States Centers for Disease Control and Prevention; EEA: European Environment Agency; HBM: human biomonitoring; RA: risk assessment; US: United States.

Sources

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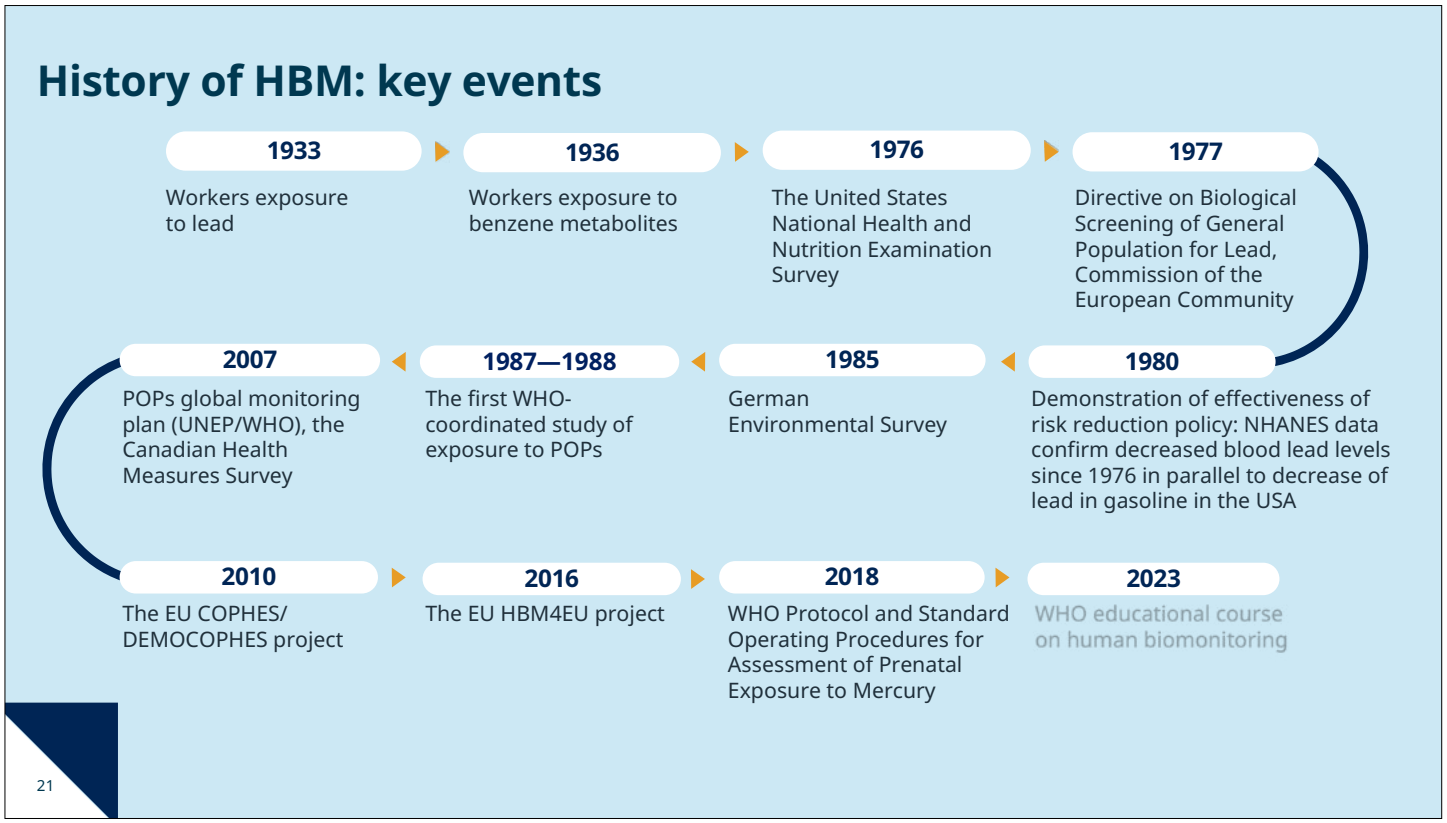

Notes: COPHES: European Coordination Action on Human Biomonitoring; DEMOCOPHES: Demonstation of a Study to Coordinate and Perform Human Biomonitoring on a European Scale; EU: European Union; HBM4EU: European Human Biomonitoring Initiative; NHANES: National Health and Nutrition Examination Survey; POPs: persistent organic pollutants; UNEP: United Nations Environment Programme; US: United States; USA: United States of America.

Sources

Angerer J, Ewers U, Wilhelm M. Human biomonitoring: state of the art. Int J Hyg Environ Health. 2007;210(3-4):201-28. doi: 10.1016/j.ijheh.2007.01.024.

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Levels of PCBs, PCDDs and PCDFs in human milk. Results from the second round of a WHO-coordinated exposure study. Environmental Health in Europe Series No. 3. Copenhagen: WHO Regional Office for Europe; 1996.

MODULE 2

Principles and objectives of HBM

World Health Organization

European Region

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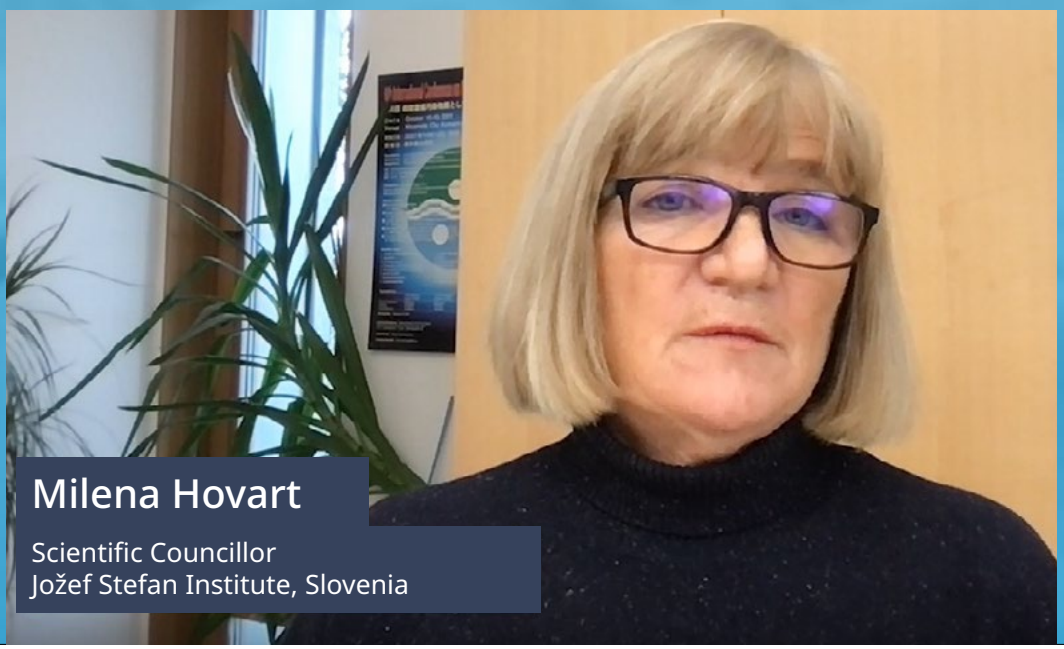

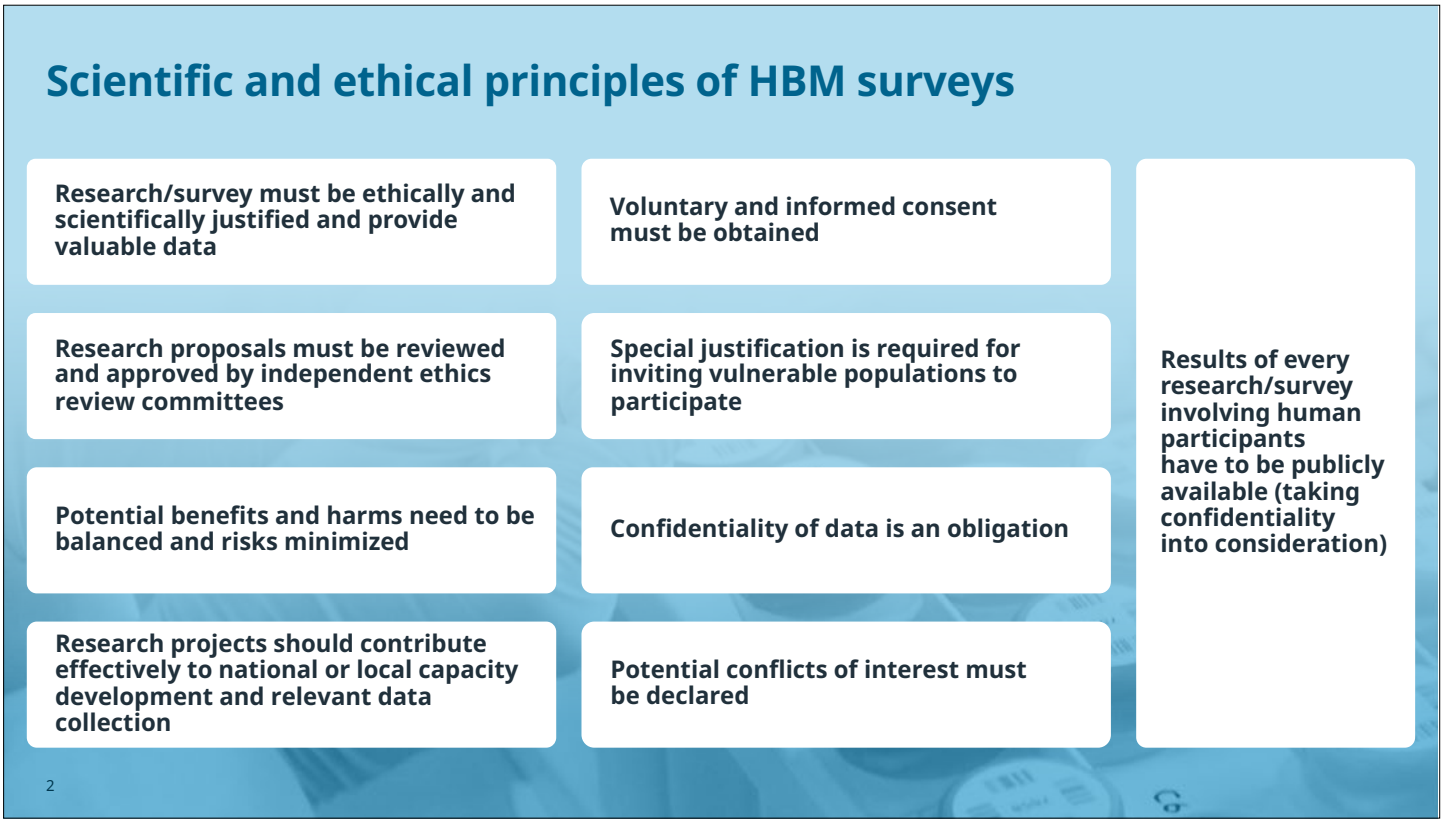

Notes: HBM: human biomonitoring.

Sources

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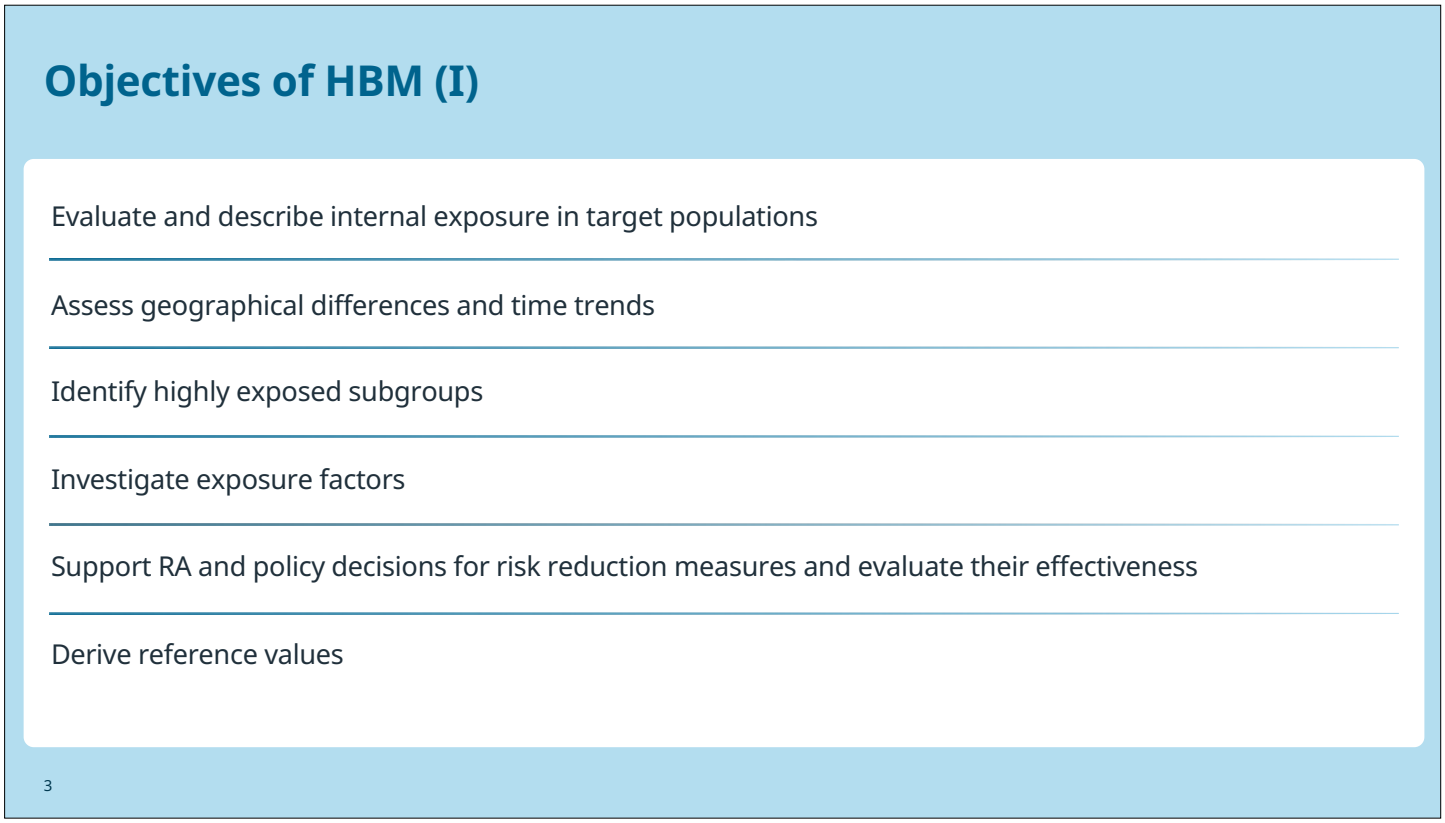

HBM studies/surveys have many objectives; the main one is to assess the internal dose of chemicals. Characterizing of exposure through HBM allows the:

- identifying and monitoring of exposure of population groups; especially groups at higher risk
- monitoring of spatial patterns and temporal trends
- evaluating of the effects of policy interventions to prevent harmful exposures.

HBM studies allow reference values to be derived for evaluating HBM data. There are other questions that HBM allows to answer.

Notes: HBM: human biomonitoring; RA: risk assessment.

Sources

Human biomonitoring: facts and figures. Copenhagen: WHO Regional Office for Europe; 2015 (https://apps.who.int/iris/handle/10665/164588, accessed 10 November 2022).

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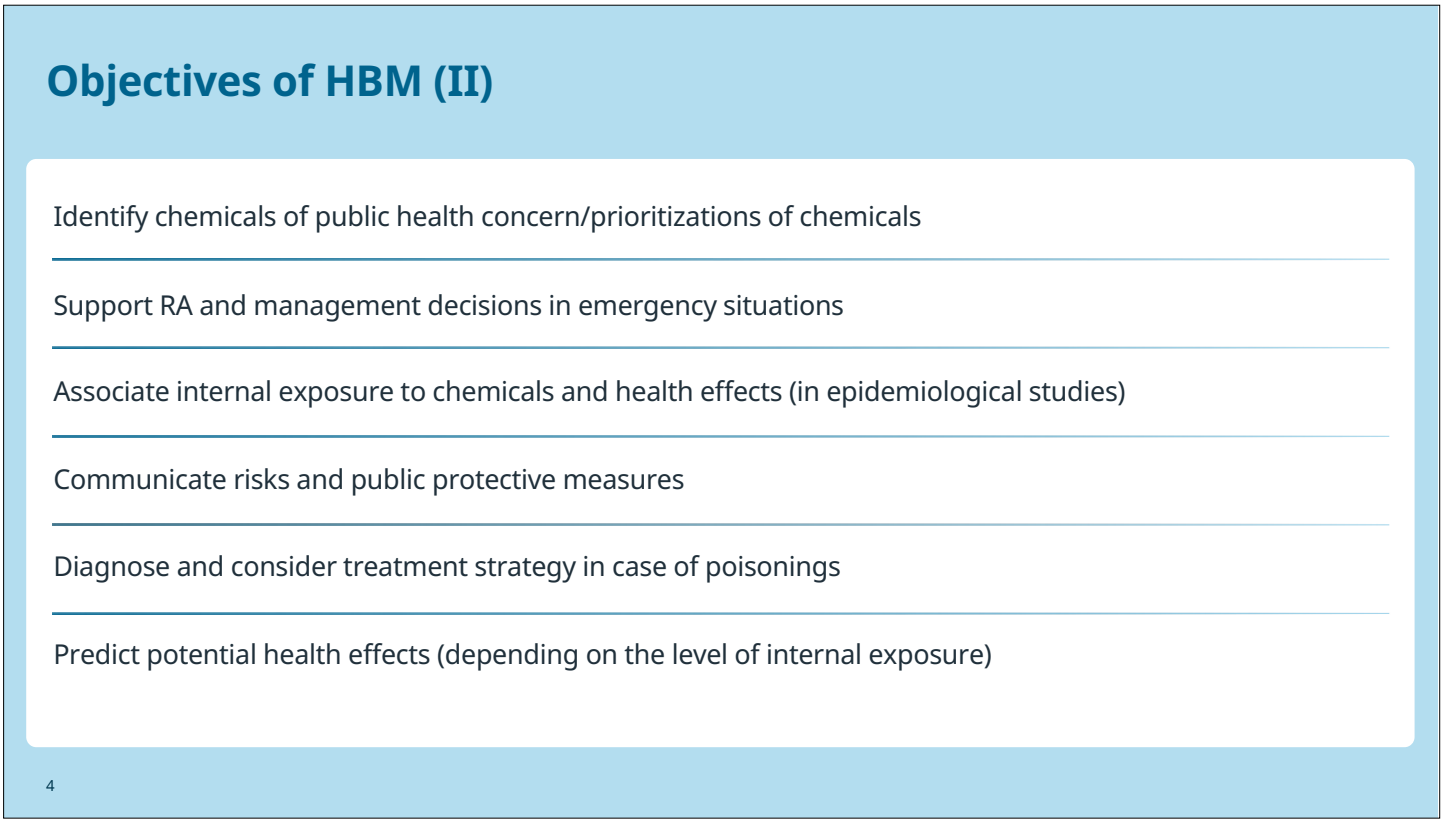
Angerer J, Ewers U, Wilhelm M. Human biomonitoring: state of the art. Int J Hyg Environ Health. 2007;210(3-4):201-28. doi: 10.1016/j.ijheh.2007.01.024.



HBM provides information that is essential for identifying emerging chemicals in specific population subgroups or specific areas, for detecting emerging threats and to provide information on emergency exposure to chemicals, for diagnosis and treatment, and predicting potential health effects.

Notes: HBM: human biomonitoring; RA: risk assessment.

Sources

Angerer J, Ewers U, Wilhelm M. Human biomonitoring: state of the art. Int J Hyg Environ Health. 2007;210(3-4):201-28. doi: 10.1016/j.ijheh.2007.01.024.

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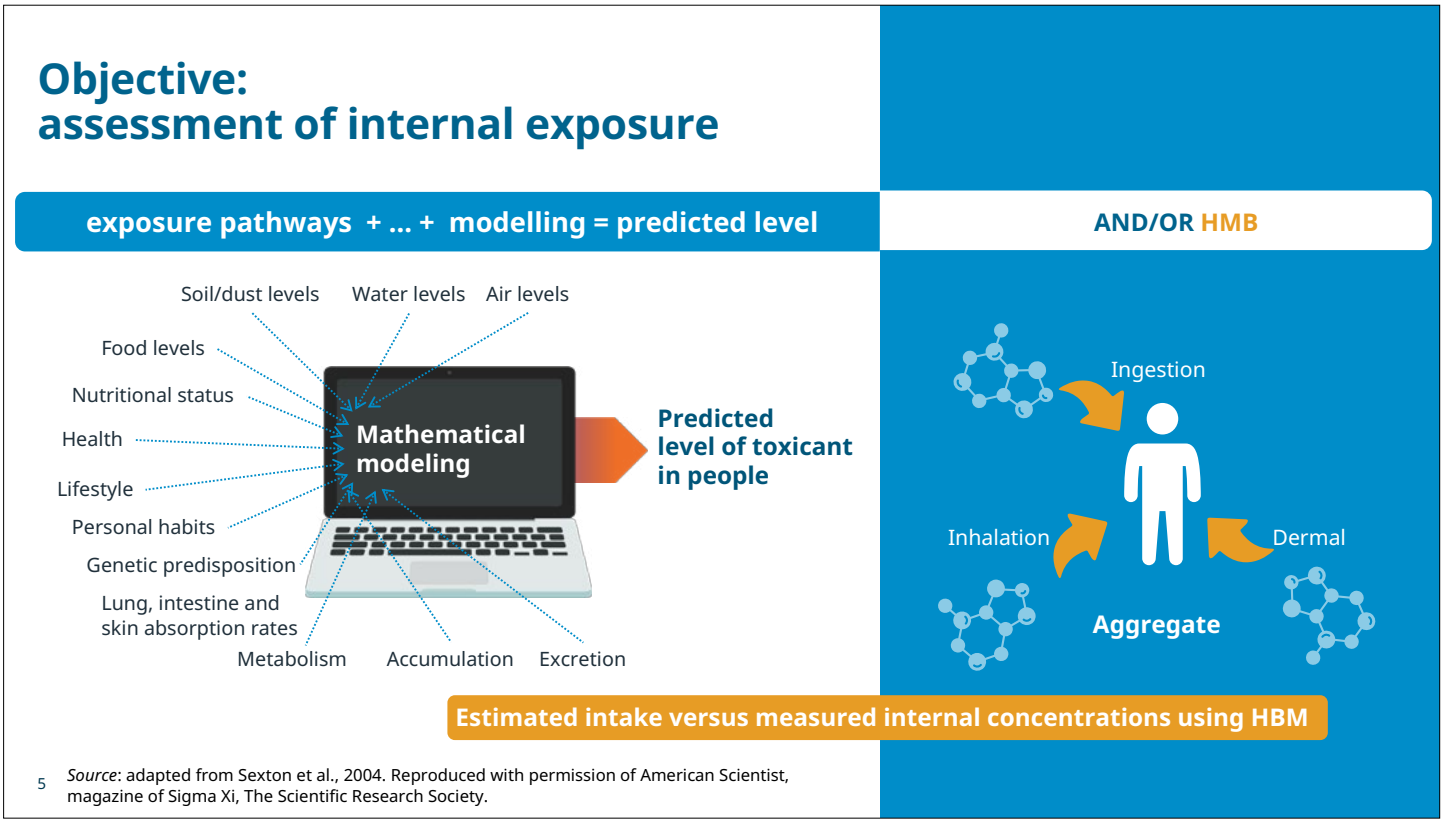


5 *Source*: adapted from Sexton et al., 2004. Reproduced with permission of American Scientist, magazine of Sigma Xi, The Scientific Research Society.

Environmental exposure is commonly complex since we are daily exposed to certain concentrations of different chemicals from different exposure sources and through different exposure routes.

There are two main approaches to assess body burden:

- mathematical/environmental modelling based on knowledge of chemical toxicokinetics, chemical levels in food and environmental media, plus issues such as nutrition status, and health and lifestyle of people; and
- measurement of chemicals directly in biological samples: HBM.

HBM data directly reflect the total body burden resulting from all routes of exposure, and interindividual variability in exposure levels. Such data are often the most relevant metric for health risks assessment, especially for bioaccumulating and/or persistent chemicals.

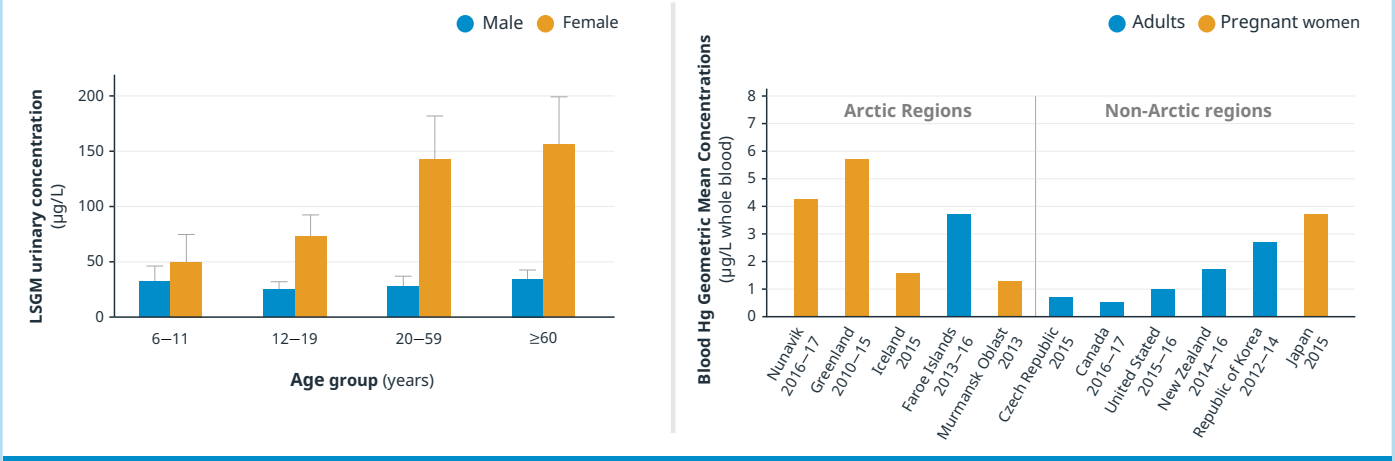
Notes: HBM: human biomonitoring.

Sources

Sexton K, Needham LL, Pirkle JL. Human biomonitoring of environmental chemicals: measuring chemicals in human tissue is the “gold standard” for assessing the people’s exposure to pollution. Am Sci. 2004;92(1):38-45.

Angerer J, Ewers U, Wilhelm M. Human biomonitoring: state of the art. Int J Hyg Environ Health. 2007;210(3-4):201-28. doi: 10.1016/j.ijheh.2007.01.024.

Objective: identification of highly exposed population subgroups (I)



Levels of methylparaben in males and females | **Hg in adult men and women and in pregnant women in different habitats: Arctic and non-Arctic**

6 *Sources*: (left) adapted from Calafat et al., 2010. Reproduced with permission from authors at Centers for Disease Control and Prevention. (right) adapted from AMAP, 2021.

When different population groups are involved in HBM study, groups with higher levels of exposure can be identified: for example, men vs women, varying age groups, Indigenous people compared with other populations.

Notes: LSGM: least-square geometric means; HBM: human biomonitoring; Hg: mercury.

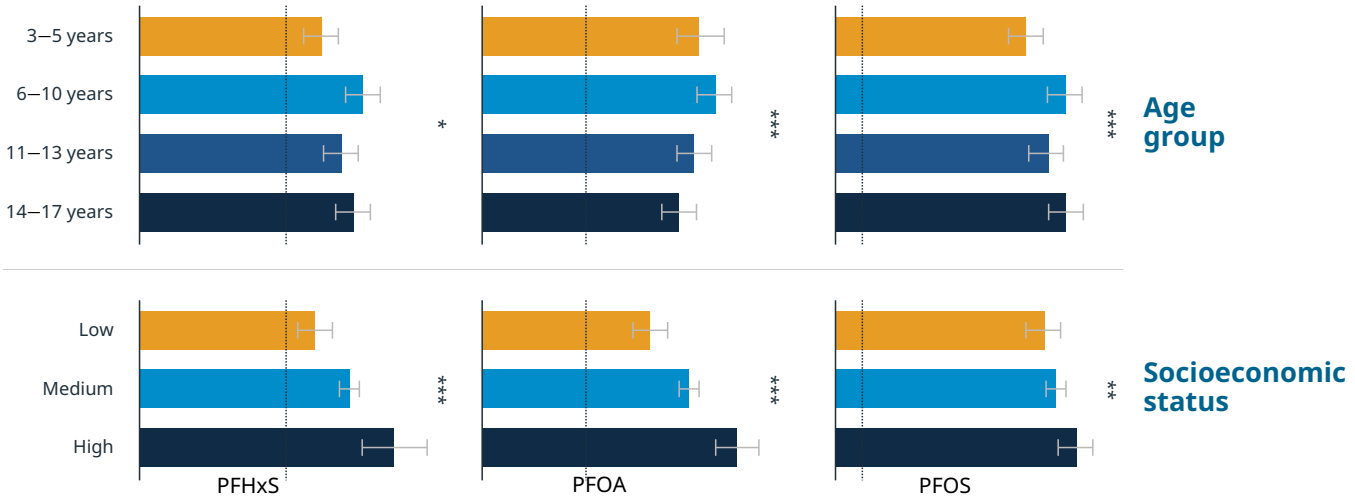
Sources

Calafat AM, Ye X, Wong L-Y, Bishop AM, Needham LL. Urinary concentrations of four parabens in the U.S. population: NHANES 2005—2006 Environ Health Perspect. 2010;118(5):679–85. doi: 10.1289/ehp 0901560.

Human health in the Arctic 2021: summary for policy-makers. Tromsø: Arctic Monitoring and Assessment Programme; 2021 (https://www.amap.no/documents/download/6756/inline, accessed 10 November 2022).

Objective: identification of highly exposed population subgroups (II)

Exposure of children and adolescents aged 3—17 years to PFASs in Germany (2014—2017)



7 *Source*: adapted from Duffek et al., 2020. Reproduced with permission from Elsevier.

If different population groups are involved in an HBM study, it is possible to identify the most exposed population subgroups and to assess any influence of other factors such as the socioeconomic status of participants on exposure level. For example, the 5th cycle of the German Environmental Survey investigated the internal exposure of children and adolescents aged 3—17 years in Germany to PFAS (2014—2017). Analysis of 12 PFAS – PFHxS, PFOS and PFOA – in 1109 plasma samples documented a still-considerable exposure of the young generation (especially those aged 6—10 years) to the phased-out chemicals PFOS and PFOA. A higher socioeconomic status was associated with higher exposure to PFAS, which might be due to the use of PFAS-containing consumer products, differences in breastfeeding or the age of the mothers when giving birth.

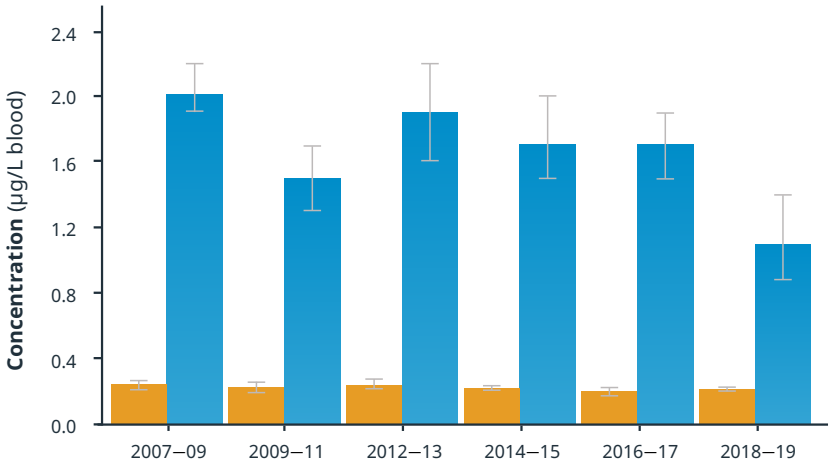
Notes: HBM: human biomonitoring; PFAS: per- and polyfluoroalkyl substances; PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulfonate; PFHxS: perfluorohexane.

Sources

Duffek A, Conrad A, Kolossa-Gehring M, Lange R, Rucic E, Schulte C et al. Per- and polyfluoroalkyl substances in blood plasma: results of the German Environmental Survey for children and adolescents 2014—2017 (GerES V). Int J Hyg Environ Health. 2020;228:113549. doi: 10.1016/j.ijheh.2020.113549.

Objective: identification of highly exposed population subgroups (III)

Cadmium concentrations in the Canadian population aged 12–79 years, by smoking status



Source: Health Canada, 2021. Reproduced with permission from Health Canada.

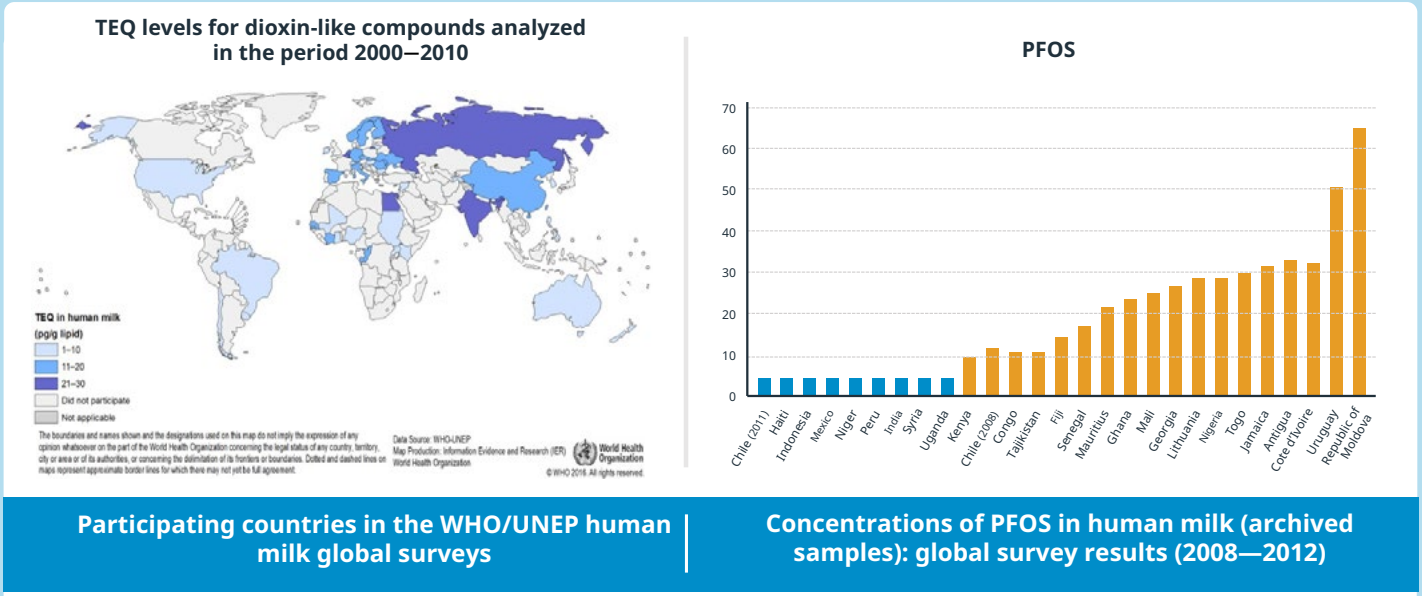
8

Internal dose of chemicals depends not only on external factors but also on lifestyle and other co-founders. For example, the geometric mean concentration of cadmium in blood (µg/L) in the Canadian population (Canadian Health Measures Survey 2007–2009) is higher in smokers than in non-smokers.

Sources

Cadmium in Canadians [website]. Ottawa: Government of Canada; 2021 (https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/human-biomonitoring-resources/cadmium-canadians.html, accessed 10 November 2022).

Objective: detection of spatial differences



Participating countries in the WHO/UNEP human milk global surveys

Concentrations of PFOS in human milk (archived samples): global survey results (2008—2012)

9 *Sources*: (left) WHO, 2016. (right) adapted from UNEP, 2013. Reproduced with permission from United Nations Environment Programme, Secretariat of the Stockholm Convention.

Differences in exposure among countries are identified when HBM results of global or regional surveys are compared. In this case, it is crucial to ensure the comparability of the data by applying harmonized protocols at all stages of the surveys. Investigation at international level within the global monitoring plan for POPs confirmed its value for identification of geographical difference in levels of exposure.

Notes: HBM: human biomonitoring; PFOS: perfluorooctane sulfonate; POPs: persistent organic pollutants; TEQ: toxic equivalent; UNEP: United Nations Environment Programme.

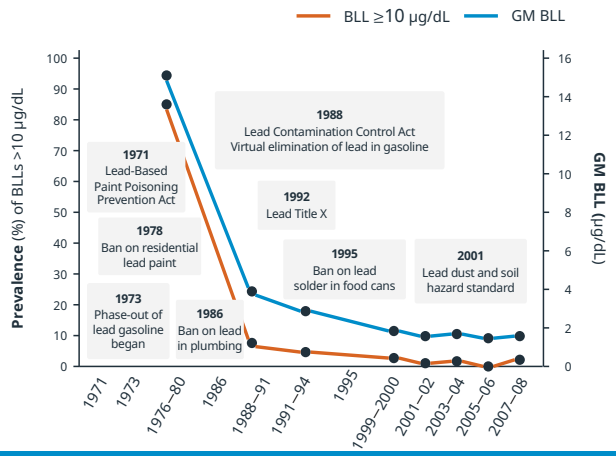
Sources

Den Hond E, Govarts E, Willems H, Smolders R, Casteleyn L, Kolossa-Gehring M et al. First steps towards harmonized human biomonoitoring in Europe: demonstration project to perform human biomonitoring on a European scale. Environ Health Perspect. 2015;123(3):255-63. doi: 10.1289/ehp 1408616.

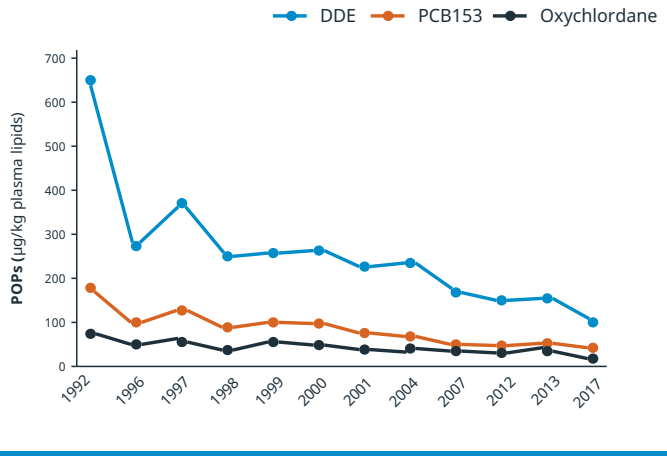
Results of the global survey on concentrations in human milk of persistent organic pollutants by the United Nations Environment Programme and the World Health Organization. Geneva: United Nations Environment Programme, Secretariat of the Stockholm Convention UNEP/POPS/COP .6/INF/33; 26 March 2013 (http://chm.pops.int/TheConvention/ConferenceoftheParties/Meetings/COP6/tabid/3074/mctl/ViewDetails/EventModID/870/EventID/396/xmid/10240/Default.aspx, accessed 10 November 2022).

van den Berg M, Kypke K, Kotz A, Tritscher A, Lee SY, Magulova K et al. WHO/UNEP global surveys of PCDDs, PCDFs, PCBs and DDTs in human milk and benefit-risk evaluation of breastfeeding. Arch Toxicol. 2017;91(1):83-96. doi: 10.1007/s00204-016-1802-z.

Objective: contribution to decisions on risk reduction and evaluating policy effectiveness



Reduction BLLs in the population in the United States



Reduction of POPs in plasma: geometric means concentration in Inuit pregnant women from Nunavik (Canada)

10 *Sources*: (left) Brown and Falk, 2017. Adapted from Centers for Disease Control and Prevention. (right) AMAP, 2021.

HBM is an important tool to support environment and health policy-making. HBM is also relevant to evaluate how effective risk-reduction measures are.

For example, the reduction of BLL in the United States population was a result of the withdrawal of lead from gasoline and paints and other regulations. In the second Centers for Disease Control and Prevention's NHANES, it was observed that lead exposure in the population decreased from 16 µg/dL to less than 10 µg/dL four years after the introduction of unleaded gasoline to the market, and the reduction of gasoline consumption with lead by 55%. The reduction was much greater than expected, prompting the United States Environmental Protection Agency to decide to accelerate the process of total elimination of lead from gasoline. It was found that less than 1% of children had BLL exceeding 5 µg/dL in 2013—2014. Another example is the significant decrease of levels of POPs in Swedish mothers after relevant regulations were implemented.

Notes: BLL: blood lead level; DDE: 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; GM: general mean; HBM: human biomonitoring; NHANES: National Health and Nutrition Examination Survey; PCB153: polychlorinated biphenyl 153; POPs: persistent organic pollutants.

Sources

Human health in the Arctic 2021: summary for policy-makers. Tromsø: Arctic Monitoring and Assessment Programme; 2021 (https://www.amap.no/documents/download/6756/inline, accessed 10 November 2022).

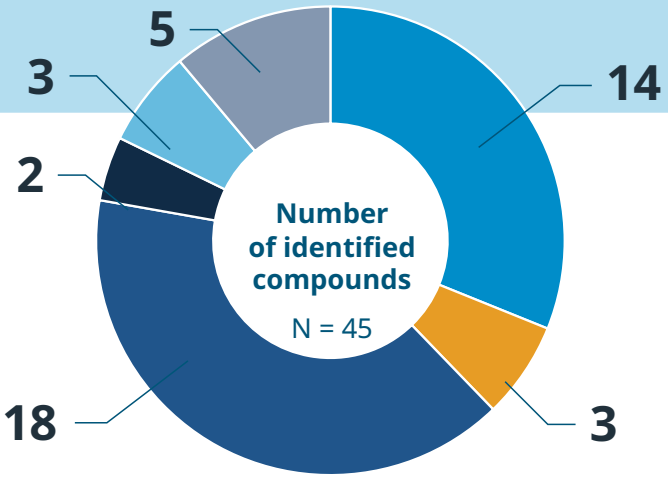
Tsoi MF, Cheung CL, Cheung TT, Cheung BM. Continual decrease in blood lead level in Americans: United States National Health Nutrition and Examination Survey 1999—2014. Am J Med. 2016 Nov;129(11):1213-18. doi: 10.1016/j.amjmed.2016.05.042.

Brown MJB, Falk H. Module C.iii: conducting blood lead prevalence studies. Atlanta (GA): US Centers for Disease Control and Prevention; 2017 (https://wedocs.unep.org/bitstream/handle/20.500.11822/21470/Module%20Ciii%20Blood%20Lead%20Prevalence%20Studies_Final%20%20July%2017.pdf?sequence=1&isAllowed=y, accessed 10 November 2022).

Objective: identification of emerging chemicals

Overview of the main groups of chemicals identified in 50 urine samples of Flemish adolescents from screening of 61 compounds

14	Pharmaceutical and personal care product
3	Pesticides
18	Plasticizers
2	Phenolic antioxidants
3	UV filters
5	Food additives



11 *Source*: adapted from Caballero-Casero et al., 2021. Reproduced with permission from Elsevier.

HBM is useful for identification of emerging chemicals. The example given here is the identification of pyrethroids, herbicides, parabens, acrylamide/glycidamide, nitrosamine and nitrate (both smoke flavouring), and PFCs as emerging chemicals in Belgium in the sense of the European Food Safety Authority's definition of an emerging risk *("a risk resulting from a newly identified hazard to which a significant exposure may occur, or from an unexpected new or increased significant exposure and/or susceptibility to a known hazard").*

Notes: HBM: human biomonitoring; PFC: perfluorinated compounds; UV: ultra violet.

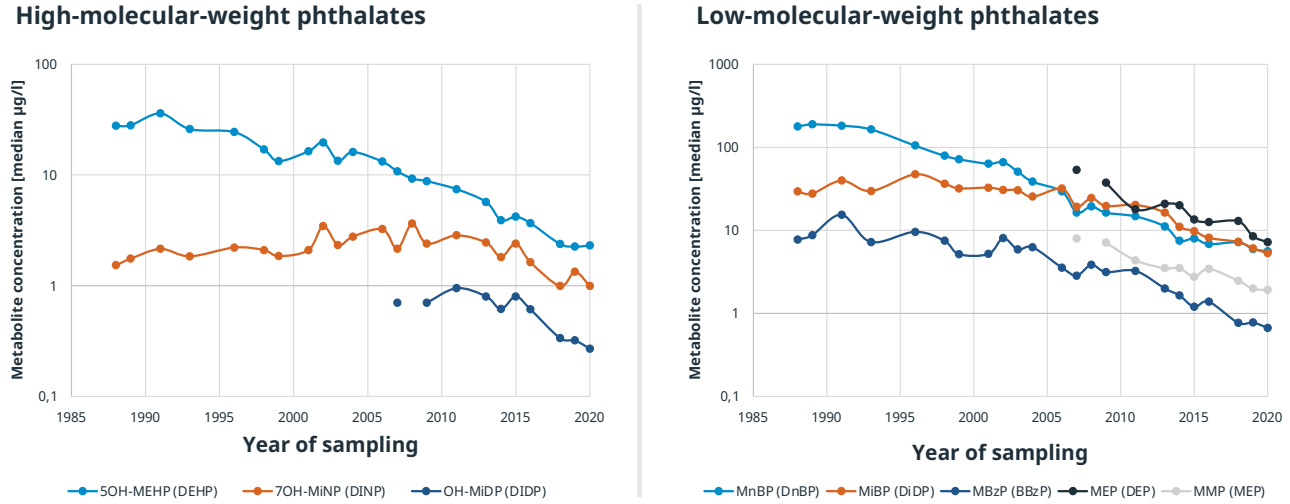
Sources

Choi J, Mørck TA, Polcher A, Knudsen LE, Joas A. Review of the state of the art of human biomonitoring for chemical substances and its application to human exposure assessment for food safety. EFSA Supporting Publication. 2015;12(2):724E. doi: 10.2903/sp.efsa.2015.EN-724.

Caballero-Casero N, Castro G, Bastiaensen M, Gys C, Larebeke N, Schoeters G et al. Identification of chemicals of emerging concern in urine of Flemish adolescents using a new suspect screening workflow for LC-QTOF-MS. Chemosphere. 2021;280:130683. doi: 10.1016/j.chemosphere.2021.130683.

Objective: estimation of time trends (I)

Concentration of key phthalate metabolites in the German Environmental Specimen Bank, 1988—2015



12 *Source*: Koch et al., 2017. Reproduced with permission from Elsevier.

The analysis of biobanked samples or several rounds of HBM surveys can give valuable information of exposure changes with time. It can reflect, for example, the effect of regulation in use/production of chemicals or the commercialization of new substances.

Notes: BBzP: benzyl butyl phthalate; DEHP: di(2-ethylexyl)phthalate; DIDP: disodecyl phthalate; DnBP: di-n-butyl phthalate; DINP: diisopropyl methilphosphonate; HBM: human biomonitoring; VBzp: methylbenzylpiperazine; MEP: 2-C-methyl-D-erythritol 4-phosphate; MiBP: mono-isobutyl phthalate; MnBP: mono-n-butyl phthalate; OH-MDP: mono-hydroxy-isodecyl phthalate; 5OH-MEMHP: mono(2-ethyl-5-hydroxyhexyl).

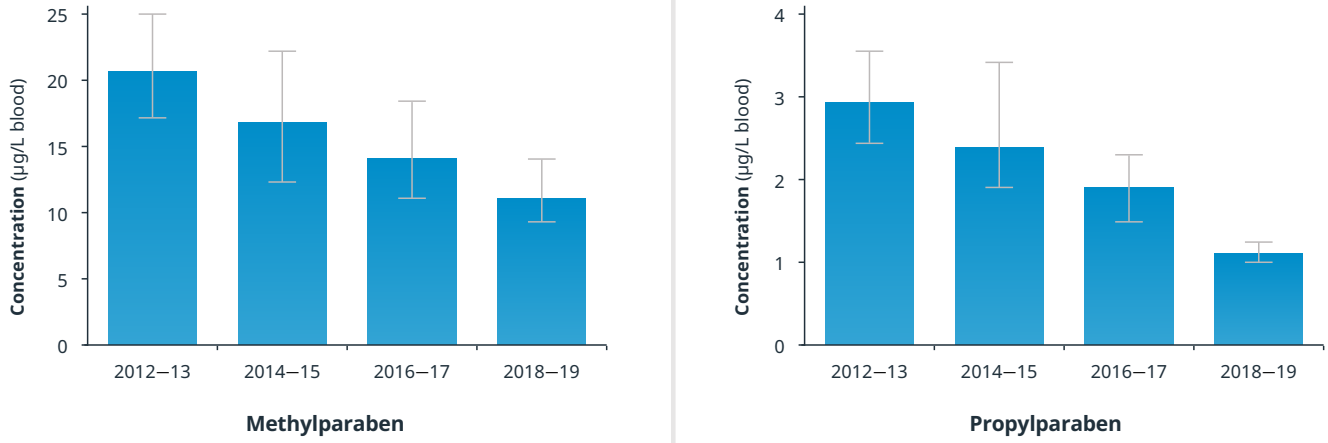
Sources

Koch HM, Rüther M, Schütze A, Conrad A, Pälmke C, Apel P, Brüning T, Kolossa-Gehring M. Phthalate metabolites in 24-h urine samples of the German Environmental Specimen Bank (ESB) from 1988 to 2015 and a comparison with US NHANES data from 1999 to 2012. J Hyg Environ Health. 2017;220(2 Pt A):130-41. doi: 10.1016/j.ijheh.2016.11.003.

Schmidtkunz C, Gries W, Weber T, Leng G, Kolossa-Gehring M. Internal exposure of young German adults to di (2-propylheptyl) phthalate (DPHP): trends in 24-h urine samples from the German Environmental Specimen Bank 1999—2017. Int J Hyg Environ Health. 2019;222(3):419-24. doi: 10.1016/j.ijheh.2018.12.008.

Objective: estimation of time trends (II)

Paraben concentrations in the Canadian population aged 3–79 years



13 *Source*: Health Canada, 2021. Reproduced with permission from Health Canada.

Another example is from survey conducted in Canada: concentrations of methylparaben and propylparaben in urine in the Canadian population aged 3–79 years significantly decreased over time: between 2012–2013 and 2018–2019, methylparaben concentrations declined by 46% and propylparaben concentrations declined by 58%.

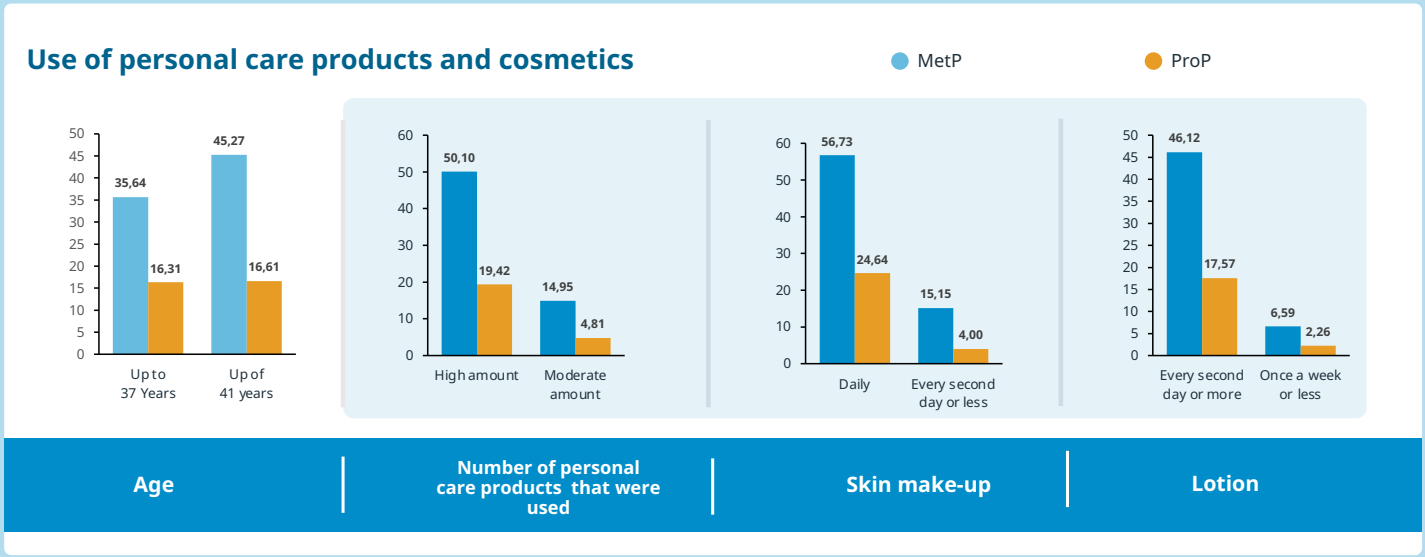
Sources

Parabens in Canadians [website]. Ottawa: Government of Canada; 2021 (https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/human-biomonitoring-resources/parabens-canadians.html, accessed 10 November 2022).

Pollock T, Karthikeyan S, Walker M, Werry K, St-Amand A. Trends in environmental chemical concentrations in the Canadian population: biomonitoring data from the Canadian Health Measures Survey 2007–2017. Environ Int. 2021;155:106678. doi: 10.1016/j.envint.2021.106678.

Objective: identification of exposure determinants

Biomarkers in mothers categorized by population characteristics and potential exposure sources (geometric mean µg/g creatinine)



14 *Source*: data taken from Larsson et al., 2014.

To reveal the main exposure factors, HBM is commonly accompanied by a questionnaire to collect information on sources of exposure and other co-founders and exposure determinants.

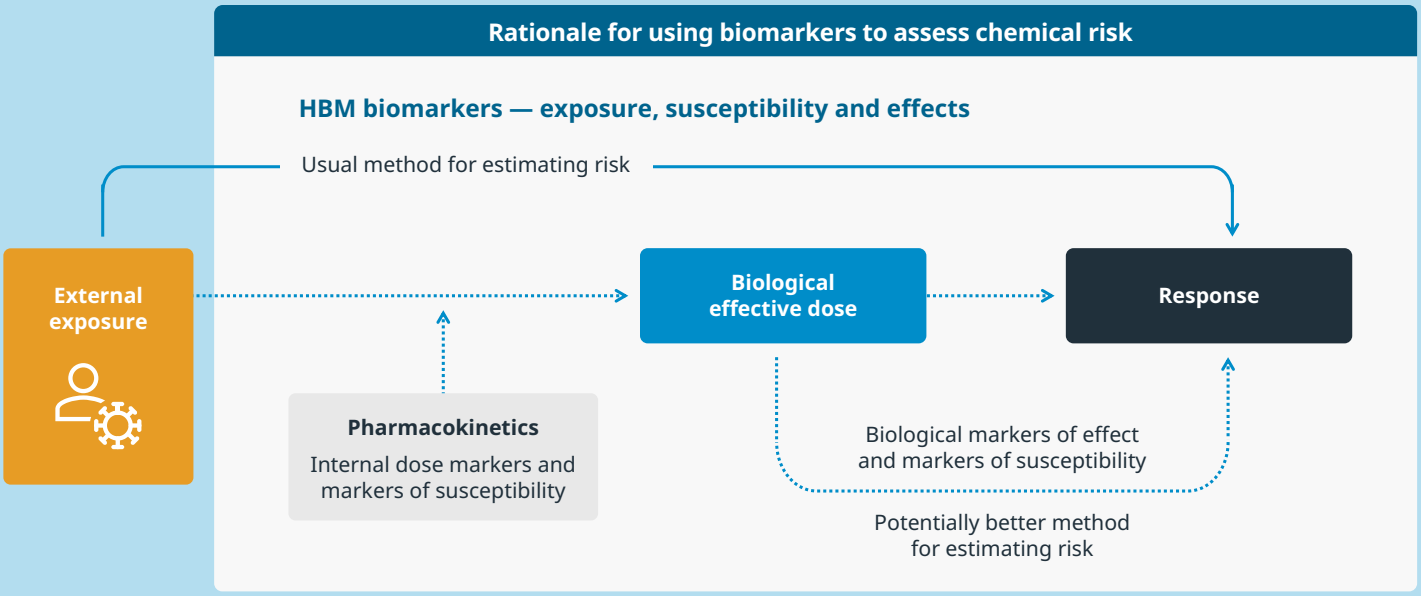
For example, evaluation of the exposure to phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children (6—11 years old) used urine samples from 98 mother–child couples living in either a rural or an urban area. A questionnaire allowed investigation of potential predictors of the exposure. The study found an association of paraben concentrations with use of cosmetics and personal care products.

Notes: HBM: human biomonitoring; MeTP: methylparaben; ProP: polypropylparaben.

Sources

Larsson K, Ljung Björklund K, Palm B, Wennberg M, Kaj L, Lindh CH, Jönsson BA, Berglund M. Exposure determinants of phthalates, parabens, bisphenol A and triclosan in Swedish mothers and their children. Environ Int. 2014;73:323-33. doi: 10.1016/j.envint.2014.08.014.

Objective: support of chemical RA (I)



15 *Source*: adapted from Schulte and Waters, 2006. Reproduced with permission from New York Academy of Sciences.

Chemical RA* is mostly based on external exposure data. HBM data can provide more accurate data on actual internal exposure for RA.

Although some good examples on the use of HBM for the RA of chemicals have occurred in recent years, there is still quite some work to do to improve HBM use in RA and health impact assessment: introduction of new and validated methods based upon new technologies to study biomarkers of exposure, effect and susceptibility at the different levels of the risk management process.

*RA is a process intended to calculate or estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.

Notes: HBM: human biomonitoring; RA: risk assessment.

Sources

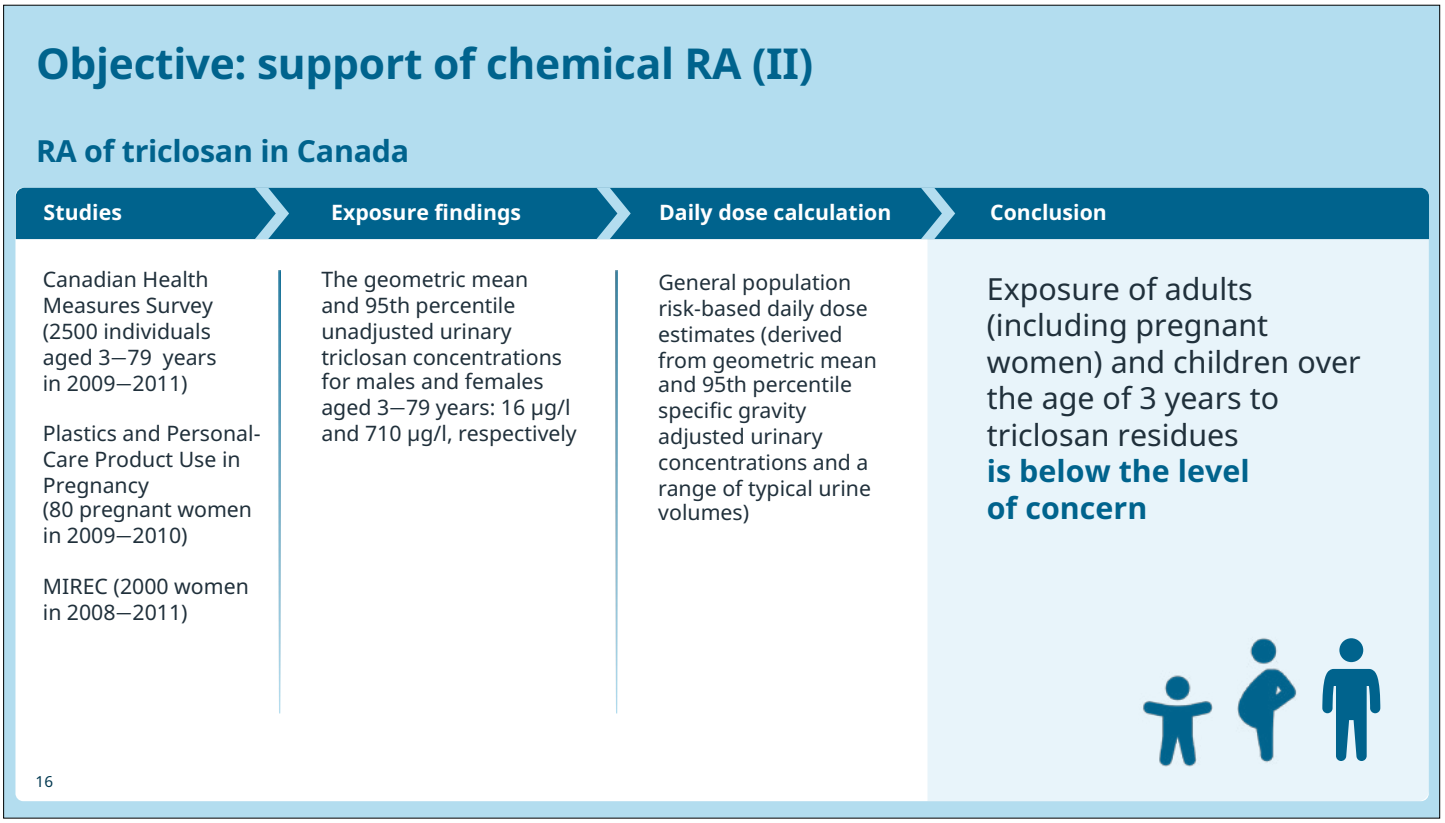
Bartell SM. Biomarkers, bioindicators, and ecological risk assessment: a brief review and evaluation. Environ Bioindic. 2006;1:60–73. doi: 10.1080/15555270591004920.

Schulte PA, Waters M. Using molecular epidemiology in assessing exposure for risk assessment. Ann NY Acad Sci. 2006;895:101–11. doi: 10.1111/j.1749-6632.1999.tb08079.x.

National Academies of Sciences, Engineering, and Medicine, Division on Earth and Life Studies, Board on Environmental Studies and Toxicology, Committee on Incorporating 21st Century Science into Risk-Based Evaluations. Using 21st century science to improve risk-related evaluations. Washington (DC): National Academies Press; 2017 (https://nap.nationalacademies.org/catalog/24635/using-21st-century-science-to-improve-risk-related-evaluations, accessed 10 November 2022).

Environmental health criteria 155: biomarkers and risk assessment: concepts and principles. Geneva: World Health Organization; 1993 (https://apps.who.int/iris/handle/10665/39037, accessed 10 November 2022).

Environmental health criteria 222: biomarkers in risk assessment: validity and validation. Geneva: World Health Organization; 2001 (https://inchem.org/documents/ehc/ehc/ehc222.htm, accessed 10 November 2022).



The potential sources of exposure to triclosan for Canadians include consumer products treated with or containing triclosan (drugs, cosmetics and natural health products), drinking-water, household dust and breastmilk (for newborn). Total triclosan (conjugated and free forms) was measured in spot urine samples for approximately 2500 individuals aged 3–79 years at 18 sites across Canada from 2009 to 2011 within the Canadian Health Measures Survey. Triclosan was detected in urine in approximately 72% of the population. It was also found in more than 80% of the 80 pregnant women's urine samples that were collected within the P4 (Plastics and Personal-care Product Use in Pregnancy) study. The MIREC study measured various substances in approximately 2000 pregnant women in their first trimester of pregnancy across Canada between 2008 and 2011. Total triclosan was detected in over 99% of the maternal urine samples using a more sensitive analytical method.

The geometric mean and 95th percentile unadjusted urinary triclosan concentrations for males and females aged 3–79 years varied from 16 µg/L to 710 µg/L, respectively. Based on the results of the aggregate RA, it was concluded that exposure of adults (including pregnant females) and children over the age of 3 years to triclosan residues was below the level of concern.

Notes: MIREC: Maternal-Infant Research on Environmental Chemicals; RA: risk assessment.

Sources

Assessment report: triclosan. Ottowa: Government of Canada; 2016 (https://www.ec.gc.ca/ese-ees/65584A12-2B7D-4273-9F7A-38EDF916ECAF/EN%20FSAR%20Triclosan%20with%20ISBN.pdf, accessed 10 November 2022).

Lang C, Fisher M, Neisa A, MacKinnon L, Kuchta S, MacPherson S et al. Personal care product use in pregnancy and the postpartum period: implications for exposure assessment. Int J Environ Res Public Health. 2016;13(1):105. doi: 10.3390/ijerph13010105.

Maternal-Infant Research on Environmental Chemicals [website]. Ottawa: Canada, 2022 (https://www.mirec-canada.ca/en/, accessed 14 May 2023).

Objective: support of chemical RA and risk management (REACH example)

Substance group	Substance	Evaluation under REACH RA scheme	Use of HBM data
Phthalates	DEHP	SVHC requiring authorization	No
		Application for authorization on formulation of recycled soft PVC-containing DEHP in compounds and dry-blends (ECHA 2014a)	Yes
		Restriction in toys and childcare articles (ECHA 2017b)	Yes
Bisphenol	BPA	Restriction in thermal paper (ECHA 2015b)	Yes
Cadmium and chromium	Cadmium	Restrictions	No
PAHs	BaP	Restrictions	No

17

The EU's REACH regulation considers HBM as most helpful in actual exposure assessment for complex scenarios and validation that operational conditions and risk management measures considered in the exposure scenarios result in safe exposures.

However, guidance on how to use HBM in risk characterization and management is limited. HBM, on its own or in conjunction with monitoring data, can, therefore, be used in the authorization process of SVHC to demonstrate that the risk-management measures in place are sufficient to appropriately control or minimize the risks. HBM is particularly relevant when dealing with substances with systemic effects and when significant absorption is expected through different routes of exposure. Several HBM4EU priority substances have been recently evaluated under REACH regulation.

Notes: BaP: benzo[a]pyrene; BPA: 4,4'-isopropylidenediphenol/bisphenol A; DEHP: bis(2-etylhexyl) phthalate; ECHA: European Chemical Agency; HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative; PAHs: polycyclic aromatic hydrocarbons; PVC: polyvinyl chloride; RA: risk assessment; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation; SVHC: substances of very high concern.

Sources

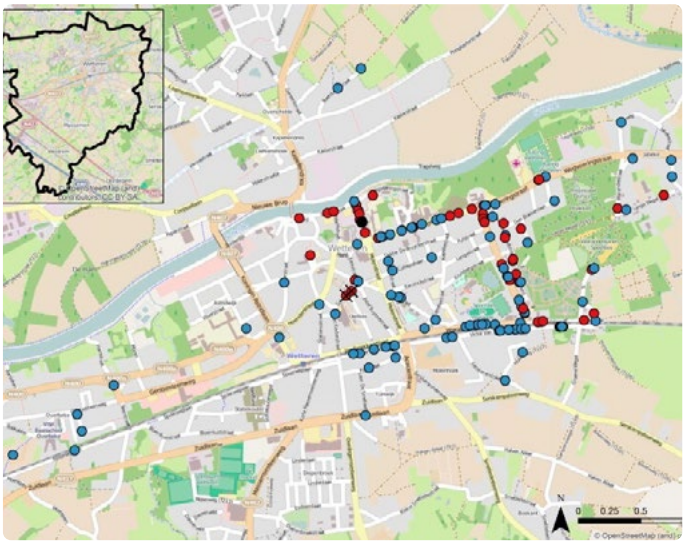
Gerofke A, David M, Schmidt P, Lobo Vicente J, Buekers J, Gilles L et al. From science to policy: How European HBM indicators help to answer policy questions related to phthalates and DINCH exposure. Int J Hyg Env Health. 2023;247:114073. doi: 10.1016/j.ijheh.2022.114073.

Louro H, Heinälä M, Bessems J, Buekers J, Vermeire T, Woutersen M et al. (2019) Human biomonitoring in health alth risk assessment in Europe: Current practices and recommendations for the future. Int J Hyg Environ Health. 2019;222(5):727-737. doi: 10.1016/j.ijheh.2019.05.009.

Louro H, Heinälä M, Bessems J, Buekers J, Vermeire T, Woutersen M et al. (2019) Human biomonitoring in health risk assessment in Europe: Current practices and recommendations for the future. Int J Hyg Env Health. 2019;27:727-737. doi: 10.1016/j.ijheh.2019.05.009.

Santonen T, Mahiout S, Alvito P, Apel P, Bessems J, Bil W et al. How to use human biomonitoring in chemical risk assessment Methodological aspects, recommendations, and lessons learned from HBM4EU. Int J Hyg Environ Health, 2023;249:114139. doi: 10.1016/j.ijheh.2023.114139.

Objective: support of RA in emergency situations



Train carrying acrylonitrile derailed in Belgium

- Extrapolated CEV concentration ≤10 pmol/g globin
- Extrapolated CEV concentration >10 pmol/g globin
- × Has been in the EZ at the moment of or in the days following the train accident
- Extrapolated CEV concentration of 4951 and 12615 pmol/g globin

EZ

Spatial distribution of the CEV concentrations extrapolated to the moment of the train accident (pmol/g globin) in 168 non-smokers in the local study population

18 *Source*: De Smedt et al., 2014. Reproduced with permission from Elsevier.

HBM is a useful tool for monitoring exposure from incidents such as chemical spills or large fires, especially for occupational exposure of firefighters, other emergency responders or bystanders. There are studies that have used HBM to assess the level of exposure of populations groups for decision-making on decontamination measures; for example, after the derailing of a train transporting acrylonitrile in Belgium in May 2013. In 37% of the evacuated non-smoking residents, the level of a biomarker of acrylonitrile exposure CEV in blood exceeded its reference value and the highest exposure was observed in humans living along the sewage system.

Benefits of HBM in emergency responses include:

- knowledge of actual body burden, including capture from all exposure routes such as through the skin;
- detecting unexpected exposures or routes of exposure;
- identifying potential health risks in individuals and population groups; and
- providing valuable information for risk communication.

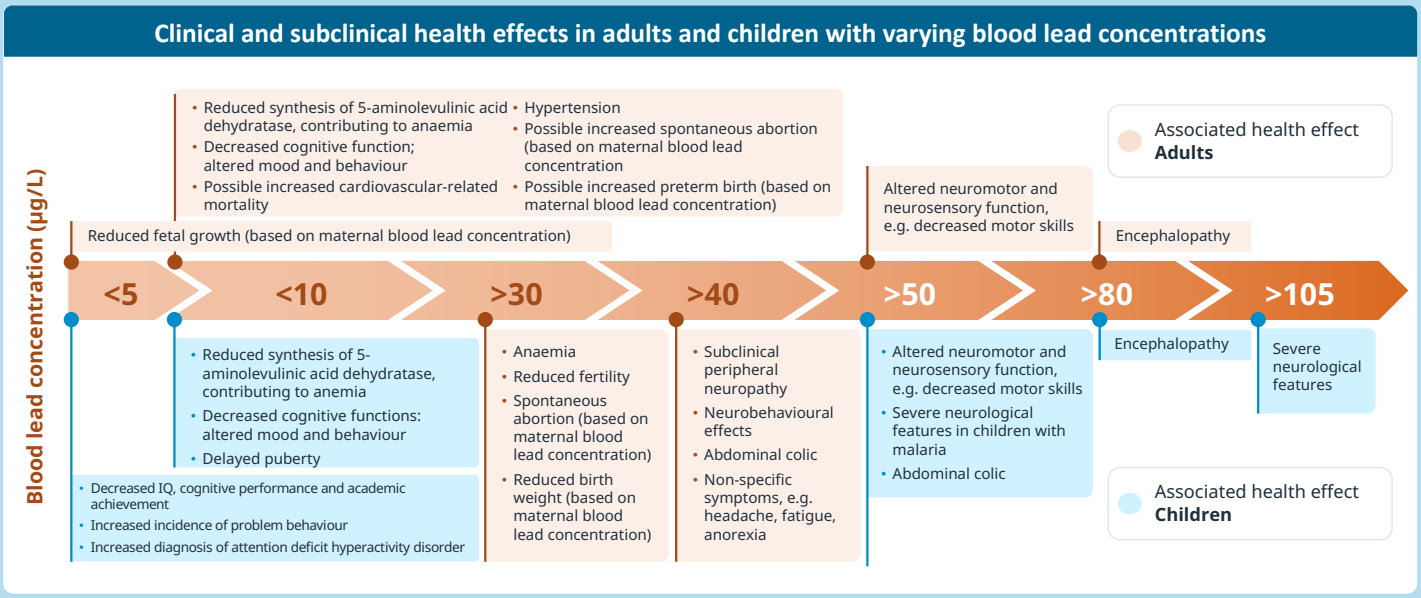
Notes: CEV: *N*-2-cyanoethylvaline; EZ: evacuation zone; HBM: human biomonitoring; RA: risk assessment.

Sources

Bader M, Bäcker S, Jäger T, Van Bortel G, van Weyenbergh T, Verwerft E et al. Human biomonitoring for emergency responders: experience, benefits and limitations. J Occup Environ Med. 2018;75(suppl 2):A116. doi: 10.1136/oemed-2018-ICOHabstracts.330.

De Smedt T, De Cremer K, Vleminckx C, Fierens S, Mertens B, Van Overmeire I et al. Acrylonitrile exposure in the general population following a major train accident in Belgium: a human biomonitoring study. Toxicol Lett. 2014;231(3):344-51. doi: 10.1016/j.toxlet.2014.09.009.

Objective: linking HBM results and expected health disorders



19 *Source*: WHO, 2021.

HBM can be used to predict a biological effect if a relationship has been established between the HBM measurement and the health outcome. For a few chemicals, such as lead, human data from occupational and other clinical studies allow the identification of body burdens for a chemical that may result in an adverse effect. For most chemicals, however, there are not enough data to be certain about health effects, particularly at very low chemical concentrations. In addition, most environmental exposures involve multiple substances, and attributing cause to a single hazard can often be difficult. Therefore, HBM studies can only provide information on correlations between health effects and internal exposure, but not a causal correlation.

Notes: HBM: human biomonitoring; IQ: intelligence quotient.

Sources

Guideline for clinical management of exposure to lead. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/347360, accessed 10 November 2022).

Objectives: treatment of poisoning and prognosis of outcomes

WHO guidelines for clinical management of exposure to lead for children ≤10 years

Blood lead concentration (µg/dl)	Recommendation	Evidence base
≥45	**Strong recommendation:** oral or parenteral chelation therapy	**Very low certainty**
40–44; where there is doubt about the accuracy of the measurement, a persistently elevated lead concentration in spite of measures to stop exposure or significant features of lead poisoning	**Conditional recommendation:** oral chelation therapy	**Very low certainty**

20 *Source*: WHO, 2021.

Sources

Guideline for clinical management of exposure to lead. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/347360, accessed 10 November 2022).

Advantages for internal exposure assessment
(versus external exposure assessment)

- Allows direct measurement of internal dose given all environmental, lifestyle and personal influencing factors from different sources and exposure routes
- Can support assessment of both aggregate and combined exposure
- Can detect low levels of exposure
- Reflects cumulative exposure over time for chemicals with long half-life
- Helps to test and validate exposure models
- Can also capture interactions between different substances
- Makes exposure to chemicals personal

21

Aggregate exposure: Exposure to the same substance from multiple sources and by multiple pathways and routes ("single chemical, all routes").

Cumulative exposure: exposure to multiple chemicals by a single route and from exposure to multiple chemicals by multiple routes (combined exposure).

Sources

Human biomonitoring: facts and figures. Copenhagen: WHO Regional Office for Europe; 2015 (https://apps.who.int/iris/handle/10665/164588, accessed 10 November 2022).

Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).

Chemical pollution of indoor air and its risk for children's health: educational course: supplementary publication to the screening tool for assessment of health risks from combined exposure to multiple chemicals in indoor air in public settings for children. Copenhagen: WHO Regional Office for Europe; 2021 (https://apps.who.int/iris/handle/10665/341984, accessed 15 December 2022).

Challenges of HBM

HBM alone does not provide information about the source and pathways of exposure or how long a chemical has been in the body: epidemiological questionnaire data are needed

Involvement of vulnerable population subgroups (e.g. children, pregnant women) may be difficult due to ethical restrictions

For emerging substances, it is difficult to identify the human biomarker that specifically reflects the exposure

Analytical reference standards for each biomarker are often not readily commercially available

HBM data need to be combined with other data and tools for interpretation in RA

22

HBM data do not differentiate exposures by source, and HBM alone cannot provide information about the source of exposure or how long a chemical has been in the body if additional information (such as questionnaire data on potential sources of exposure) is not available. Having both HBM data and modelling information helps to identify the relative contribution from different sources of exposure.

For many chemicals, especially chemicals of emerging concern, the most suitable biomarkers of exposure for humans are not yet known. The quality of HBM studies heavily relies on the well-considered choice of the biomarker.

The non-persistent nature of many novel chemicals creates new challenges in interpreting the extent and duration of exposures. Special sample collection strategies are required.

Interpretation of HBM data is challenging, mostly because of the lack of guidance values. HBM should be enriched and synergized with other tools to improve interpretation and understanding of the exposure–disease continuum, including biomarkers of effects, human susceptibility, toxicokinetics and toxicodynamics and the combination of data from both HBM and health surveys.

Another limitation is that HBM raises important ethical and privacy issues.

Despite all the challenges, HBM is worthwhile because it is the direct way to identify and quantify human exposure and risk, to elucidate the mechanism of toxic effects and to ultimately decide if measures have to be taken to reduce exposure.

Notes: HBM: human biomonitoring; RA: risk assessment.

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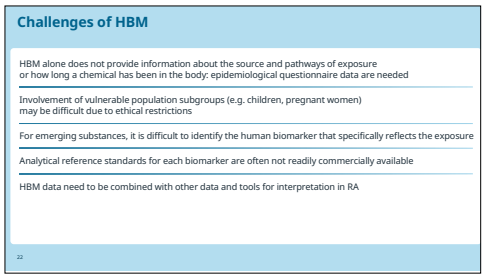

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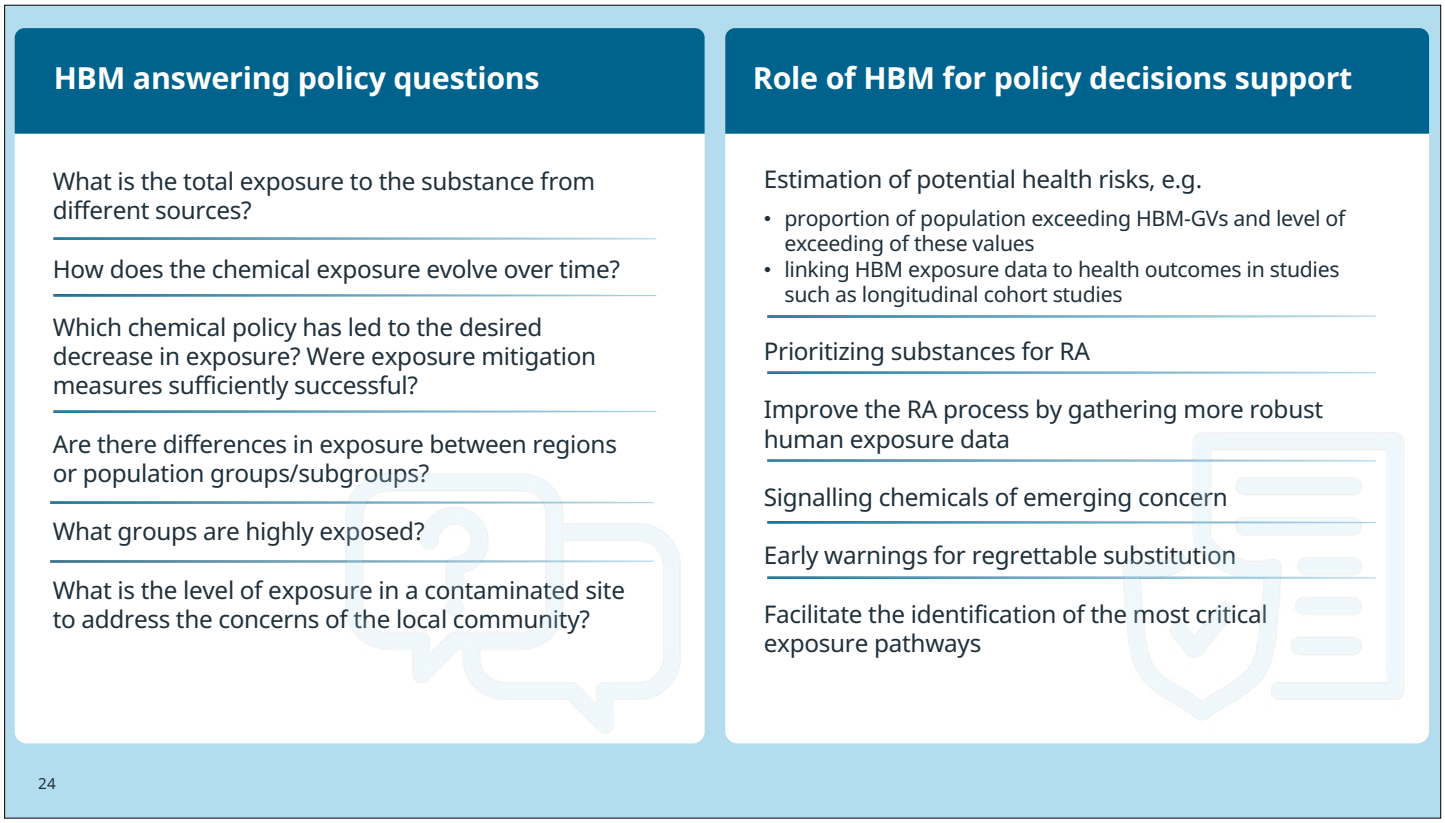
https://dreambroker.com/channel/674dr9pv/kra98c22

Andromachi Katsonouri

Senior Chemist, Head
Human Biomonitoring and Control of Industrial Products Laboratory,
Ministry og Health, Cyprus

Notes: HBM: human biomonitoring.



HBM is needed to support policies by providing information on human exposure to chemicals, demonstrating gaps in protection of the public against critical substances and measuring the success of chemical regulations.

The UNEP and WHO have integrated HBM as a tool to control success of activities within the framework of the Stockholm Convention on Persistent Organic Pollutants and the Minamata Convention on Mercury.

In the EU, the Environment and Health Action Plan 2004–2010 stated that there was a need for the development of a coherent approach to human biomonitoring in Europe. The Action Plan considered a new approach to environmental policy-making by revising and improving the health impact and RA strategies, including improving the information chain to understand the links between sources of pollution and health effects. In 2006, a report entitled "Toxic inheritance – more than 300 pollutants in breastmilk" was presented in the European Parliament to support debates on REACH.

At the national level, HBM has been used in Germany, for example, for verification of policy effectiveness and identification of new risks related to phthalates, based on a retrospective analysis of biobanked data. The reduction in DnBP/DiBP consumption resulting from a stepwise restriction in cosmetics and toys at the end of the 1990s and early 2000 was coupled with a parallel decline in body burdens of corresponding phthalate metabolites, whereas the levels of the unrestricted compounds remained stable.

Notes: DnBP: di-n-butyl phthalate; DiBP: diisobutyl phthalate; EU: European Union; HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values; RA: risk assessment; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation; UNEP: United Nations Environment Programme.

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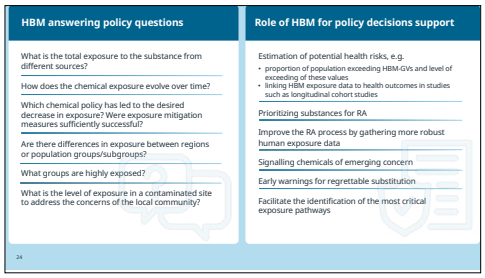

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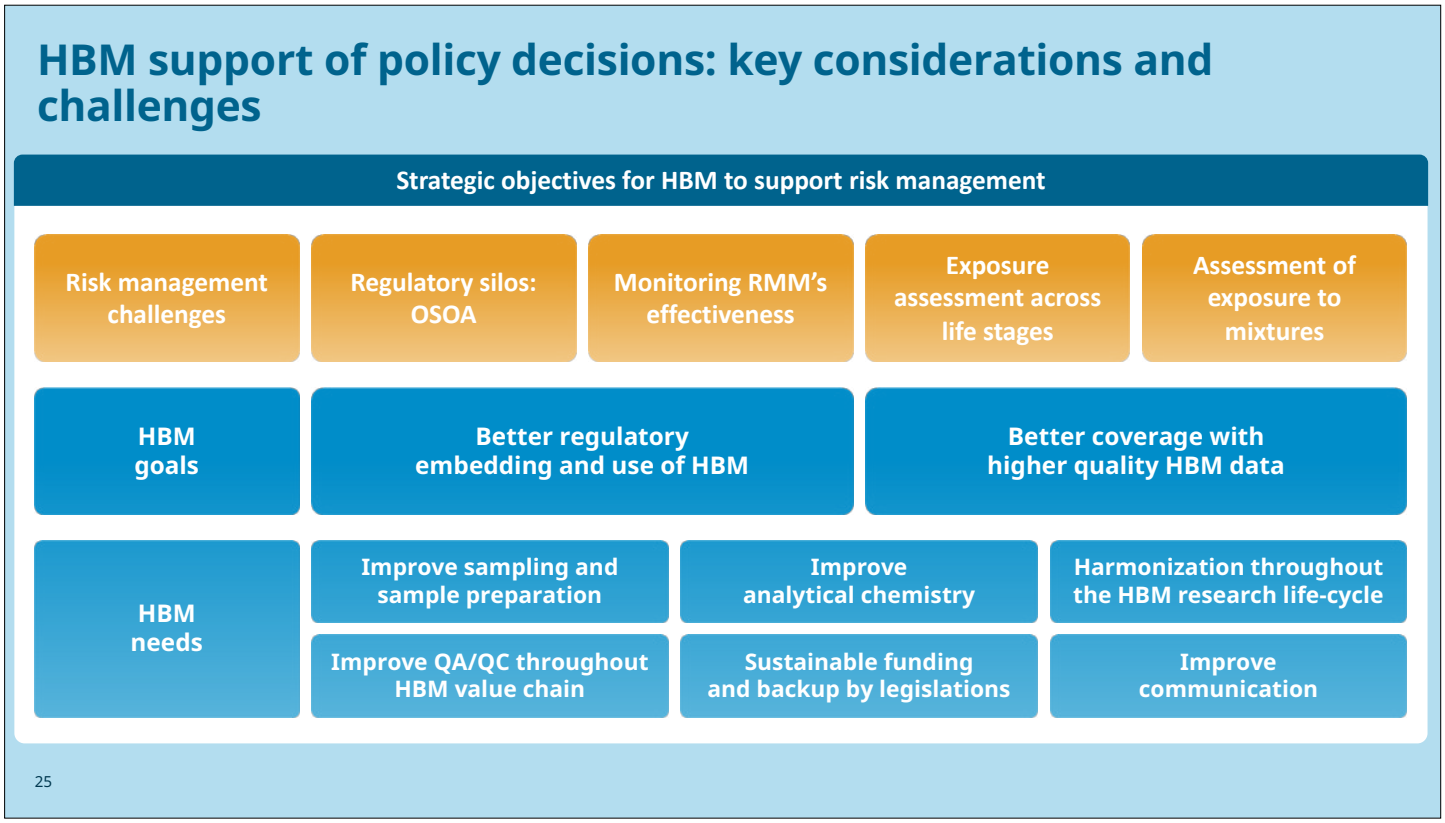

To tackle the challenges associated with assessment of exposure to chemicals, there is a need to generate high-quality, robust and informative data, across the life course and across regulatory silos; this will include many chemicals (mixtures) and aggregate exposure across all routes (oral, dermal and inhalation). High-quality HBM (meta)data sustained over time are needed, with better coverage of the chemical substances, the relevant regulatory silos and specific subpopulations (more age groups, more regions, more socioeconomic groups, among others), and better regulatory use of HBM defined as a solution for risk management challenges.

Notes: HBM: human biomonitoring; OSOA: One Substance, One Assessment principle; QA/QC: quality assurance/quality control; RMM: risk management measures.

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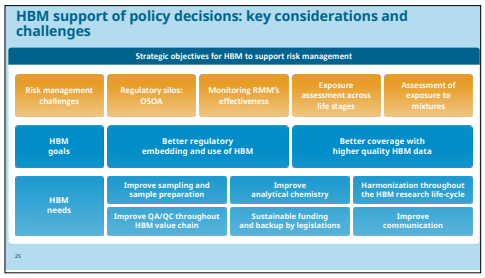

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HBM data use for policy decisions: example of chromium hexavalent

Industrial processes with highest exposure to chromium were revealed

Urinary chromium showed its value as a first approach for the assessment of total internal exposure

The study

Provided relevant information to support policy actions aiming to reduce occupational exposure to chemicals

Allowed evaluating of effectiveness of existing policies (REACH and OSH) and effectiveness of the RMM in each company as well as ways to improve them

Showed that occupational biomonitoring studies can be conducted successfully by multinational collaboration

26

Analysis of chromium exposure is an example of risk-reduction measures in occupational practice and role of HBM. A cross-sectional study was conducted in nine countries in the EU used chromium to assess exposure and examined levels in red blood cells. Chromium was measures in urine as the primary biomonitoring method for Cr(VI) and exhaled breath condensate as potential new methods. The highest internal exposures were observed from the use of Cr(VI) in electrolytic bath plating. A high correlation was observed between chromium urinary levels and air Cr(VI) exposure or dermal total chromium exposure. Urinary chromium showed its effectiveness as a first approach for the assessment of total internal exposure. This study provided relevant information to support policy actions to reduce occupational exposure to chemicals and showed that occupational biomonitoring studies can be conducted successfully by multinational collaboration.

Notes: Cr(V): hexavalent chromium; EU: European Union; HBM: human biomonitoring; OSH: Occupational Health and Safety Directive; REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation; RMM: risk management measures.

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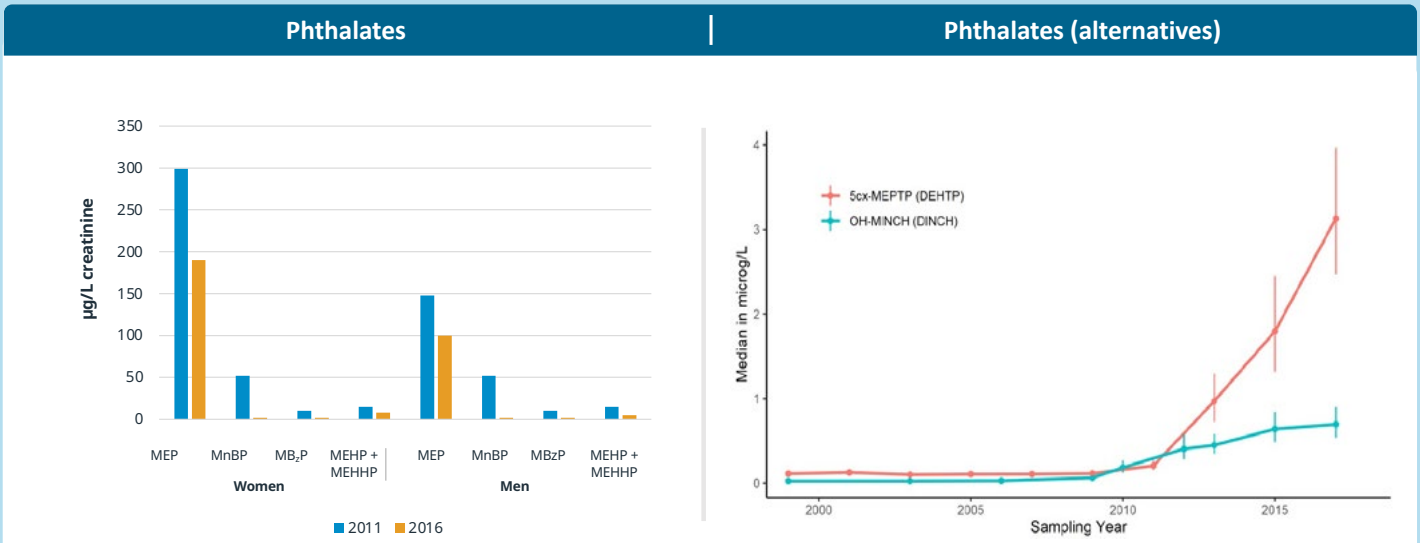
HBM data use for policy decisions: example of phthalates



27 *Sources*: (left) adapted from Tranfo et al., 2018. Reproduced with permission from authors. (right) Data taken from Schütze et al., 2014, Kasper-Sonnenberg et al., 2019, Lessmann et al., 2019. © Phillipp Schmidt, reproduced with permission.

The four phthalates (DEHP, DBP, BBP and DIBP) affect testicular functions, have adverse effects on sexual differentiation during the developmental process and exert anti-androgenic effects. They can enter the body through direct contact between the article and the skin or mucous membranes and are also emitted from articles and can be inhaled.

In the slide, the left graphs indicate the effectiveness of a ban on placement on the market regarding all articles containing one or more of the four phthalates in a concentration greater than 0.1 % of each by weight of any plasticized material.

Over the past years, substitutes such as DINCH and DPHP have become increasingly used. Consequently, monitoring of the trends of exposure with these substitutes should continue to be of importance for years to come.

Notes: BBP: benzyl butyl phthalate; EU: European Union; DBP: dibutyl phthalate; DEHP: di(2-ethylhexyl)phthalate; DINCH: di(isononyl) cyclohexane-1,2-dicarboxylate; DIBP: diisobytil phthalate; DPHP: di(2-propylheptyl) phthalate; HBM: human biomonitoring; MEHHP: mono(2-ethyl-5-hydroxyhexyl)phthalate; MEHP: mono-2-ethylhexyl phthalate; MEP: 2-C-methyl-D-erthritol 4-phosphate; 5cxMEPTP (DEHTP): di-(2-ethylhexyl) terephthalate; MnBP: mono-n-butyl phthalate; OH-MINCH: 2- (((hydroxy-4-methyloctyl) oxy) carbonyl)cyclohexanecarboxylic-d8 acid; RCR: risk characterization ratio.

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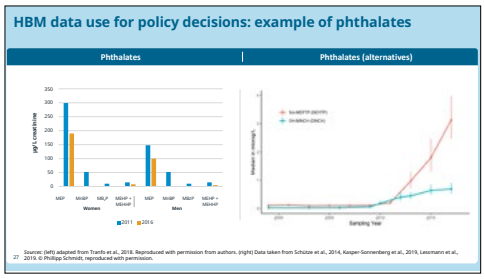

27 Sources: (left) adapted from Tranfo et al., 2018. Reproduced with permission from authors. (right) Data taken from Schütze et al., 2014, Kasper-Sonnenberg et al., 2019, Lessmann et al., 2019, © Philipp Schmidt, reproduced with permission.

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Key challenges of using HBM in regulatory decisions

Unharmonized presentation of the HBM data (not well structured or aligned), unclear quality (e.g. lacking QA/QC for chemical analysis), and missing contextual information (metadata)

Not sufficient coverage of regulatory enforcement by legislation, gaps in aligned and connected legal frameworks that require the use of HBM

Long-term consistent programmes that would allow regular use of HBM in regulatory context exist in a limited number of countries

Availability of HBM data in time and in full is needed

Methodologies of enforcement of HBM science–data–policy interface should be improved and harmonized

28

Notes: HBM: human biomonitoring; QA/QC: quality assurance/quality control.

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MODULE 3

Biomarkers

Basics of toxicokinetics and toxicodynamics

Types of biomarkers

HBM in the exposome

World Health Organization

European Region

Basics of toxicokinetics and toxicodynamics

See video:

2

Toxicokinetics:

the absorption, distribution, metabolism, storage and excretion of chemicals in an organism

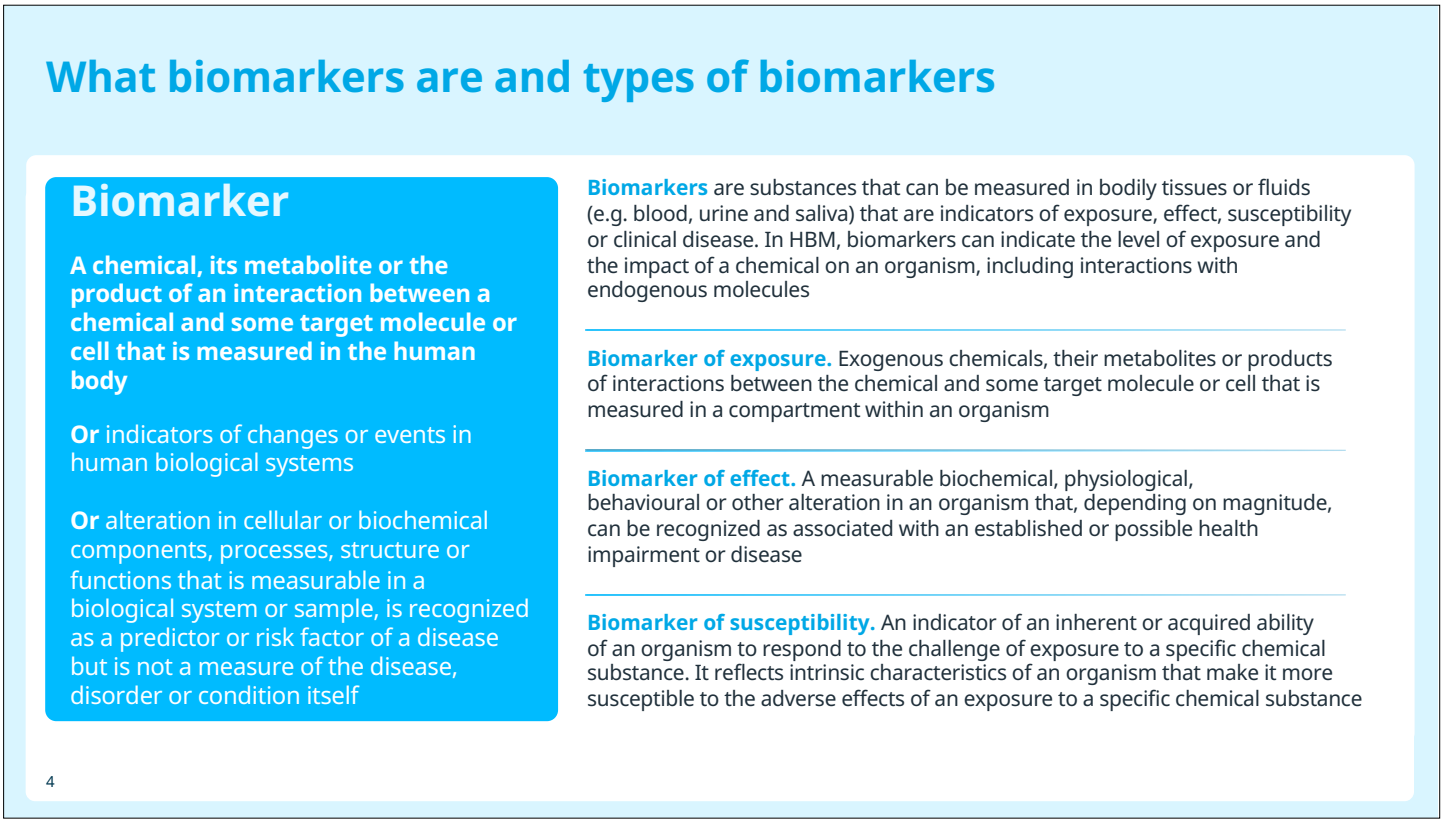
Toxicodynamics:

the alterations in a biological system resulting from exposure to chemicals

Sources

Introduction to toxicokinetics and toxicodynamics [YouTube video]. WHO Regional Office for Europe; 22 December 2022 (https://www.youtube.com/watch?v=LAcVdM1a8eQ, accessed 13 may 2023).

Types of biomarkers



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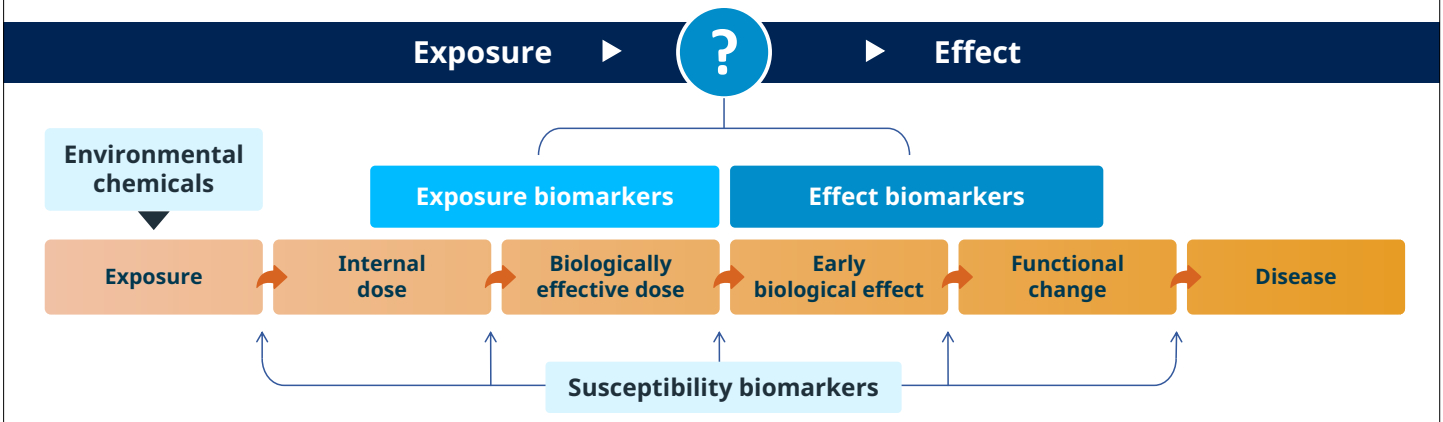
Environmental health paradigm



5 *Source*: adapted from Mustieles et al., 2020. Reproduced with permission from Elsevier. Adapted from National Research Council, 1989. Reproduced with permission from the National Academy of Sciences, Courtesy of the National Academies Press, Washington, D.C.

Human populations are exposed to a complex mixture of chemicals from multiple sources and varying durations, and these exposures have impact on the health.

The development of an adverse effect from exposure depends on several factors such as:

- the route of exposure
- the internal dose at the target organ
- the critical window of exposure
- individual susceptibility
- adaptive mechanisms and feedback regulations.

Once the exposure has taken place, the chemical substances may be absorbed into the human body. Biomarkers of exposure characterize this internal dose. Once they have reached target organs, the chemicals can initiate early molecular or biochemical/cellular response (early biological effects). Effects biomarkers indicate what is the organism's response to the chemical. Susceptibility biomarkers provide information on individual differences (e.g. genetically mediated predisposition to chemical-induced toxicity).

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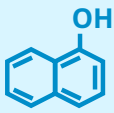
Biomarkers of exposure (I)

Biomarkers of exposure allow the assessment of systemic exposure to a chemical based on its measurement in a biological matrix

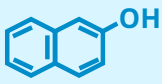
Biomarkers of exposure/internal dose

Chemical substances or their metabolites

1-OHP



1-Naphthol



2-Naphthol

Urinary 1-OHP is a biomarker of exposure to PAHs

1-naphthol is a metabolite of the insecticide carbaryl while both the 1- and 2-isomers are metabolites of naphthalene

6

Notes: PAHs: polycyclic aromatic hydrocarbons; 1-OHP: 1-hydroxypyrene.

Sources

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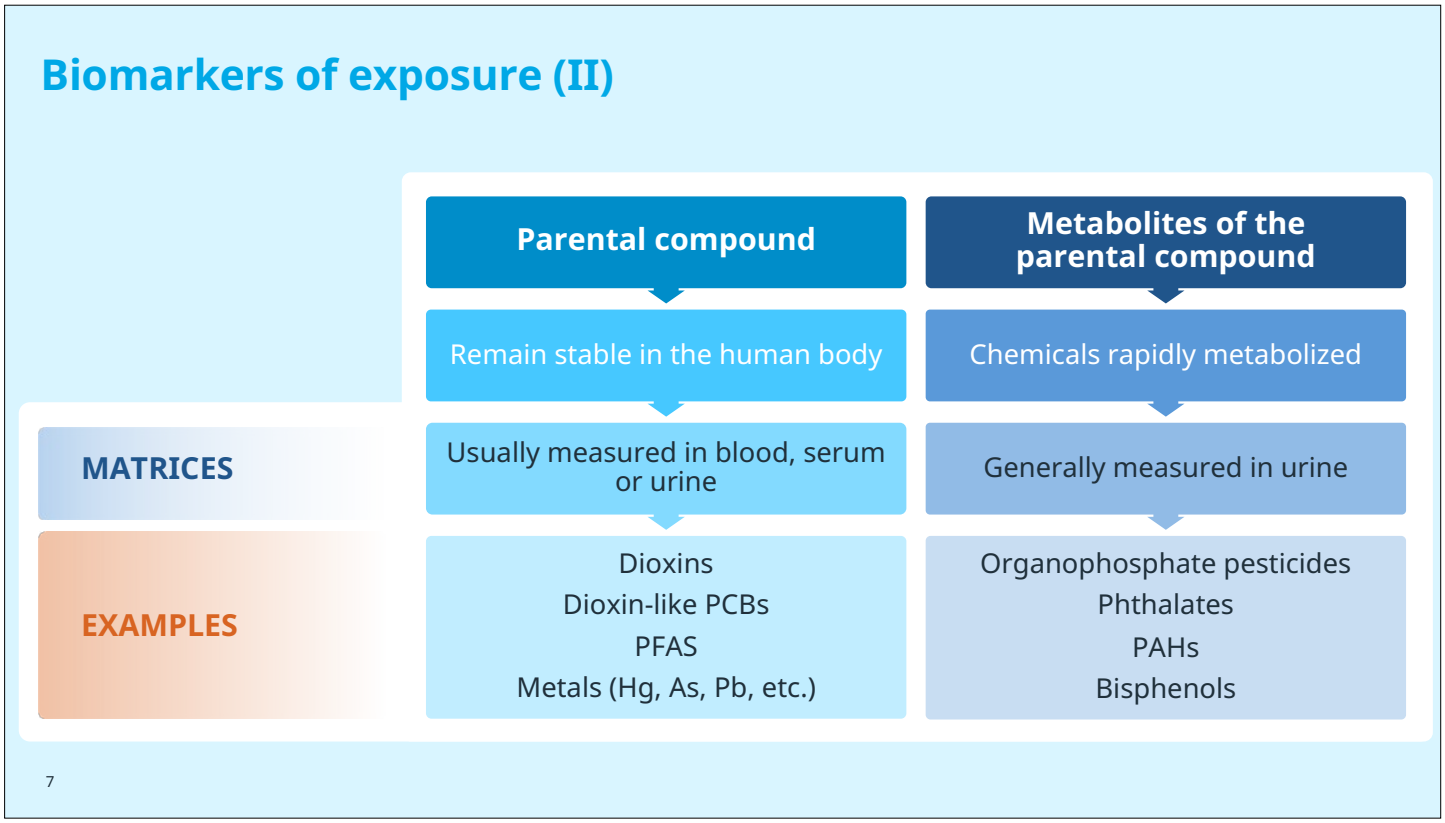

As a general rule, to assess exposure to persistent compounds (e.g. dioxins, dioxin-like PCBs and metals), concentrations of the parent compound are analysed in blood, serum or other matrices as biomarkers of exposure. For non-persistent chemicals that are metabolized rapidly (e.g. organophosphate pesticides and phthalates), one or more metabolites of the parental compound are often used as biomarkers of exposure; these are generally measured in urine.

Notes: As: arsenic; Hg: mercury; PAHs: polycyclic aromatic hydrocarbons; Pb: lead; PCBs: polychlorinated biphenyls; PFAS: per-and poly-fluoroalkyl substances.

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Biomarkers of exposure: example (I)

Matrix	Population	Advantages	Limitations	Compounds measured in the matrix
Blood	General	In equilibrium with all organs and tissues; well-established SOPs for sampling	Invasive; trained staff and special materials required; volume limitation; special conditions for transport and shipment	POPs, metals/trace elements, organic and tobacco smoke compounds; e.g. alkylphenols, mercury, lead, BFRs, dioxins, water disinfection byproducts, fluorinated compounds, organochlorine pesticides, phthalates, PCBs
Urine	General	Non-invasive, easy collection, no volume limitation; allows analysis of metabolite	Not ideal for essential elements - spot urine samples can add significant variation due to within-day and within-individual variation	Metals/trace elements - mercury, cadmium, arsenic, organic and tobacco smoke compounds;. organochlorines, BPA, organophosphate pesticides, parabens, phthalates, PAHs, benzene
Hair	General	Non-invasive; minimum training for sampling; no special requirements for transport and storage; information about cumulative exposure during previous months; segmental analysis possible	Hair is exposed to the environment and can be contaminated; potential variations with subject's hair colour, hair care or race	Metals/trace elements, e.g. total mercury, methylmercury, arsenic, cadmium, POPs, parabens, organochlorine compounds
Breast milk	Specific	Provides information about mother and child; enriched with lipophilic compounds	Somewhat invasive; restricted period of availability; depuration of chemicals during lactation should be considered	POPs, metals/trace elements - lead, cadmium, mercury; organic and tobacco smoke compounds, BPA, dioxins, BFRs, fluorinated compounds, PCBs, organochlorine pesticides, phthalates

8 *Source*: WHO, 2015.

Notes: BPA: bisphenol A; BFRs: brominated flame retardants; PCBs: polychlorinated biphenyls; POPs: persistent organic pollutants; SOPs: standard operating procedures.

Sources

Human biomonitoring: facts and figures. Copenhagen: WHO Regional Office for Europe; 2015 (https://apps.who.int/iris/handle/10665/164588, accessed 10 November 2022).

Biomarkers of exposure: example (II)

Some properties of different non-invasively collected matrices for routine human biomonitoring application

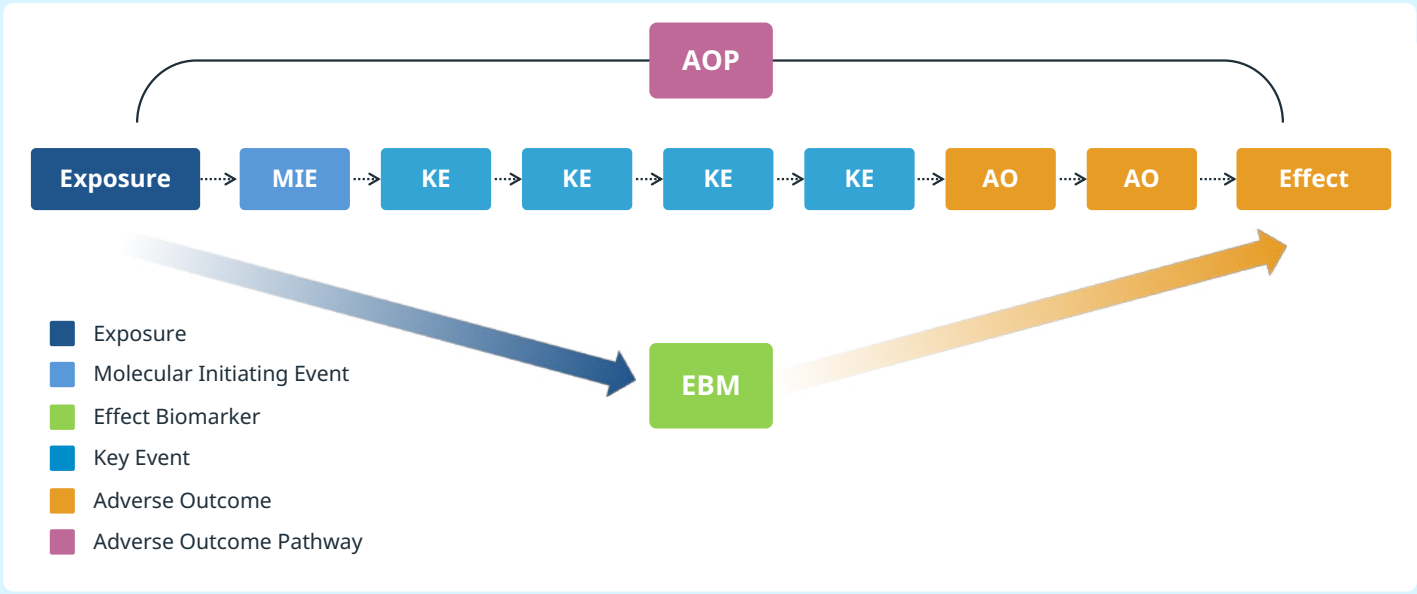
Exhaled breath	+ Direct assessment of exposure through air - Mainly volatile chemicals
Hair	+ Can provide historical overview of exposure - External contamination
Breast milk	+ Lipophilic compounds + Transfer to newborn - Only women during short period
Placenta/ cord blood	+ Procedures similar to peripheral blood + Exposure of unborn child - Only women during short period
Urine	+ Routine collection + Metabolites + Non-persistent chemicals - Correction for dilution
Meconium	+ Can provide historical overview of exposure + Exposure of unborn child - Representative sample
Finger/ toenails	+ Can provide historical overview of exposure - External contamination

9 *Source*: adapted from Smolders et al., 2009. Reproduced under CC BY 2.0 (https://creativecommons.org/licenses/by/2.0/).

Sources

Smolders R, Schramm KW, Nickmilder M, Schoeters G. Applicability of non-invasively collected matrices for human biomonitoring. Environ Health. 2009;8:8. doi: 10.1186/1476-069X-8-8. Published under the CC BY 2.0 (https://creativecommons.org/licenses/by/2.0/).

Biomarkers of effect (I)



10 *Source*: adapted from Mustieles et al., 2020. Reproduced with permission from Elsevier.

Effect biomarkers serve as a forecasting tool of adverse health effects, representing a link between exposures to chemicals and their health effects.

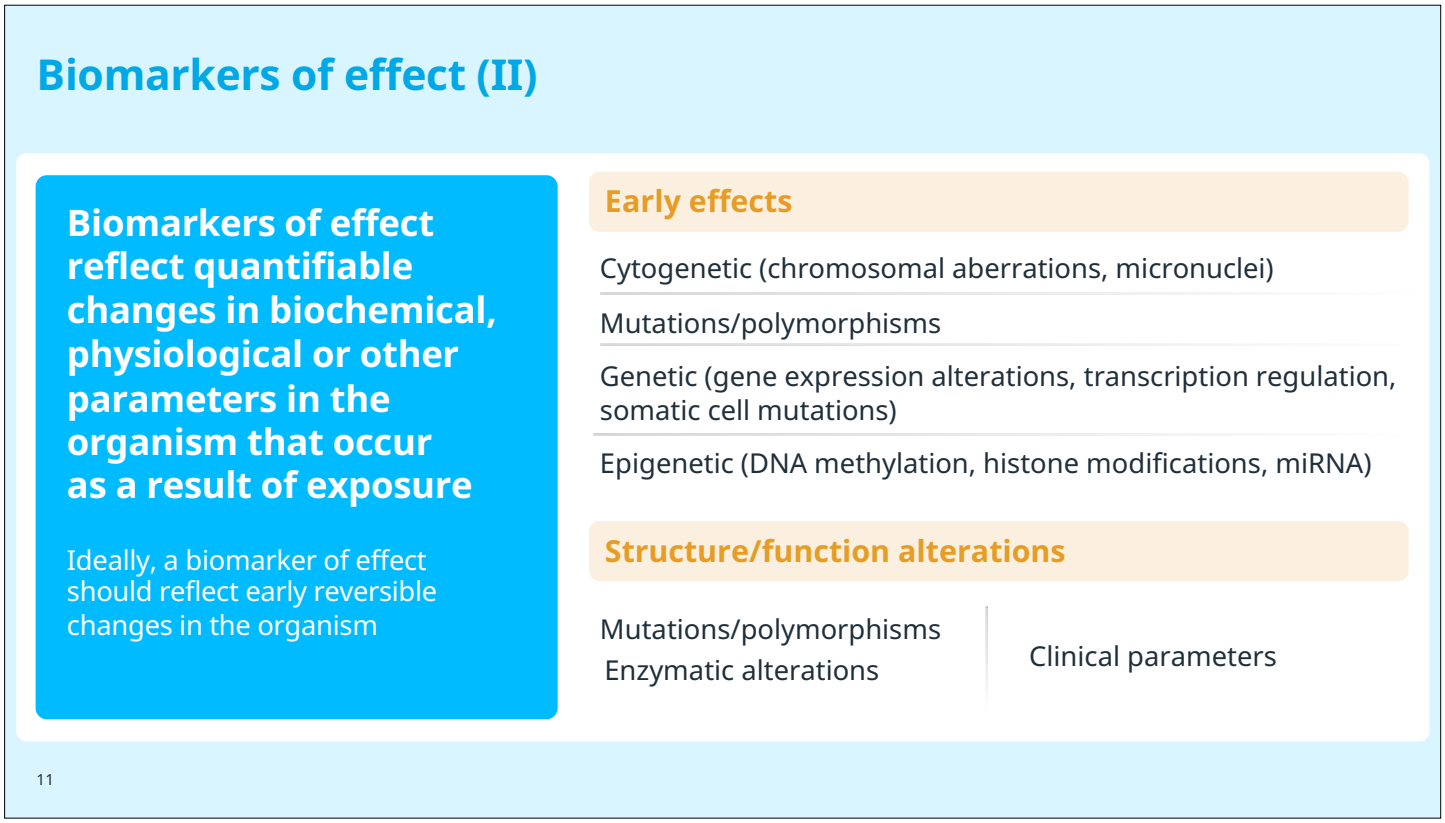
The key events and triggered adverse outcomes can be multiple occurring at the same time, giving rise to cumulative effects and, finally, the onset of the illness.

Both early key events (i.e. early biological changes such as epigenetic modifications and altered gene expression) and late key events (i.e. altered structure or function markers such as sexual hormones) in a given adverse outcomes pathway could be used as effect biomarkers.

Sources

Mustieles V, D'Cruz SC, Couderq S, Rodríguez-Carrillo A, Fini JB, Hofer T et al. Bisphenol A and its analogues: a comprehensive review to identify and prioritize effect biomarkers for human biomonitoring. Environ Int. 2020;144:105811. doi: 10.1016/j.envint.2020.105811.

Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD et al. Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. Env Toxicol Chem. 2010;29:730-41. doi: 10.1002/etc.34.



Depending on the health end-point considered, a series of biomarkers of effect may be identified from biomolecules found in tissue or fluids. These biomarkers include chromosomal aberrations, mutations/polymorphisms, micronuclei, transcription regulators, alterations in gene expression, enzyme alterations or epigenetic modifications. Cytogenetic biomarkers are the most frequently used end-point in HBM studies; for example, the Commet assay (a simple method for measuring DNA strand breaks in eukaryotic cells) has been popular because of its simplicity.

Notes: HBM: human biomonitoring; DNA: deoxyribonucleic acid; miRNA: micro ribonucleic acid.

Sources

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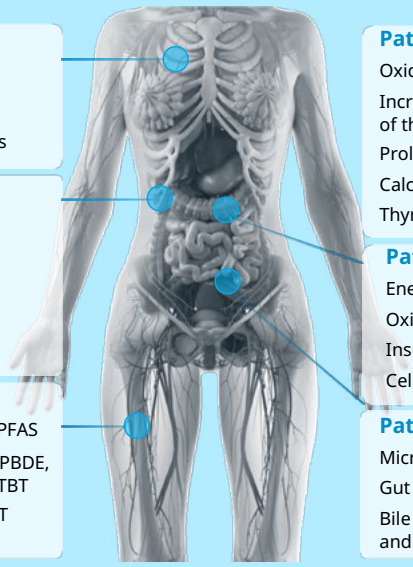
Zare Jeddi M, Hopf NB, Viegas S, Bal Price A, Paini A, van Thriel C et al. Towards a systematic use of effect biomarkers in population and occupational biomonitoring. Environ Int. 2021;146:106257. doi: 10.1016/j.envint.2020.106257.

Biomarkers of effects and pathways associated with specific chemicals: example



Pathway/mechanism	Pollutant
Oxidative stress	PAHs, dioxins
FA pathways	PAHs
Mitochondrial and AA metabolism	PAHs, dioxins, furans

Pathway/mechanism	Pollutant
FA uptake	BPA, PCB, dioxins
DNL	PFAS, BPA, PCB
ROS production/oxidative stress	Metals, PFAS, pesticides
BA biosynthesis	PFAS, PCB
FA β-oxidation	PFAS

Pathway/mechanism	Pollutant
Increased adipogenesis	BADGE, tributyltin, PFAS
Adipocyte differentiation	PFAS, BPA, dioxins, PBDE, pesticides, BADGE, TBT
Adipocyte proliferation	BPA, PBDE, PCB, TBT
Lipid uptake	BPA, PCB, TBT

Pathway/mechanism	Pollutant
Oxidative stress	Pesticides, PAHs
Increased permeability of the blood brain barrier	PFAS
Proliferation of astrocyte cells	Dioxins
Calcium-homeostasis	PFAS
Thyroid hormone balance	PFAS

Pathway/mechanism	Pollutant
Energy metabolism	BPA, phenols
Oxidative stress	Metals
Insulin secretion	BPA, PCB, dioxin
Cell death, cell division	Cadmium, phthalates

Pathway/mechanism	Pollutant
Microbial diversity	PFAS ↓, PCB ↓
Gut permeability	PFAS ↑, PCB ↑
Bile acid metabolism and circulation	PFAS

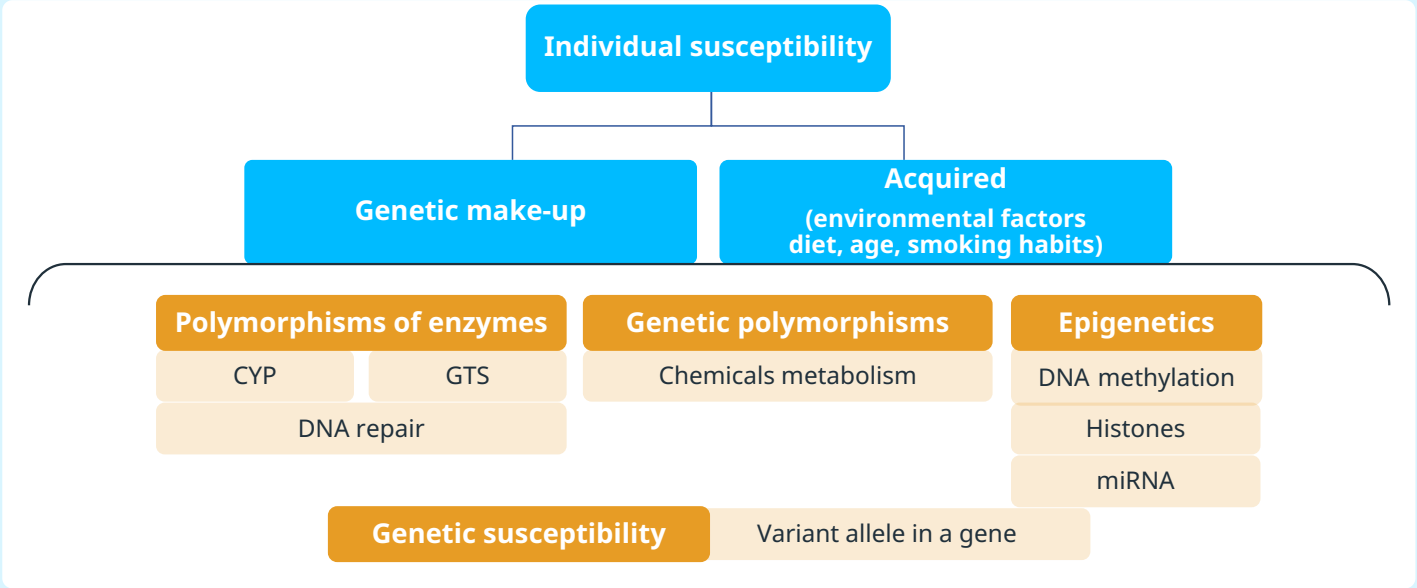
12 *Source*: adapted from Orešič et al., 2020. Reproduced with permission from authors.

Notes: AA: amino acids; BA: bile acids; BADGE: bisphenol A diglycidyl ether; BPA: bisphenol A; DNL: de novo lipogenesis; FA: fatty acid; PAHs: polycyclic aromatic hydrocarbons; PBDE: polybrominated biphenyl ethers; PCB: polychlorinated biphenyls; PFAS: per- and polyfluoroalkyl substances; ROS: reactive oxygen species; TBT: tributyltin.

Sources

Orešič M, McGlinchey A, Wheelock CE, Hyötyläinen T. Metabolic signatures of the exposome: quantifying the impact of exposure to environmental chemicals on human health. Metabolites 2020;10:454;. doi: 10.3390/metabo10110454.

Biomarkers of susceptibility



13

Biomarkers of susceptibility reflect intrinsic characteristics of a given organism that make it more susceptible to the adverse effects of exposure to a specific chemical substance.

Both in vivo and in vitro studies clearly show that, even under similar exposure conditions to environmental chemicals, there are significant variations in response from one individual to other.

Differences in susceptibility can be attributed either to the genetic make-up of the individual or to variables and environmental factors, such as diet, age or the uptake and absorption of chemicals.

An example of a xenobiotic-metabolizing enzyme is CYP, responsible for oxidative metabolism of a multitude of xenobiotic compounds. Another important detoxification enzyme is glutathione-*S*-transferase.

In addition to enzymes involved in detoxification, other potential susceptibility biomarkers are DNA repair enzymes, receptors proteins, oncogenes, tumor suppressor genes and immune system components.

Finally, several epigenetic mechanisms, including DNA methylation, histone modification, and miRNA expression, can, as a result of chemical exposure, change genome function and, therefore, might also constitute biomarkers of susceptibility.

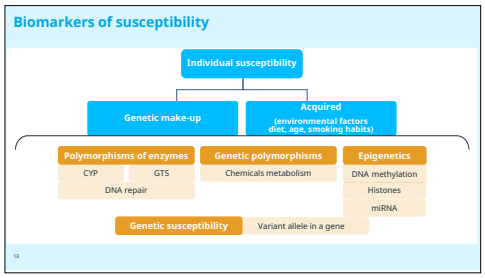
Identification of the variant allele in a gene has been found to be useful in assessing risk and in providing information regarding several diseases. For example, *APOE*, the locus for apolipoprotein E, a protein involved in the metabolism of fats, has been identified as a genomic biomarker that confers susceptibility to Alzheimer's disease, while glial fibrillary acidic protein is a proteomic biomarker for this disease.

Notes: APOE: apolipoprotein E locus; CYP: cytochrome P450; DNA: deoxyribonucleic acid; GTS: glutathione S-transferases; miRNA: micro ribonucleic acid.

Sources

Ladeira C, Viegas S. Human biomonitoring: an overview on biomarkers and their application in occupational and environmental health. Biomonitoring. 2016;3:15-24. doi: 10.1515/bimo-2016-0003.

continued



Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Curr Opin Pediatr. 2009;21:243–51. doi: 10.1097/mo 0b013e32832925cc.

Cimino Reale G, Coccini T, Manzo L. Genomic-level effects of carbon nanotubes. In: Conference Proceedings of the 2012 AIChE Annual Meeting, Pittsburgh, PA, 28 October–2 November 2012 (https://www.aiche.org/conferences/aiche-annual-meeting/2012/proceeding/paper/209d-genomic-level-effects-carbon-nanotubes, accessed 14 May 2023).

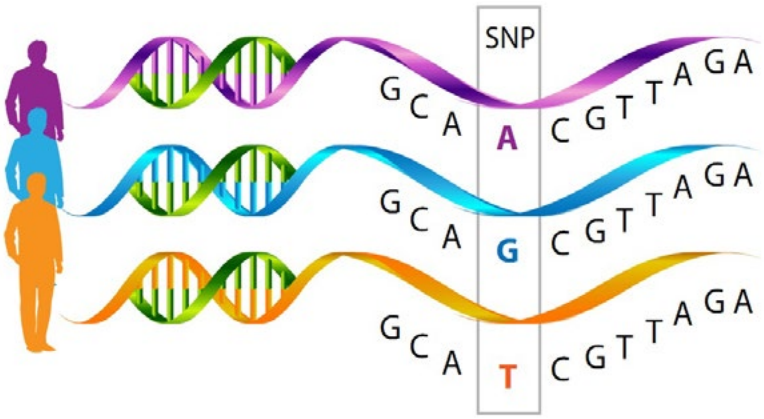
Robeson RH, Siegel AM, Dunckley T. Genomic and proteomic biomarker discovery in neurological disease. Biomark Insights. 2008;3:73-86. doi: 10.4137/BMI.S596.

Molecular biomarkers (I)

Polymorphism A genetic variation in the DNA sequence that occurs in more than 1% of the population

SNPs associated with chemical exposure

Studied genes with characterized biological function linked to adverse effects



14

Most of the biomarkers of effect and of susceptibility include molecules associated with environmental exposure: genes or molecules related to the metabolism of the chemical or altered genes as consequence of the exposure.

A polymorphism is a genetic variation in the DNA sequence that occurs in more than 1% in the general population. Single nucleotide polymorphisms are the most common type of genetic variation in humans and the most used in HBM. Genes well known and with characterized biological function linked to chemical adverse effects can be used as biomarkers of susceptibility or effect.

Notes: HBM: human biomonitoring; SNP: single nucleotide polymorphism.

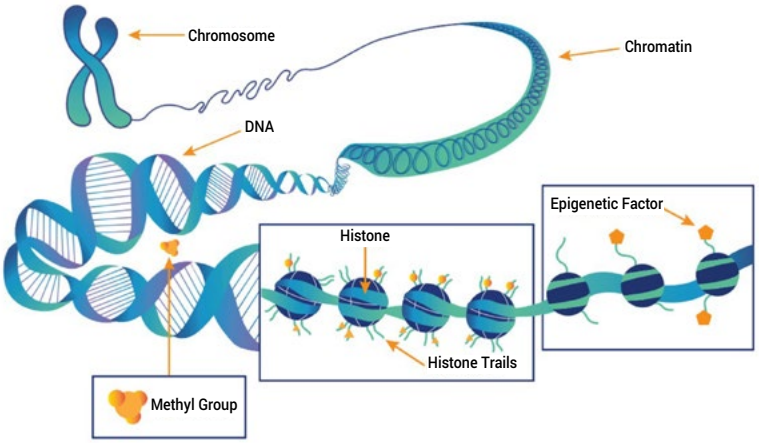
Sources

Teodoro M, Briguglio G, Fenga C, Costa C. Genetic polymorphisms as determinants of pesticide toxicity: recent advances. Toxicol Reports. 2019;6:564-70. doi: 10.1016/j.toxrep 2019.06.004.

Molecular biomarkers (II)

Epigenetics

Investigates heritable changes in gene expression occurring without changes in DNA sequence
Can change genome function under exogenous influence



miRNA

DNA methylation

Histones

15 *Source*: Savelieff et al., 2018. Reproduced with permission from Technology Networks Limited.

Epigenetics investigates heritable changes in gene expression occurring without changes in the DNA sequence, where gene expression and genome function change under exogenous influence.

Investigations in vitro, in animals and in humans have identified several classes of environmental chemical that modify epigenetic marks. Epigenetic mechanisms may mediate specific mechanisms of toxicity and responses to certain chemicals.

There are three main epigenetics tools of interest from the point of view of chemical exposure and health effects.

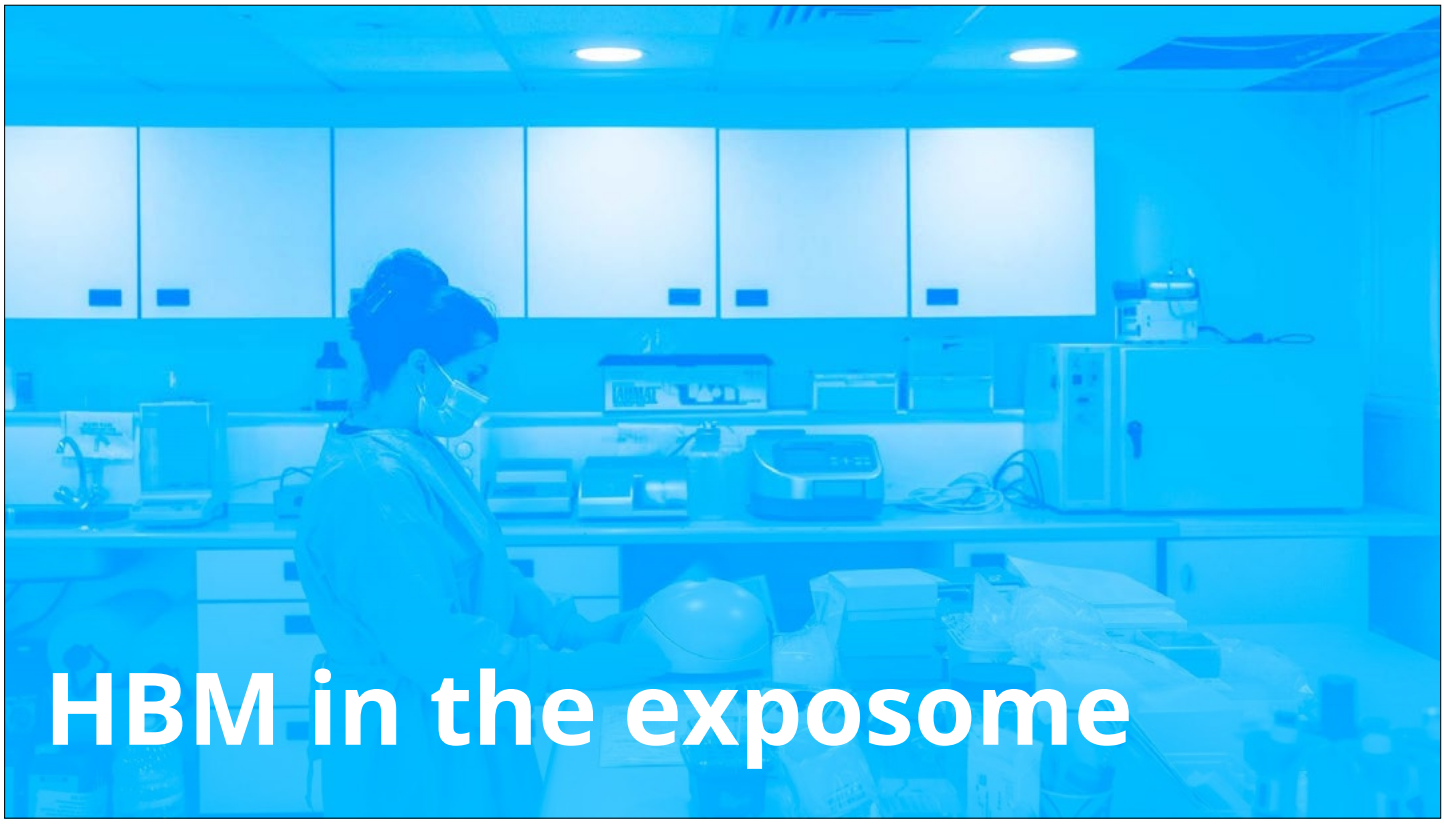
- DNA methylation is a covalent modification, heritable by somatic cells after cell division, where a methyl group is added to the cytosine nucleotide of the genome. It has been associated with reduced chromosomal stability and altered genome function.
- Histones are globular proteins that undergo post-translational modifications that alter their interaction with the DNA and other nuclear proteins.
- miRNA is single-stranded RNA of about 21—23 nucleotides in length that is transcribed from DNA but not translated into protein (non-coding RNA). The main function of microRNA is to downregulate gene expression.

Notes: DNA: deoxyribonucleic acid; miRNA: micro ribonucleic acid: RNA: ribonucleic acid.

Sources

Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Curr Opin Pediatr. 2009;21:243-51. doi: 10.1097/mo 0b013e32832925cc.

Savelieff M. Above the genome: how epigenetics influences cancer and obesity. Technology Networks. 26 September 2018 (https://www.technologynetworks.com/genomics/articles/above-the-genome-how-epigenetics-influences-cancer-and-obesity-310015, accessed 10 November 2022).



Notes: HBM: human biomonitoring.

Exposome: terminology

Exposome

represents the totality of exposures from conception onwards, simultaneously identifying, characterizing and quantifying the exogenous and endogenous exposures and modifiable risk factors that predispose to and predict diseases throughout a person's life span

Metabolome

is the profile of metabolites in an organism that reflects the accumulated effects of multiple exposures or gives an indication of susceptibility to disease and underlying pathology, being dynamic through life. The human metabolomic profile can be influenced by genetic and epigenetic alteration leading to altered gene expression

Epigenetic

is the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence

17

Sources

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Stein RA. Epigenetics and environmental exposures. J Epidemiol Community Health. 2012;66(1):8-13. doi: 10.1136/jech.2010.130690.

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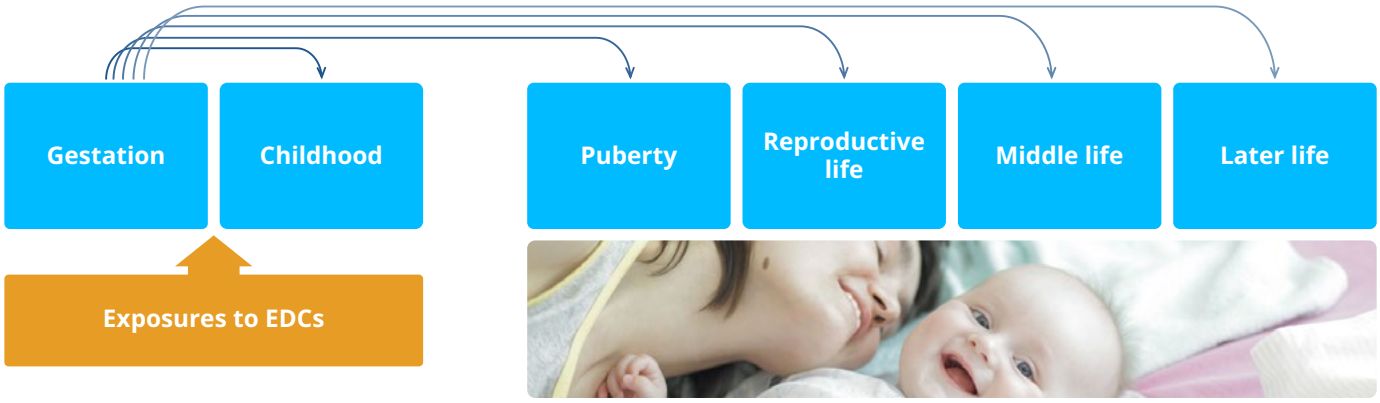
Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005;14:1847-50. doi: 10.1158/1055-9965.EPI-05-0456.

Wild CP. The exposome: from concept to utility. Int J Epidemiol. 2012;41:24-32. doi: 10.1093/ije/dyr236.

Exposome concept: environmental exposures through the life course

"the exposome encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards"



18 *Source*: adapted from UNEP/ WHO, 2013.

For years it was believed that genetic heritage defined an organism's destiny; for humans, if an individual would grow to be healthy or if he or she would suffer from chronic illness or cancer. Recent scientific evidence has shown that both the internal and the external environments influence genetic function. Research in the developmental origins of health and disease shows that environmental factors can affect the development of the next generation even before conception and can continue throughout pregnancy and into early childhood.

Notes: EDC: endocrine-disruptiing chemical; UNEP: United Nations Environment Programme.

Sources

World Health Organization, United Nations Environment Programme, Inter-Organization Programme for the Sound Management of Chemicals, Bergman Å, Heindel JJ et al. State of the science of endocrine disrupting chemicals 2012: summary for decision-makers. Geneva: World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/78102, accessed 10 November 2022).

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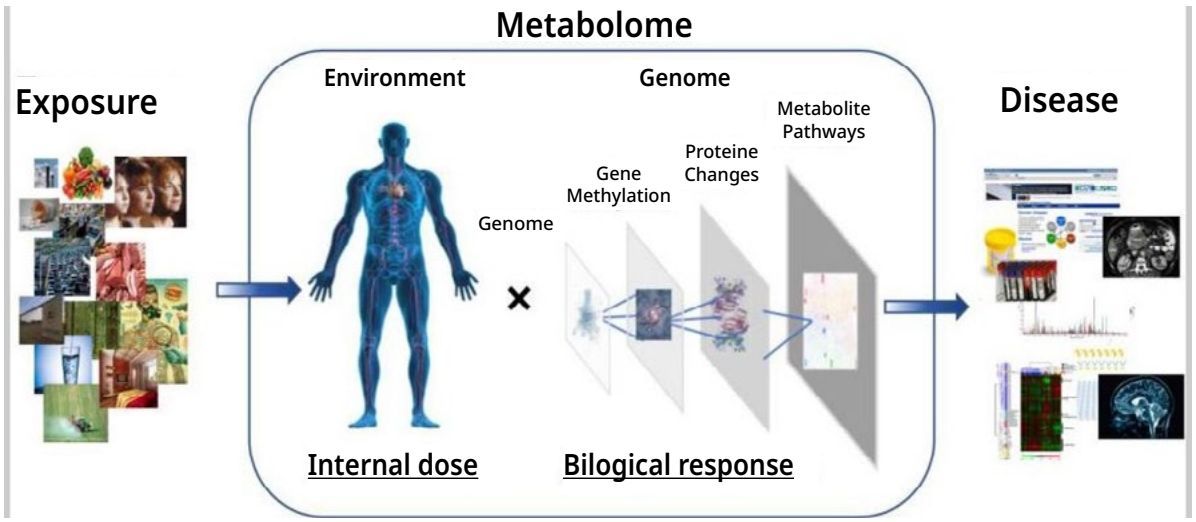
Exposome concept



19 *Source*: Walker at al., 2019. Reproduced with permission from Elsevier.

Many important chronic diseases are likely to result from the combination of environmental exposure and human genetics. Whereas the genetic influences on health have been extensively studied, we are only beginning to understand the impact of the complex environmental exposures on health. The sequencing of the genome, the development of molecular tools and biomarkers and the use of large-scale genome-wide association studies have greatly contributed to describing the influence of genetic factors for the development of diseases. In a similar way, the genome can be complemented by a concept that integrates the environmental exposures: the exposome.

Sources

Walker DI, Valvi D, Rothman N, Lan Q, Miller GW, Jones DP. The metabolome: a key measure for exposome research in epidemiology. Curr Epidemiol Rep. 2019;6:93-103.

Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005;14:1847-50. doi: 10.1158/1055-9965.EPI-05-0456.

Dennis KK, Marder E, Balshaw DM, Cui Y, Lynes MA, Patti GJ et al Biomonitoring in the era of the exposome. Environ Health Perspect. 2017;125:502–10. doi: 10.1289/EHP474.

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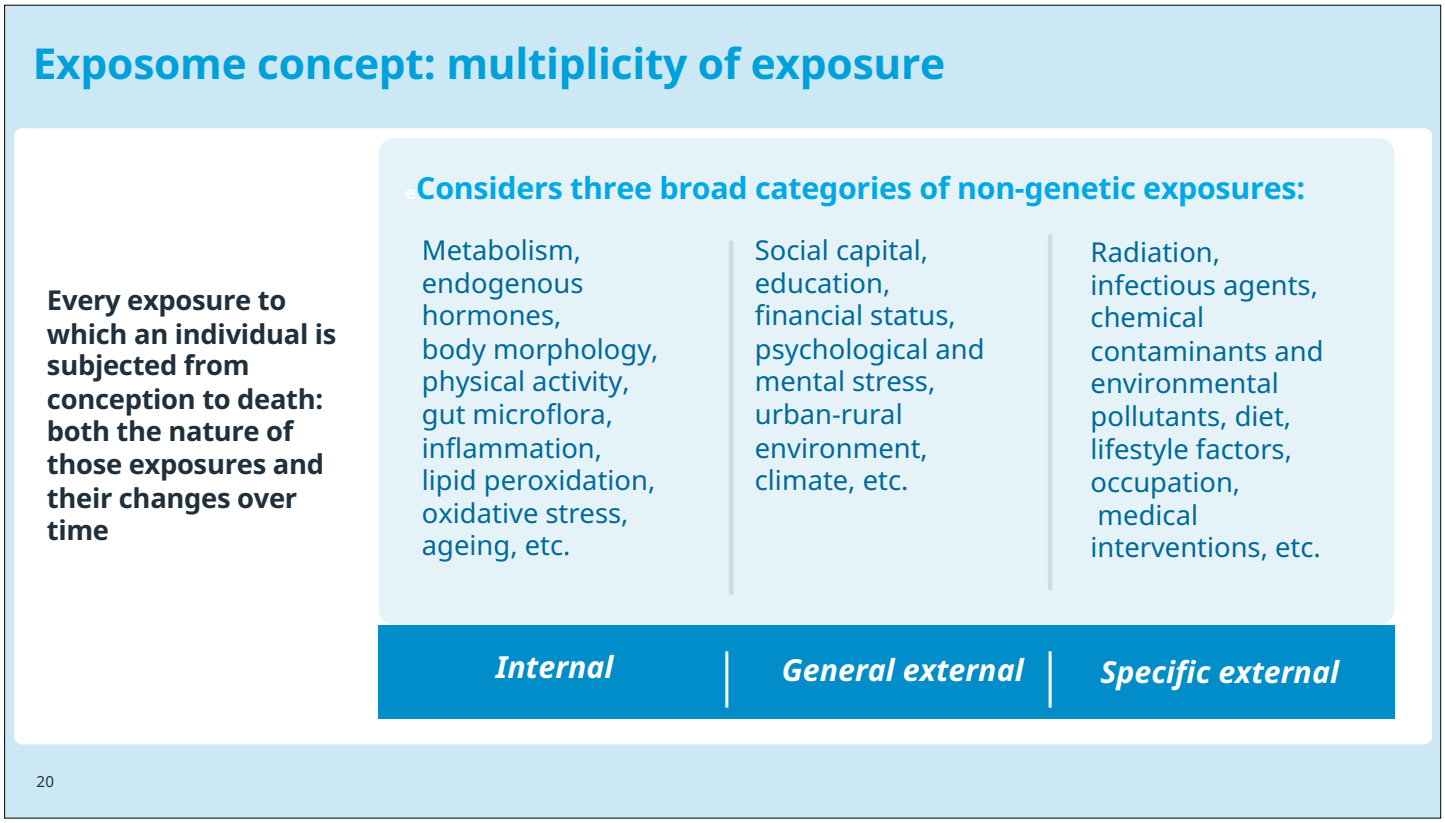

To simplify the concept, three categories of non-genetic exposures were described:

- a general external environment including wider social, economic and climate factors;
- a specific external environment representing the extensive range of external exposures such as chemical contaminants, environmental pollutants, diet, lifestyle factors; and
- an internal environment to include internal biological factors such as metabolic factors, hormones, body morphology, inflammation or oxidative stress.

The exposome, therefore, integrates the many external and internal exposures from different sources spanning a lifetime, which poses methodological and analytical challenges.

Sources

Wild CP. Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005;14:1847-50. doi: 10.1158/1055-9965.EPI-05-0456.

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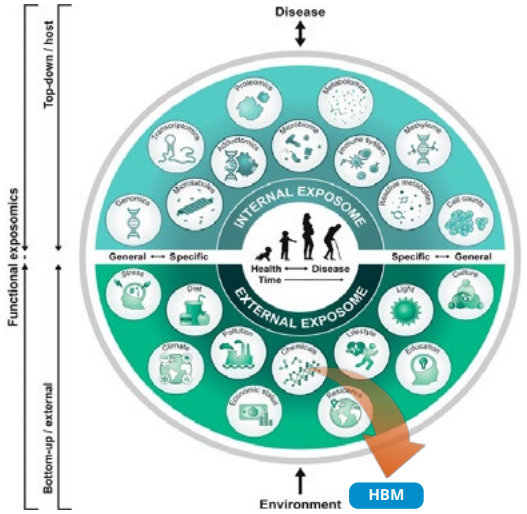
HBM and the exposome

HBM studies are starting point for exposome studies

Data on exposures available to be integrated; however mostly at individual "known" chemical compound level:

- ✓ Need to evaluate mixtures
- ✓ Need to develop methods for chemical of emergency concern
- ✓ Need for combining targeted + untargeted high resolution mass spectrometry methods (suspect screening analysis and non-target analysis): addresses the above

Functional exposomics approach to study the exposome



21 *Source*: Zhang et al., 2021. Reproduced under CC BY 4.0 licence (https://creativecommons.org/licenses/by/4.0/).

Assessment of the exposome can include traditional measures of exposure (e.g. traditional biomonitoring, environmental monitoring) but also includes untargeted discovery of unknown chemicals of biological importance. Exposomic approaches, therefore, go a step beyond traditional HBM, aiming to capture all exposures that potentially affect health and disease.

Note: HBM: human biomonitoring.

Sources

Bocato MZ, Ximenez JPB, Hoffmann C, Barbosa F. An overview of the current progress, challenges, and prospects of human biomonitoring and exposome studies. J Toxicol Environ Health B Crit Rev. 2019;22:131-56. doi: 10.1080/10937404.2019.1661588.

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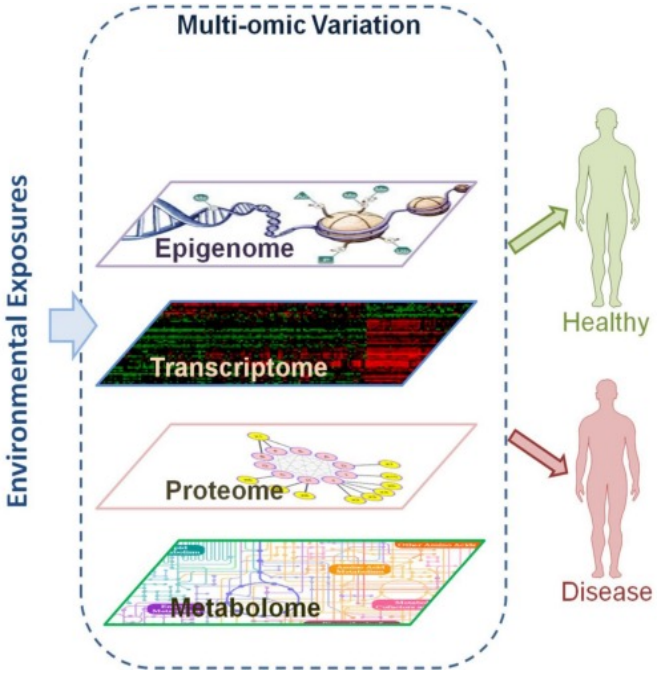
Concept evolution

Use of "omics" high-throughput platforms

- transcriptomic
- proteomic
- metabolomic/adductomic/lipidomic
- metallomic

to measure internal exposome

Systems biology



22

Source: adapted from Sun et al., 2016. Reproduced with permission from Elsevier.

Since the initial concept of the exposome, the definition has evolved to provide a more comprehensive view. It also includes the use of several omics high-throughput platforms to measure the internal exposome. The strategy uses the concept of "systems biology", which involves a quantitative analysis of large networks of molecular and functional changes that occur in multiple levels of biological organization. The combination of data acquired on a large scale, through multi-omic platforms (transcriptomic, proteomic, metabolomic/adductomic/lipidomic, metallomic) with a specific health condition, and/or with multiples and specific biological markers of disease, can provide also knowledge on possible mechanisms of action.

Sources

Sun YV, Hu YJ. Integrative analysis of multi-omics data for discovery and functional studies of complex human diseases. Adv Genet. 2016:93;147–90. doi: 10.1016/bs.adgen.2015.11.004.

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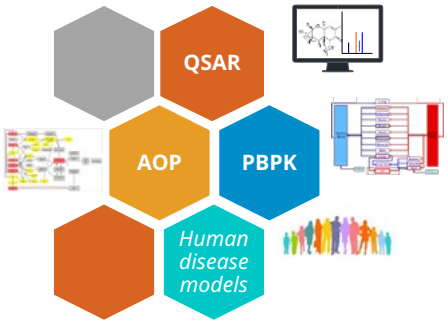
Vermeulen R, Schymanski EL, Barabási AL, Miller GW. The exposome and health: where chemistry meets biology. Science. 2020;367:392–6. doi: 10.1126/science.aay3164.

Methodologies for chemical-specific RA

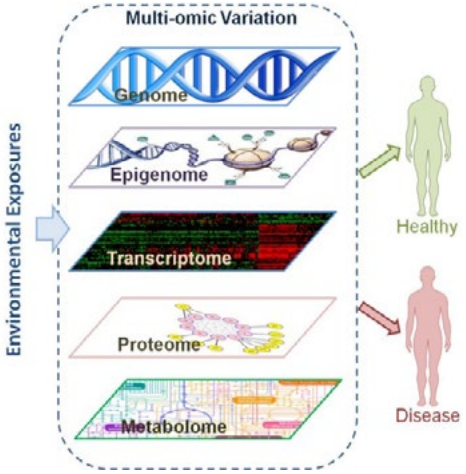
In silico methodologies

Data integration, modelling



23

Omics technologies: the new generation of effect



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Traditional chemical RA based on animal testing is not sufficient for exposome studies, and the lack of toxicological investigations on chemical mixtures remains a major regulatory challenge. The HBM data generated over recent decades have included internal exposure and early effect data, which has facilitated a better understanding of exposure–health relationships.

An integrated aproach of in vivo, in vitro and in silico data, together with systematic reviews or meta-analysis of high-quality epidemiological, HBM and omics data, will improve the robustness of RA of chemicals and will provide a stronger basis for regulatory decisions.

Notes: AOP: adverse outcome pathway; HBM: human biomonitoring; PBPK: physiologically based pharmacokinetic modelling; QSAR: quantitative structure–activity relationship modelling; RA: risk assessment.

Sources

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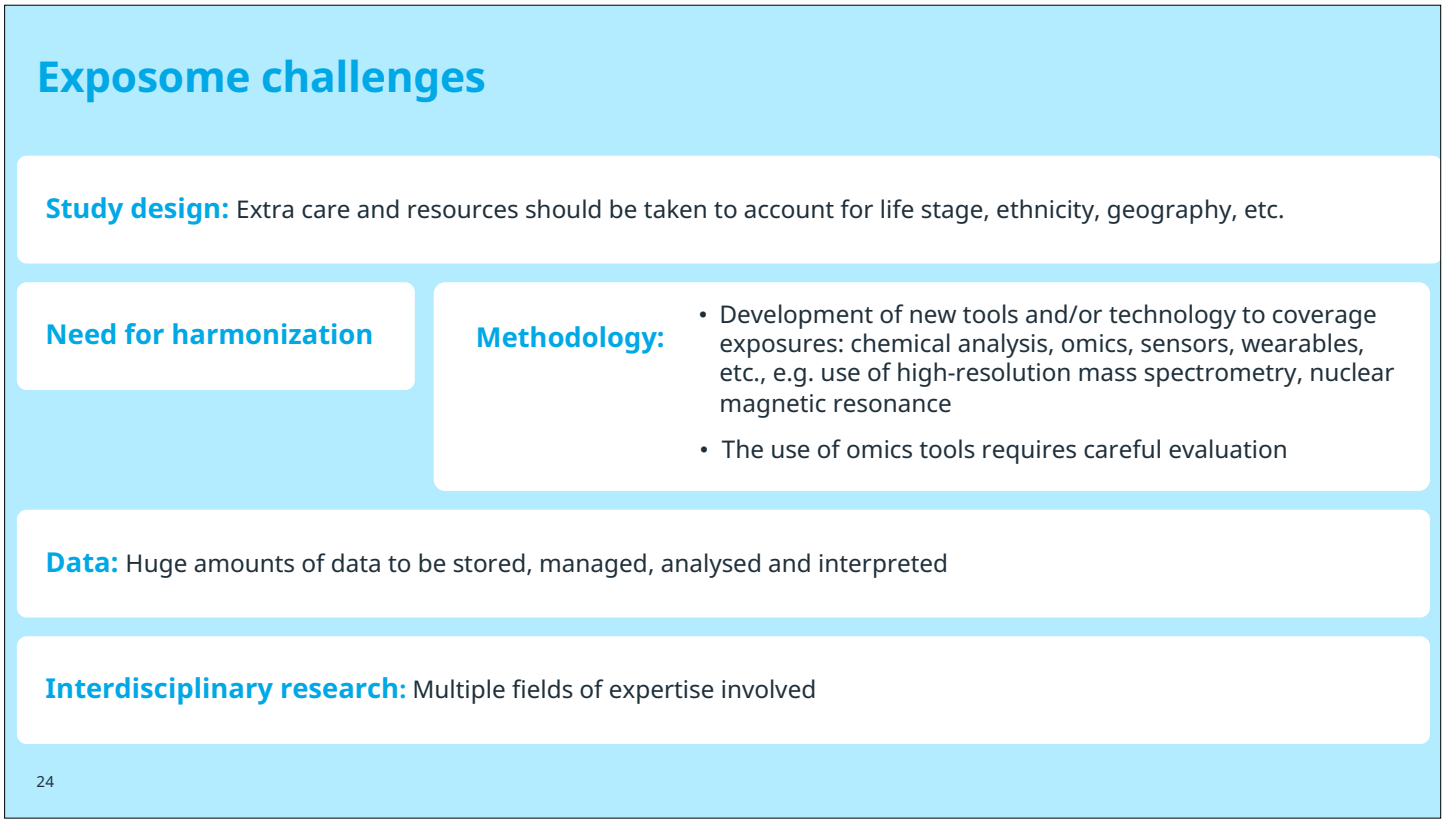

The holistic definition of the exposome, as a complex system in which multiple exposures and mixtures of exposures and factors in the life course of individuals are integrated, creates many challenges.

- Study design. Since the exposome varies by many factors, such as life stage, ethnicity, geography and so on, extra care and resources should be taken when designing studies.
- Methodology. Development of new tools and/or technology that provide the proper coverage and accuracy of exposures (including chemical analysis, omics, sensors, wearables, etc.) is needed. For example, high-resolution mass spectrometry allows the simultaneous measurement not only of huge numbers of endogenous compounds but also of exogenous compounds such as chemical contaminants.
- Databases. Collection of data on many chemical and physical exposures and on molecular omics profiles generates huge amounts of data, which have to be stored, managed, analysed and interpreted.
- Interdisciplinary research. Multiple fields of expertise are involved in exposome analysis, including environmental research, toxicology, molecular mechanisms, biotechnology, bioinformatics, biostatistics, epidemiology, social sciences and clinical research.

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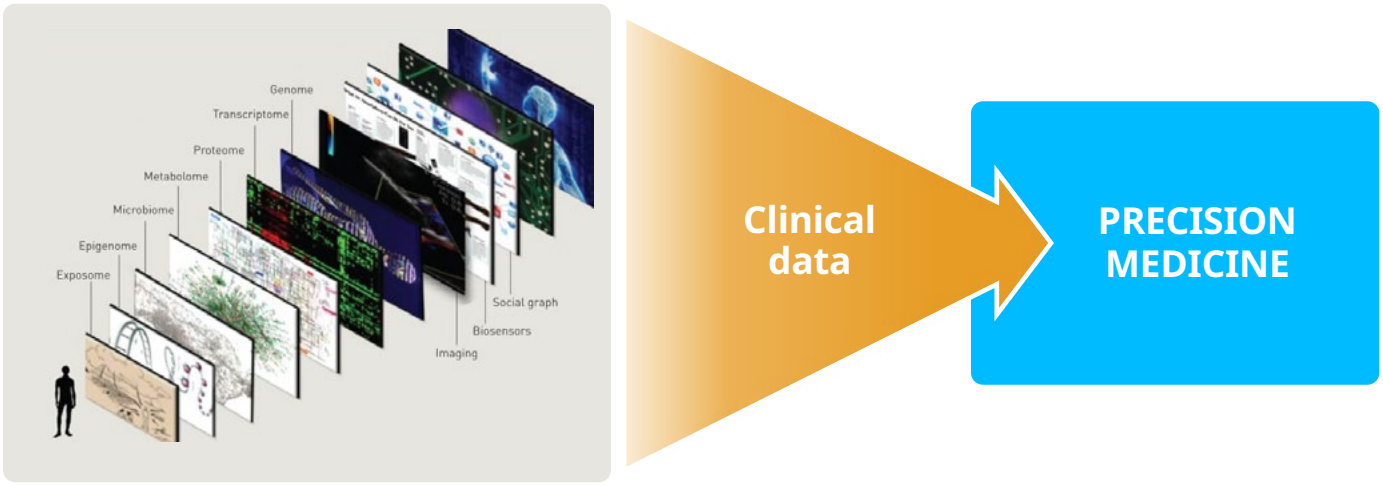
Towards precision medicine



25 *Source*: Topol et al., 2014. Reproduced with permission from Elsevier.

The integration of the comprehensive assessment of the exposome and the genome with additional clinical data of an individual will constitute important steps towards precision medicine.

Sources

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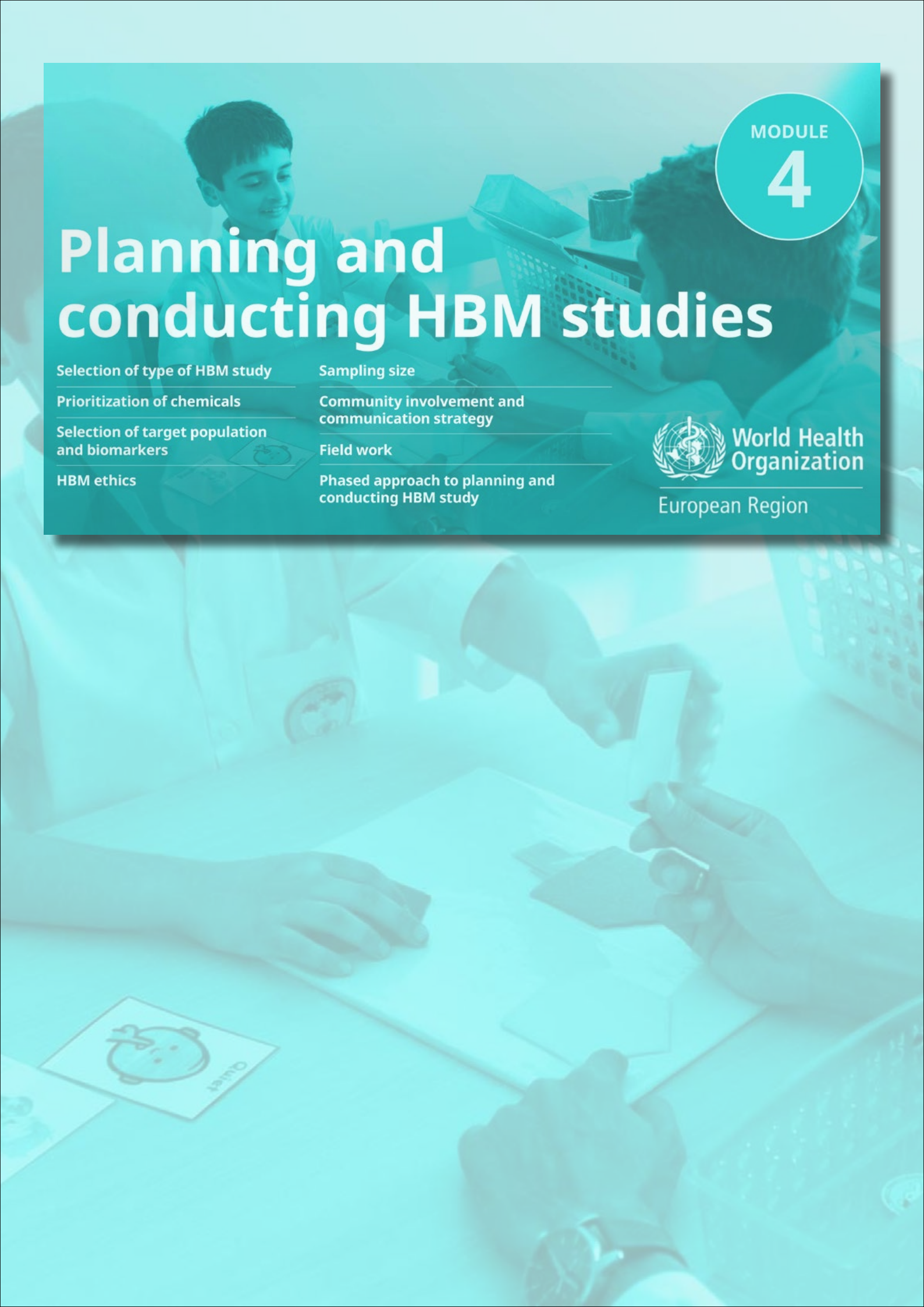
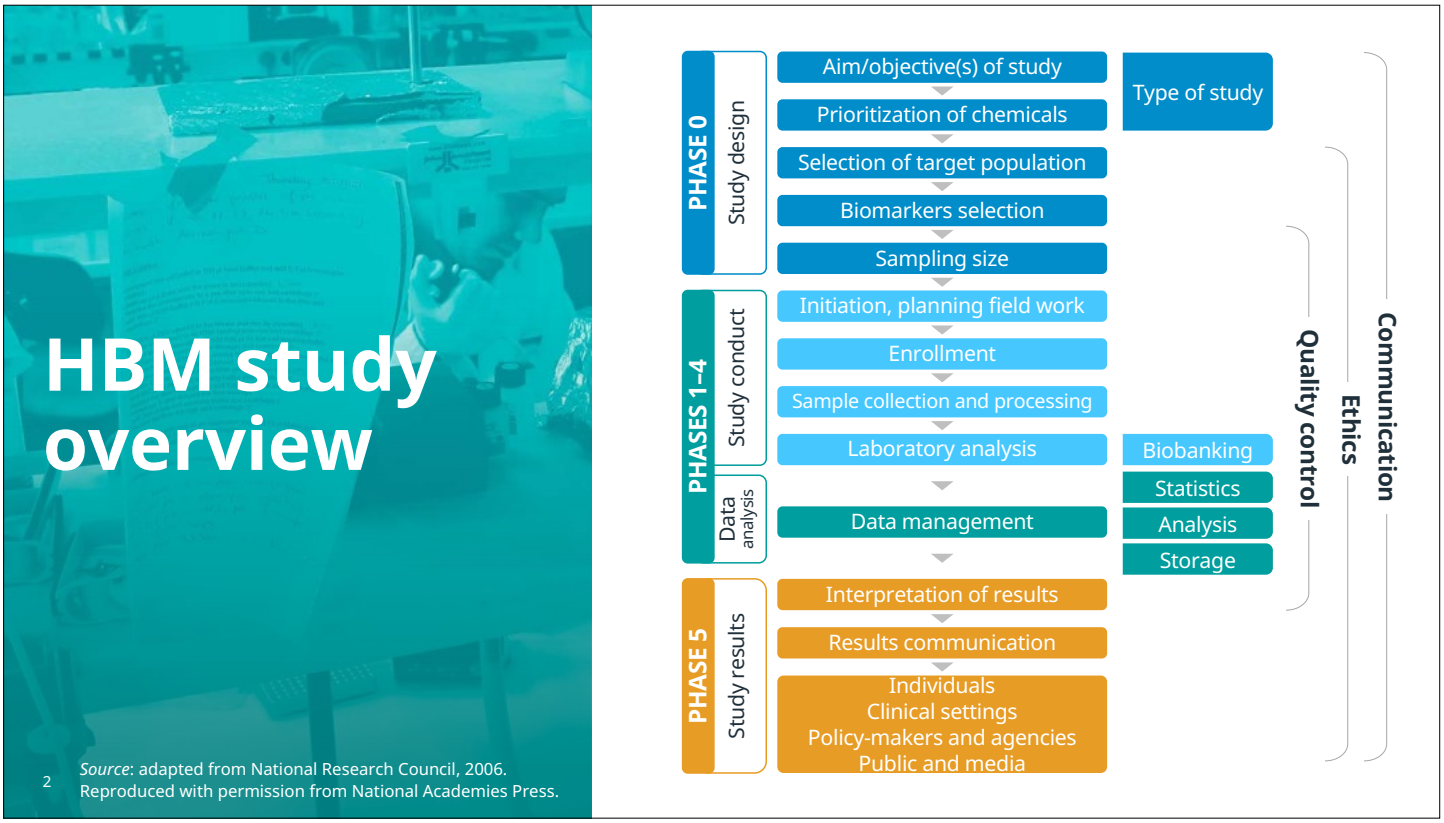


MODULE 4

Planning and conducting HBM studies

- Selection of type of HBM study
- Prioritization of chemicals
- Selection of target population and biomarkers
- HBM ethics
- Sampling size
- Community involvement and communication strategy
- Field work
- Phased approach to planning and conducting HBM study

World Health Organization
European Region



2 *Source*: adapted from National Research Council, 2006. Reproduced with permission from National Academies Press.

HBM is a complex process with several stages/phases and requiring multidisciplinary expertise. HBM starts with planning and designing; followed by conducting the field work; analysis and summarizing the results; and communicating the results to relevant stakeholders. Ethics consideration, communication and QC should be considered at any stage/phase of HBM study.

Notes: HBM: human biomonitoring; QC: quality control.

Sources

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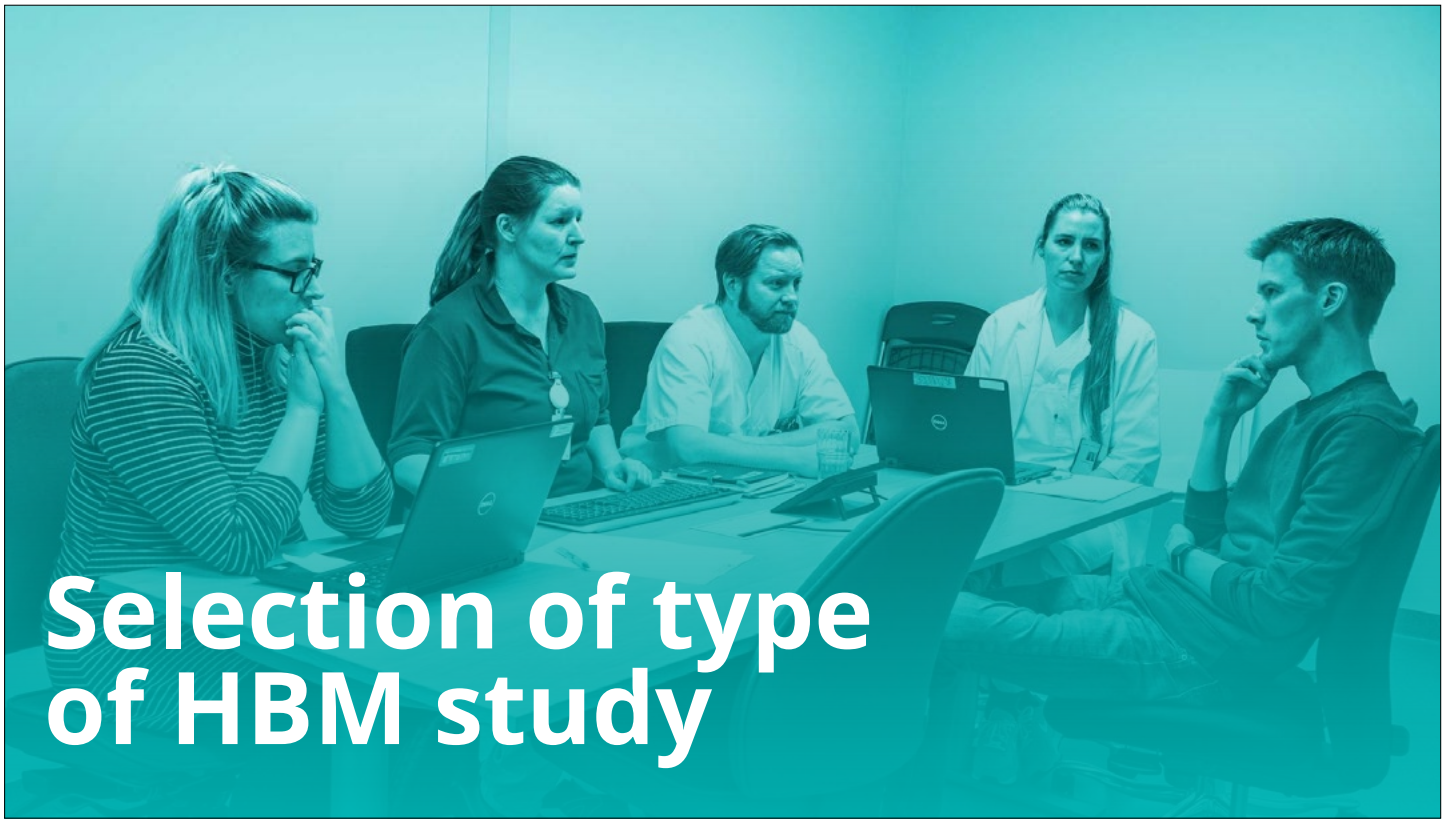
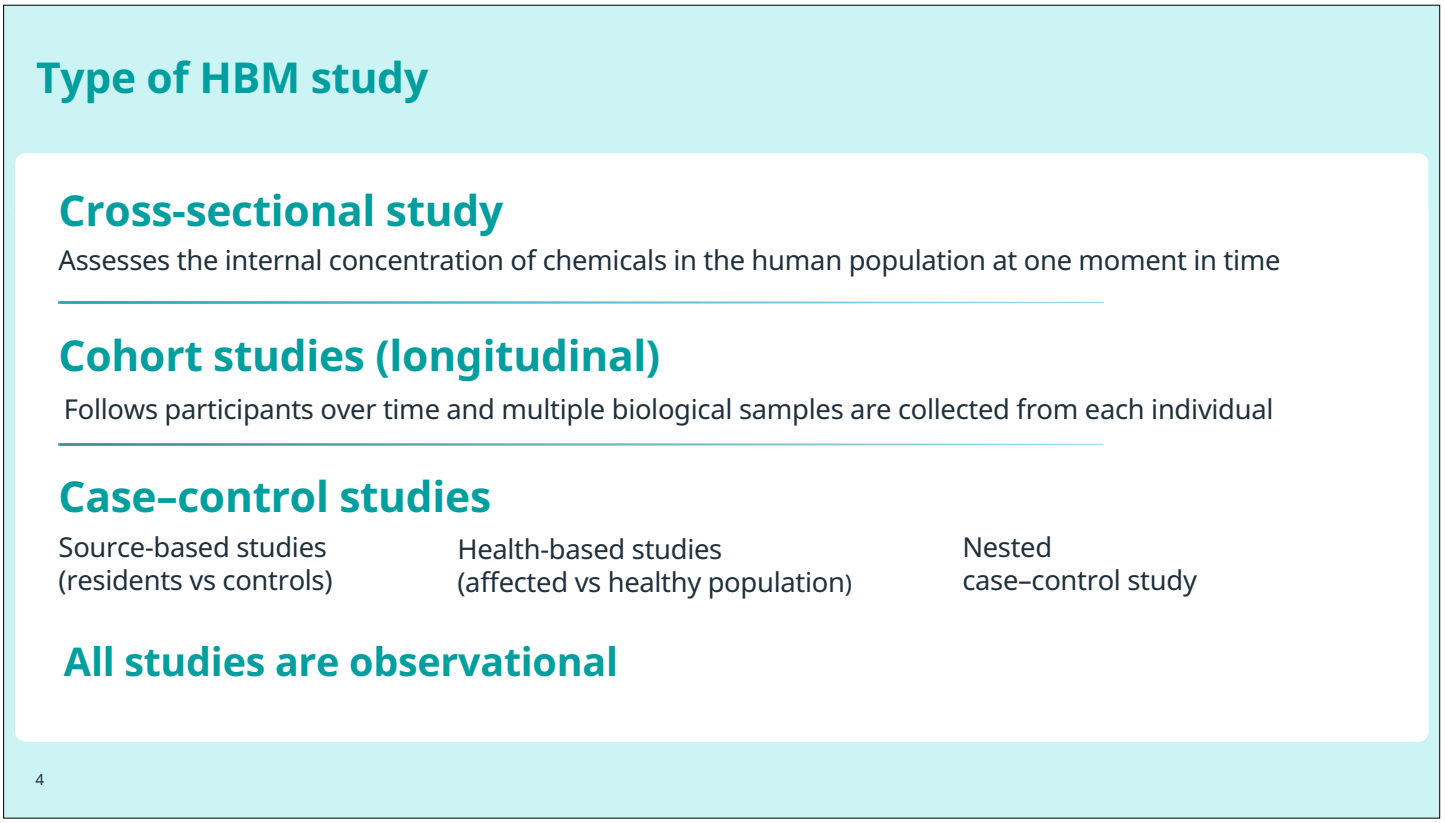


Notes: HBM: human biomonitoring.



The type of study should be determined based on the objectives from the very beginning of the design process; the objectives have implications for each aspect of the study to be conducted and also on the scientific significance, especially if elucidating causality is the intention. Cross-sectional, cohort (longitudinal) and case–control studies provide data corresponding to specific objectives of an HBM sstudy. Cross-sectional studies, for example, can answer policy questions related to the actual exposure levels of the target population but cannot be used to answer questions on causality.

Notes: HBM: human biomonitoring.

Sources

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Cross-sectional study (I)

Information that can be obtained	Examples
Provides an estimate of exposure to several types of environmental and industrial chemical at a certain time	**CHMS (Canada), CZ-HBM (Czechia)**
Allows establishment of reference values for the general population or a specific population group	**GerES (Germany), PROBE (Italy)**
Investigates related time trends if performed more than once	**NHANES (United States), ESB (Germany)**
Evaluates exposure during periods of increased susceptibility such as the period around birth and during early infancy	**COPHES/DEMOCOPHES (Europe-wide), FLEHS (Belgium), SLO-HBM (Slovenia)**
Allows investigation of exposure determinants (if epidemiological data are available) and potential health risks	**HBM4EU**

5

Large-scale cross-sectional studies/surveys in some countries/regions (Canada, EU, United States) simultaneously collect information on exposure and health status and allow researchers to make comparison between groups of individuals with various exposure criteria. Examples of such large cross-sectional studies in the United States are the NHANES, with several rounds; National Children's Health and Nutrition Examination Survey; and the NHIS. Associations between chemical burden and health disorders could be found because extensive data are collected in each round of the study. There are many other examples of cross-sectional surveys that include an HBM component. One of the biggest in Europe is the German Environmental Survey and, currently, studies conducted in the framework of HBM4EU project.

Notes: CHMS: the Canadian Health Measures Survey; COPHES: Consortium to Perform Human Biomonitoring (EU); CZ-HBM: Czech Human Biomonitoring Project; DEMOCOPHES: Demonstration of a Study to Coordinate and Perform Human Biomonitoring on a European Scale (EU); ESB: German Environmental Specimen Bank; EU: European Union; FLEHS: Flemish Environment and Health Study; GerES: German Environmental Survey; HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative; NHANES: National Health and Nutrition Examination Survey; NHIS: National Health Interview Survey; PROBE: Programme for Biomonitoring the Italian Population Exposure; SLO-HBM: Slovenian National HBM program.

Sources

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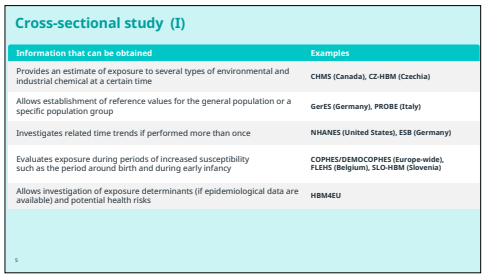

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Allows investigation of exposure determinants (if epidemiological data are available) and potential health risks	HBM4EU

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Cross-sectional study (II)

Pros

Can be completed in a relatively short period of time

Could be based on whole population (population-based studies) or representative of the targeted population; recruitment of big population groups is possible

Can be retrospective if samples are saved in biobank

Cons

Inability to assess causality or the temporal relation between exposure and health outcome

6

Cross-sectional studies examine the relationship between exposure and other variables of interest in a defined population at one particular time. Exposure is determined in each member of the study population or in representative samples. If national-wide exposure is planned to be assessed, it can be a large project to ensure that the data collected are representative for the general population and subgroups, such as children or pregnant women.

Sources

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Cohort study (longitudinal) (I)

Information that can be obtained	Examples
Obtains evidence on the interactions of environmental exposures with processes of ageing; prospective as epidemiological follow-up from the newborn stage	**ENVIRONAGE (Belgium)**
Investigates the effects of environmental exposures, parental conditions and social factors experienced during prenatal and early postnatal life on infant and child health and development	**Piccolipiù (Italy) (since 2001)**
Can elucidate environmental factors that affect children's health and development	**JECS (Japan) (since 2011)**
Maps the levels of environmental toxicants (in breast milk), identifies factors related to high levels and can see if there are regional differences in a multicentre birth cohort of mother–child pairs	**HUMIS (Norway)**
Examines the effects of prenatal exposure to environmental chemicals on the health of pregnant women and their infants	**MIREC (Canada) (since 2007)**

7

A birth cohort study is a type of longitudinal survey that involves assessing perinatal exposure (e.g. biomarkers measured in the blood or urine of the pregnant mother, in cord blood or the hair of mothers) and following the children over time to assess associated health effects occurring later in life. The main feature of a longitudinal study is that they are conducted over a long period (commonly years), with comparison of incidence rates in groups that differ in exposure levels.

In Europe, 12 cohorts related to environmental exposure from around 100 ongoing investigations address several aspects: genetic and biological, psychological/social environments, medical care and medications, and lifestyle and environmental parameters. In this regard, new cohorts are periodically being created to address the more pressing issues, such as child health and pollution.

The German Environment Agency has commissioned the conceptual work for a birth cohort study (100 000–200 000 parent–child pairs) to investigate environmental health problems in children.

To characterize epidemiological signatures of disease in young children in Japan, the JECS started recruitment in January 2011. Approximately 100 000 expecting mothers were recruited over a three-year period. It is planned that participating children will be followed until they reach 13 years of age.

Notes: ENVIRONAGE: Environmental Influence on Early Ageing; HUMIS: Norwegian Human Milk Study; JECS: Japan Environment and Children's Study; MIREC: Maternal–Infant Research on Environmental Chemicals; Piccolipiù: Italian Prospective Birth Cohort.

Sources

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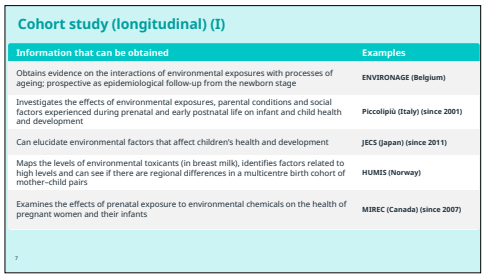

Cohort study (longitudinal) (I)

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7

Schmidt B, Schulz C, Moebus S, Seiwert M, Kolossa-Gehring M, Jöckel KH. Konzept für eine umweltepidemiologische Geburtskohorte des Bundes [Concept for a German national birth cohort for environmental health research]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2012;55(6-7):852-7. In German. doi: 10.1007/s00103-012-1484-5.

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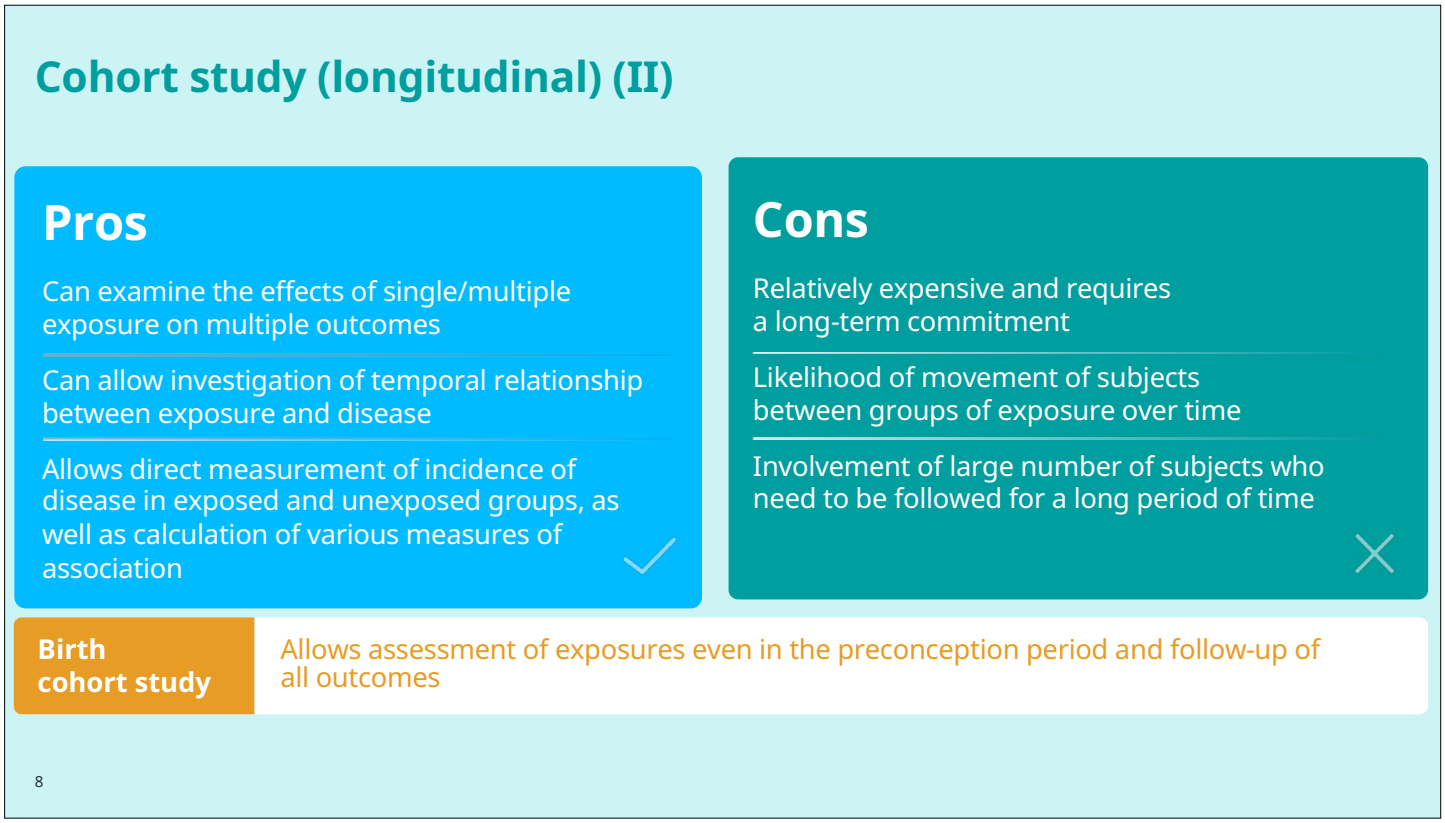

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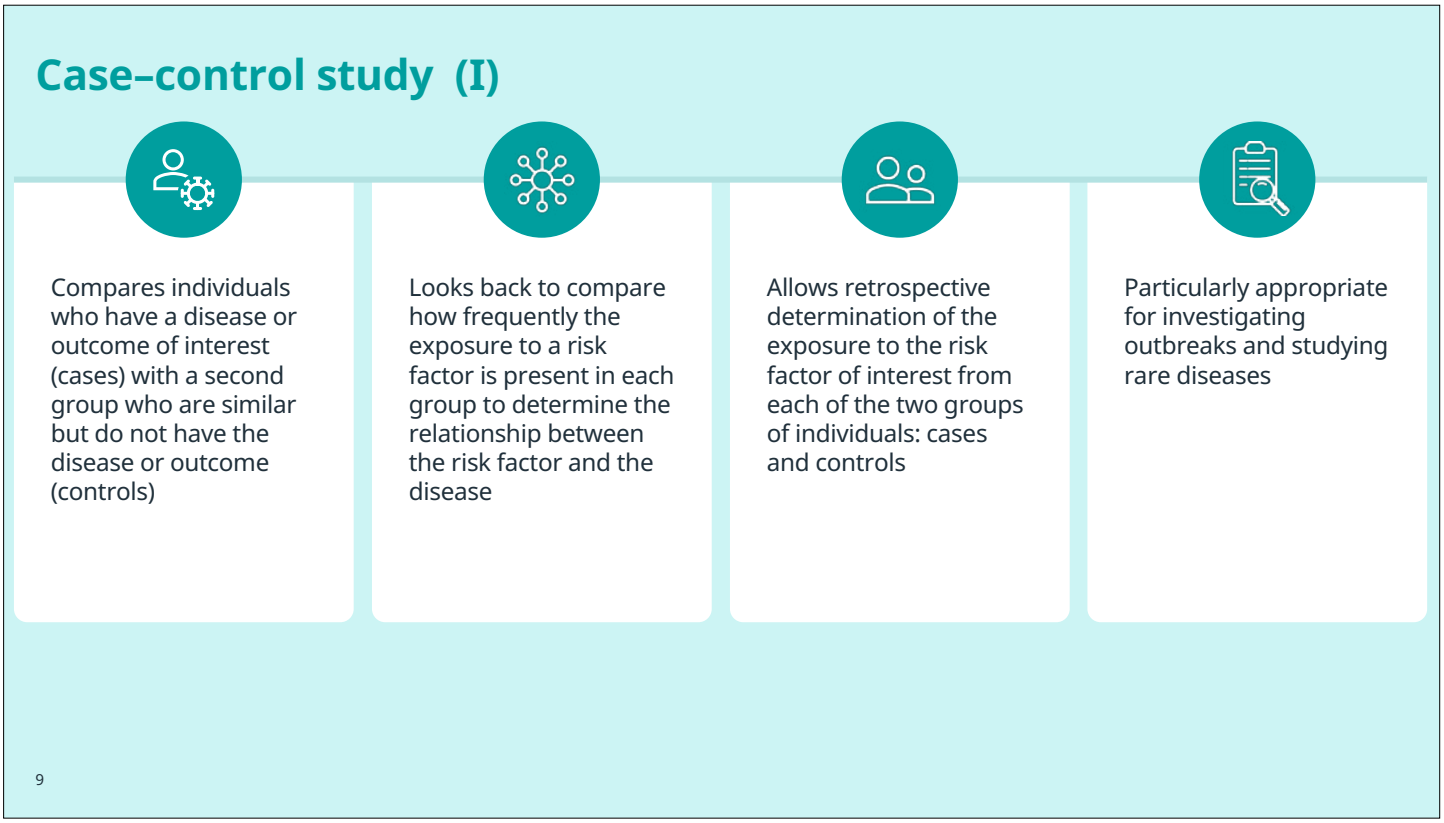

The epidemiological study of people with a disease (or another outcome variable) of interest is compared with a suitable control group of people without the disease (comparison group, reference group). The potential relationship of a suspected risk factor or an attribute to the disease is examined by comparing the case and the control subjects regarding how frequently the factor or attribute is present (or, if quantitative, the levels of the attribute) in each of the groups (case and control).

There are several types of case–control study:

- source-based studies, looking for elevated levels of contaminants in specimens affected by a known source of pollution;
- health-based studies, looking for elevated levels of contaminants in specimens from people affected by a certain type of disease to identify biomarkers of effects; and
- dose-effects studies, where the relationship between internal dose and observed health effects is examined.

In comparison with cross-sectional and longitudinal studies, only tens to hundreds of samples can be gathered in case-control studies. Case-control studies are often used to identify factors that may contribute to “some condition” by comparing subjects who have that condition with subjects who do not.

Sources

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Case–control study (II)

Pros

- Efficient in time and cost (at least compared with prospective cohort studies)
- Provides the opportunity to investigate a wide range of possible risk factors
- Is particularly suitable for investigating rare diseases or diseases with a long induction period
- Generally requires few study subjects

Cons

- May be difficult to select an appropriate control group (selection bias)
- Difficult to obtain accurate unbiased measures of past exposures (information bias)
- Temporal sequence between exposure and disease may be difficult to establish (reverse causality)
- Not suitable for investigating rare exposures (unless the exposure is responsible for a large proportion of cases)
- Not possible to obtain estimates of disease incidence among those exposed and those unexposed to a putative risk factor (unless the study is population based)

10

Sources

Case–control studies. In: Principles and methods. Lyon: International Agency for Research on Cancer; 1999:Ch09 (https://publications.iarc.fr/Non-Series-Publications/Other-Non-Series-Publications/Cancer-Epidemiology-Principles-And-Methods-1999, accessed in 15 May 2023).

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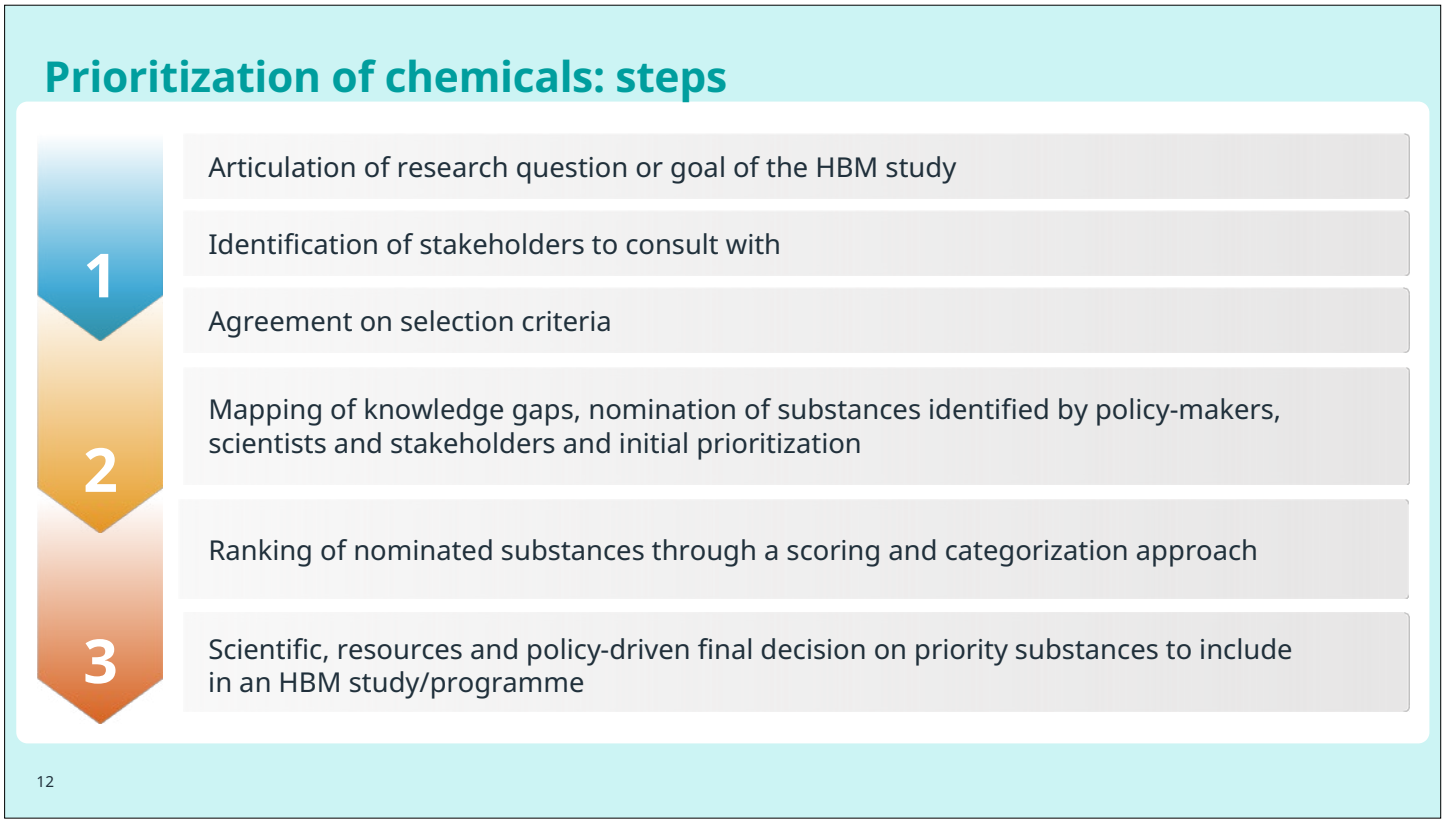
Prioritization of chemicals



HBM requires considerable coordination efforts, harmonized and comparable methods and financial investment. Therefore, the selection of substances for inclusion in HBM surveys needs to be well thought through in advance. It is analytical process that includes several steps, starting from formulation of the study objectives, followed by identification of stakeholders, selection of prioritization criteria and ranking chemicals of particular interest.

Notes: HBM: human biomonitoring.

Sources

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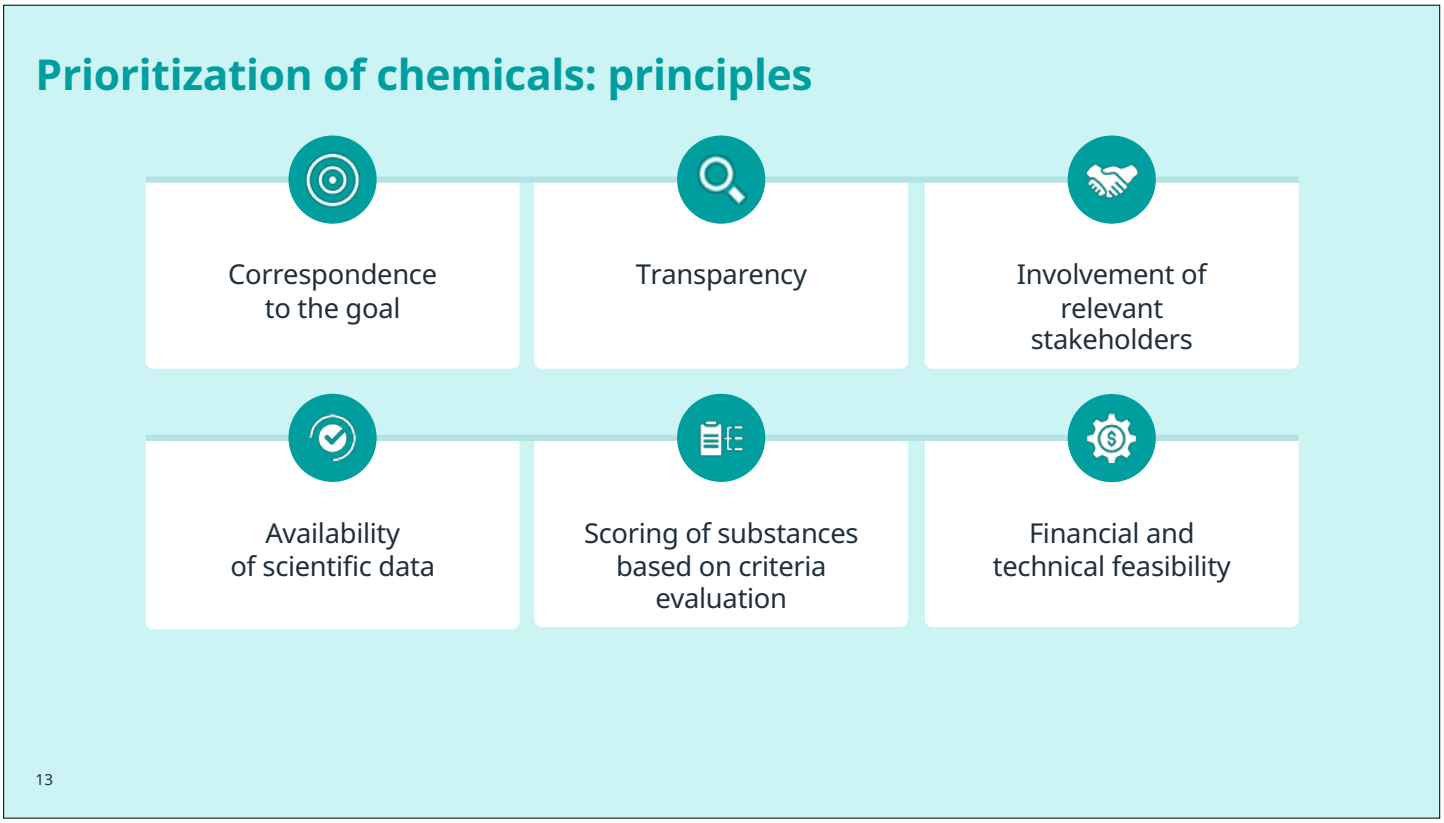

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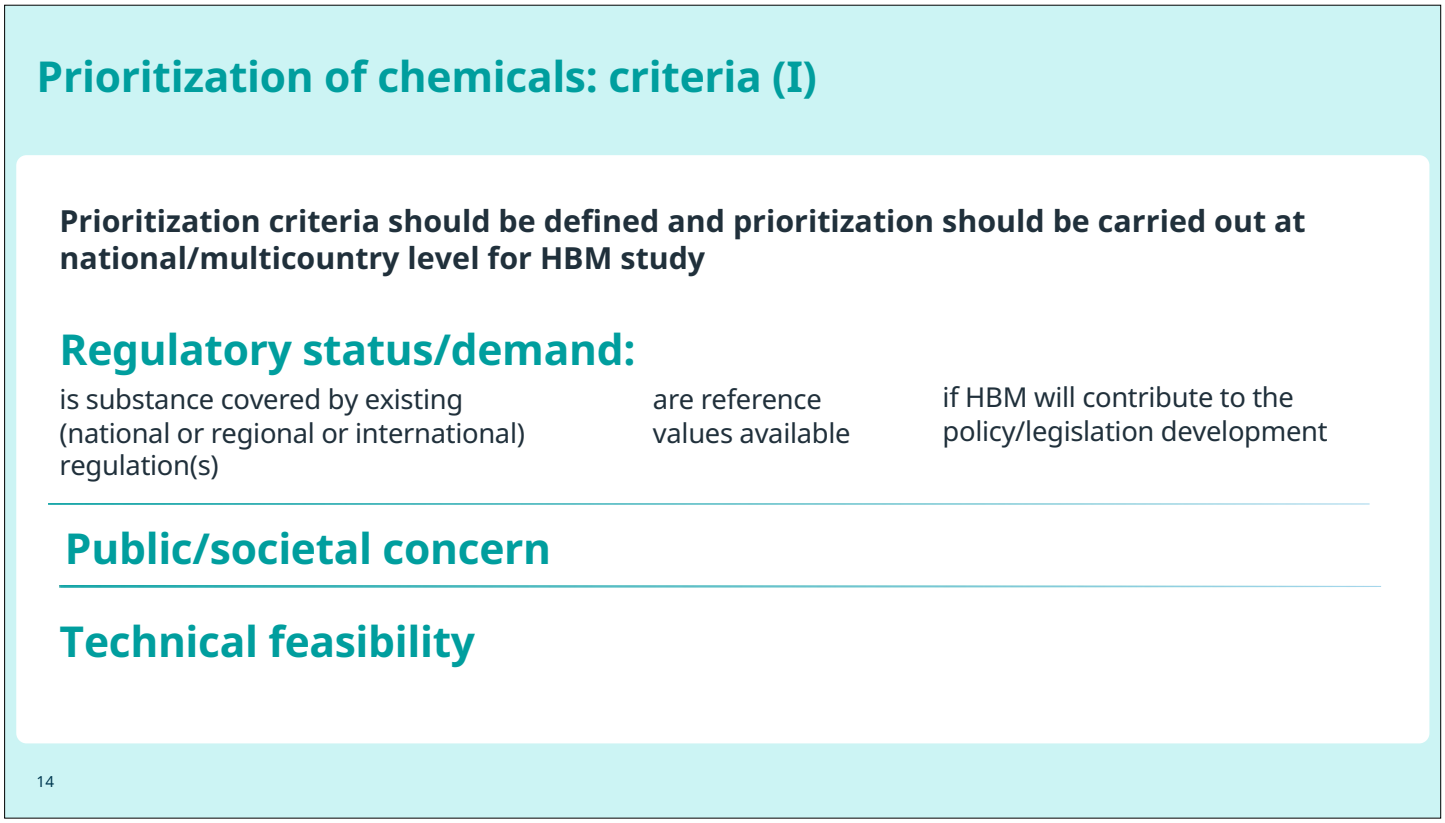

The identification of policy-relevant chemicals to be included in an HBM initiative is important. Technical feasibility and public concern are other important criteria.

Notes: HBM: human biomonitoring.

Sources

European Human Biomonitoring Initiative [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5b738ede7&appId=PPGMS, accessed 15 May 2023).

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Prioritization of chemicals: criteria (II)

Hazard properties:

(according to GHS, persistent and bioaccumulation potential)

Exposure characteristics

including results of previous HBM or other environmental studies, if any:

- media (multiple, water, food, soil, consumer products)
- human exposure (dermal, inhalation, ingestion, transplacental, combined)
- exposure sources
- prevalence of population exposure (widespread or certain subpopulations or hot spots)
- potentially exposed and vulnerable groups

15

Additional prioritization criteria are:

- frequency of detection;
- potential for exposure to a considerable extent of the general population; and
- seriousness of suspected effects at prevailing exposure levels.

Selection of chemicals to be included in an HBM survey influences the selection of biomarkers and the target population.

Notes: GHS: Globally Harmonized System of Classification and Labelling of Chemicals; HBM: human biomonitoring.

Sources

European Human Biomonitoring Initiative [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5b738ede7&appId=PPGMS, accessed 15 May 2023).

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Ougier E, Ganzleben C, Lecoq P, Bessems J, David M, Schoeters G et al. Chemical prioritisation strategy in the European Human Biomonitoring Initiative (HBM4EU): development and results. Int J Hyg Environ Health. 2021;236:113778. doi: 10.1016/j.ijheh.2021.113778.

Evaluation of availability of data needed for prioritization

Exposure	Toxicology/ toxicokinetic	Epidemiology	Analytical methodology/ biomarker of exposure	RA /risk management
Are source(s) identified?	Are there sufficient data including longer duration studies?	Are reasonable cause–effect inferences supported?[a]	Were standard reference materials used in the biological matrix of interest?	Are there toxicology data sufficient and relevant?
Is/are pathway(s)/route(s) understood?	Do routes used in toxicology studies compare with anticipated human exposure?	Has an adverse health effect been observed in humans?	Have specificity and sensitivity of methods been described?	Is the relationship between biomarker of exposure and human health effect known?
Is human exposure relationship to existing toxicology data identified?	Are toxicokinetic data in animals available?	Has the pathogenesis of the health effect been described?	Is biomarker of exposure valid for intended use (i.e. exposure accurately reflects the intended uses)?	Are toxicokinetic data applicable?
Is exposure–dose relationship understood?	Is/are the critical effect(s) known?	Is there a health effect in the exposed population?	Does sampling strategy consider potential sources of error?	If applicable, is there evidence that remediation efforts are working?
Is temporality/duration understood[b]	Is the mode/mechanism of action understood?	Have toxicokinetic and/or toxicodynamic genetic polymorphisms been described (that may impact risk)?	Does sampling strategy consider stability of biomarker and incorporate toxicokinetics of exposure?	

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[a]Based on fulfilling the Bradford–Hill criteria (nine principles used in establishing epidemiological evidence of a causal relationship between a presumed cause and an observed effect; widely used in public health research)

[b]Temporality refers to the relationship between when the exposure occurred and when the sample was collected; duration refers to how long the exposure occurred relative to when the sample was collected

Data availability is the key to enable prioritization of chemicals.

To evaluate data availability, a series of key questions should be asked to inform the use and evaluation of biomonitoring data in exposure and human health RA. The criteria can be outlined for the following categories: exposure, toxicology/toxicokinetics, epidemiology, analytical methods/biomarkers of exposure and RA/risk management. To use data for health RA of chemical substances, it is essential to assess the quality, reliability and suitability of the data obtained both in animal experiments and epidemiological studies.

Notes: RA: risk assessment.

Sources

Arnold SM, Angerer J, Boogaard PJ, Hughes MF, O'Lone RB, Robison SH et al. The use of biomonitoring data in exposure and human health risk assessment: benzene case study. Critical reviews in toxicology. 2013;43(2):119-53. doi: 10.3109/10408444.2012.756455.

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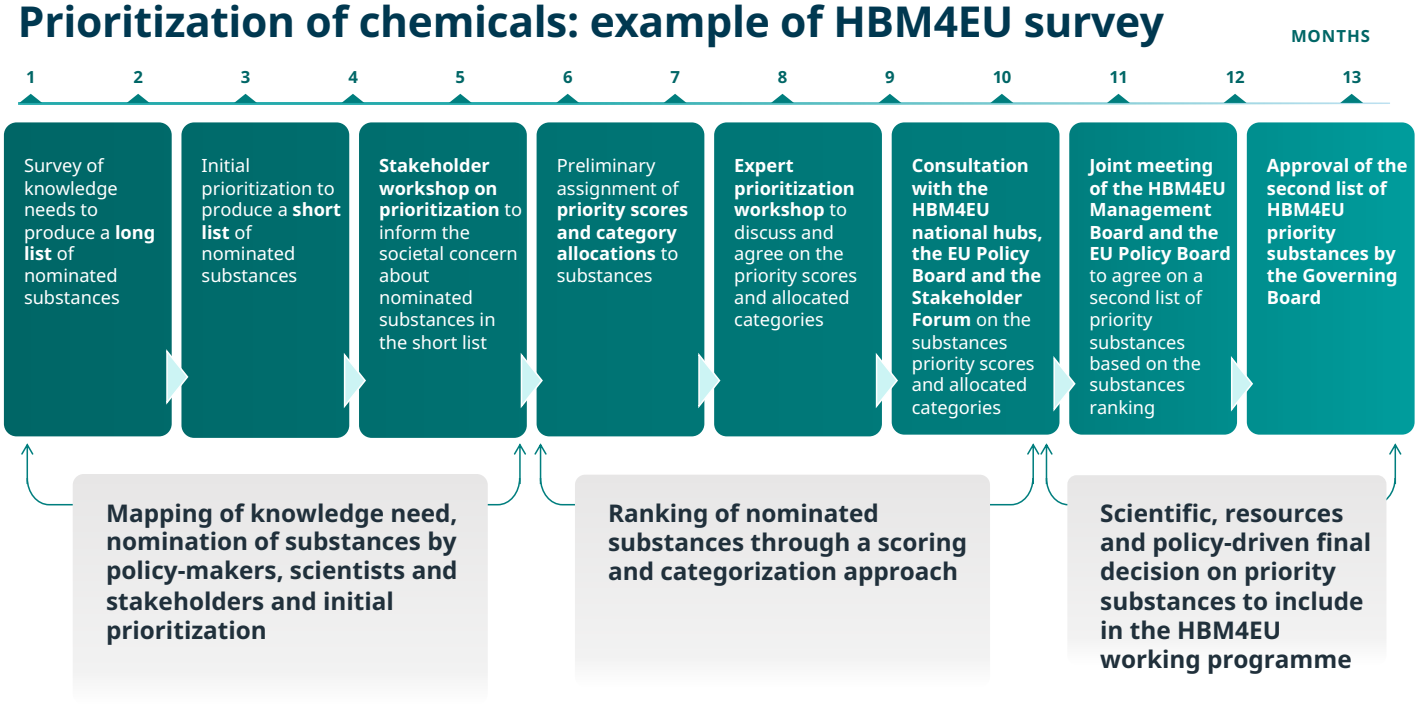
Prioritization of chemicals: example of HBM4EU survey



17 *Source*: adapted from Ougier et al., 2021. Reproduced with permission from Elsevier.

An example of chemical prioritization for HBM is taken from the HBM4EU. The first step decided on the chemicals for prioritizing by discussion with relevant ministries and agencies at EU and national levels, as well as members of the Stakeholder Forum. Each entity could nominate up to five substances (or groups of substances) of concern for policy-makers by completing the full online survey for each nominated substance/substance groups. These nominations were collated into a preliminary list of 48 substances/substance groups, which was subsequently shortened to a list of 23 after considering the total number of nominations received for each substance/substance group and the nature of the nominating entities.

For the second step, a panel of 11 experts in epidemiology, toxicology, exposure sciences and occupational and environmental health scored each of the substances/substance groups using prioritization criteria. Scoring was a three-step process: (1) setting a consensus weighting value to be applied to each prioritization criterion; (2) scoring the substances against each chosen prioritization criterion; and (3) calculating the substance's overall score. In addition, substances were categorized according to the level of current knowledge about their hazards, extent of human exposure (through the availability of HBM data), regulatory status and availability of analytical methods for biomarker measurement. A final priority list of nine substances/substance groups were defined for research activities and surveys within the framework of the HBM4EU project.

Notes: EU: European Union; HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative.

Sources

Ougier E, Ganzleben C, Lecoq P, Bessems J, David M, Schoeters G et al. Chemical prioritisation strategy in the European Human Biomonitoring Initiative (HBM4EU): development and results. Int J Hyg Environ Health. 2021;236:113778. doi: 10.1016/j.ijheh.2021.113778.

Prioritization of chemicals: example of national approaches

Chemicals included in the National Exposure Reports and updates are selected applying the following:

- scientific data that suggest exposure in the United States population
- the seriousness of health effects known or thought to result from some levels of exposure
- the need to assess the effectiveness of public health actions to reduce exposure to a chemical
- the availability of an analytical method that is accurate, precise, sensitive, specific, rapid
- the availability of adequate blood or urine samples (from the NHANES survey)
- the analytical costs

Chemicals measured in each cycle of the CHMS selected based on one or more of the following considerations:

- known or suspected health effects
- level of public concern
- evidence of exposure in the Canadian population
- new or existing requirements for public health action
- the ability to detect and measure the chemical or its breakdown metabolites in humans
- similarity to chemicals monitored in other national and international programmes to allow for meaningful comparisons
- the analytical costs

18

Notes: CHMS: Canadian Health Measures Survey; NHANES: National Health and Nutrition Examination Survey.

Sources

National report on human exposure to environmental chemicals. Atlanta (GA): US Centers for Disease Control and Prevention; 2022 (https://www.cdc.gov/exposurereport/index.html, accessed 10 November 2022).

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Selection of target population and biomarkers

Selection of target population

The aim is the selection of representative group of the population of interest

A target population is a certain group of the population with similar characteristics and identified as the intended audience for research

The target population is the subset of people for whom the programme is designed, who are actively recruited and retained, and for whom the programme investigators will be accountable for achieving outcomes

The target population defines those units for which the findings of the research are meant to generalize

The study population or target population should be a representative group of individuals and it should be feasible to recruit them (eligible or ineligible for the survey). The group should also be as homogeneous as possible (similar characteristics) and geographical and temporal characteristics of the target population should be delineated.

To conduct an appropriate study, an investigator must consider some fundamental questions in the early design stages.

What population (or subpopulation) is the target of the study?

How many people (study subjects) from this population can be included in the study?

How should we identify the study subjects (individuals) to be included in the study?

Should we aim to identify a “representative” sample? If so, how do we select this?

Sources

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Choi J, Mørck TA, Joas A, Knudsen LE. Major national human biomonitoring programs in chemical exposure assessment. Environ Sci. 2015;3:782–802. doi: 10.3934/environsci.2015.3.782.

Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).

Criteria for selection of target population

Objectives:

- pollutants
- expected outcomes
- policy questions
- other

Define

the target population considering various factors:

- geographical area
- age groups (children, adolescents, adults, newborns, etc.)
- sex
- habitation
- risk-exposure group
- socioeconomic status

Design

can be a representative sample of a general or specific population (e.g. vulnerable groups)

- of a specific region or
- of an entire country

21

Sample size. The feasible sample size of the population (the number of study participants) should be considered and will depend on the hypotheses to be tested. If specific subpopulations are of interests for the programme, the calculations of the power of the study to detect differences within specified subpopulations should be included for proper numbers of participants to be enrolled.

Geographical area. The area should be delineated at national level in terms of type of area (e.g. rural, semi-rural or urban) at national level. It should also be delineated across regions, for example, northern, western, eastern and southern Europe or according to WHO regions for global surveys.

Population group. The intended population group to cover in the survey has to be set at the survey planning stage: permanent residents, citizens, population of hotspots, pupil/students and so on. Ethical principle of research and specific requirements of target groups (such as children or pregnant women) must be considered when selecting target populations.

Sources

Committee on Human Biomonitoring for Environmental Toxicants, National Research Council. Human biomonitoring for environmental chemicals. Washington (DC): National Academies Press; 2006 (https://www.nationalacademies.org/our-work/human-biomonitoring-for-environmental-toxicants, accessed 15 May 2023).

Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).

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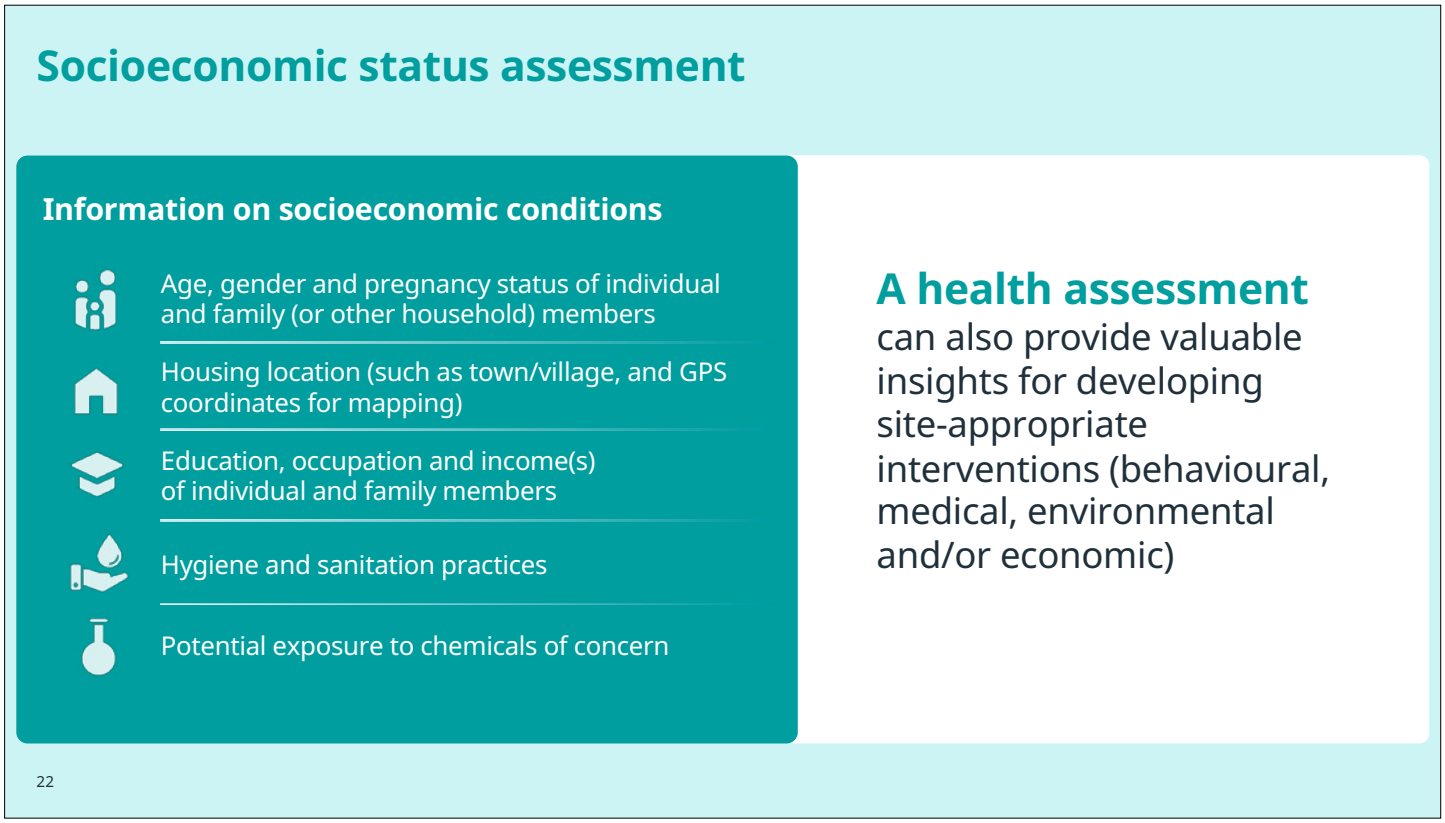
Description of national programmes. In: European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5babccc1c&appId=PPGMS, accessed 15 May 2023).



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Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).

Target population for cross-sectional studies: examples

Country, region	Study	Objective	Study population	Number
United States	NHANES	To assess the health and nutritional status of adults and children	American population of all ages	4000
Germany	GerES (2014–2017)	To assess exposure and recommend risk reduction measures	Children 3–17 years	2294
EU	HBM4EU	To assess actual exposure in EU and to define geographical difference	6–11 years 12–19 years 20–39 years	3431 2950 3716
Canada	CHMS	To provide human biomonitoring data to scientists and health and environment officials to help them to assess Canadians' exposure to environmental chemicals and develop policies to reduce exposure to toxic chemicals for the protection of population health	3–79 years old living in one of the 10 provinces; targets 96–97% of the general population	5700

23

Notes: CHMS: Canadian Health Measures Survey; EU: European Union; GerES: German Environmental Survey; HBM4EU: European Human Biomonitoring Initiative; NHANES: National Health and Nutrition Examination Survey.

Sources

Description of national programmes. In: European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5babccc1c&appId=PPGMSm accessed 15 May 2023).

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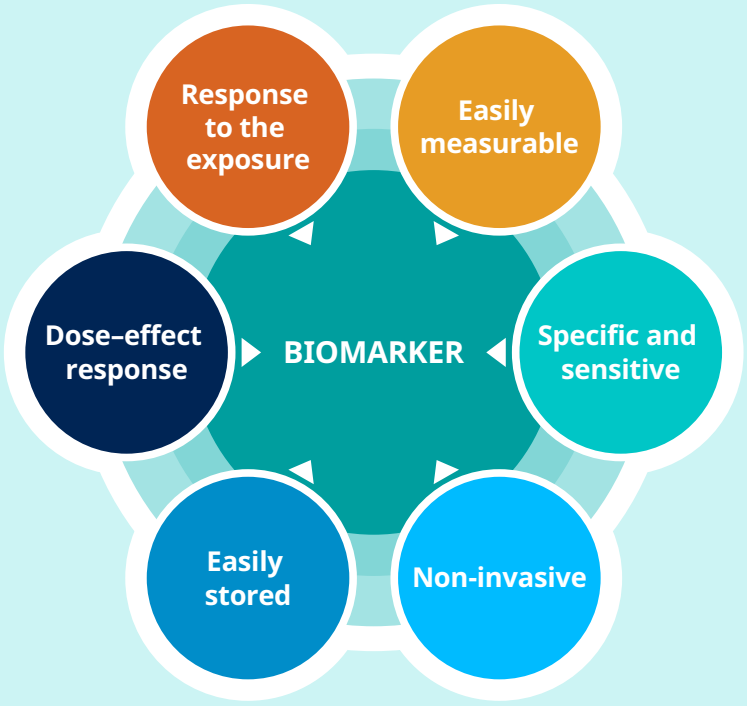
Criteria for selection of exposure biomarkers



24 *Source*: adapted from Poblete-Naredo and Albores, 2016. Reproduced with permission from Instituto Nacional de Salud.

Biomarkers of exposure should have certain characteristics to be considered good and reliable; they should:

- respond to a biologically active chemical;
- have a dose-effect response, correlated with the levels of the target chemical;
- preferably be non-invasive; this also can increase responsiveness of the study participants and compliance rates;
- be measurable with the available analytical techniques and the analytical methods used have to achieve limits of quantification that are low enough to quantify the biomarker in the range of concentrations present in the study population; and
- be specific so that the exposure can be associated to the given chemical.

Sources

Poblete-Naredo I, Albores A. Molecular biomarkers to assess health risks due to environmental contaminants exposure. Biomedica. 2016;36:309-35. doi: 10.7705/biomedica.v36i3.2998.

Lionetto MG, Caricato R, Giordano E. Pollution biomarkers in environmental and human biomonitoring. Open Biomark J. 2019;9:1-9. doi: 10.2174/1875318301909010001.

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Selection of exposure biomarkers

Selection of biomarker

Specific compound or their metabolites

Analytical methods
Certified reference material

Biological matrix

- Blood
- Urine
- Hair
- Cord blood
- Saliva
- Breast milk
- Nails
- Meconium
- Other tissues or fluids

Kinetics of chemicals

Exposure period Recent Chronic

Correction of results

Creatinine or specific gravity in urine

Lipids in serum

Example: variation of lead half-life:

- in blood: about 1 month
- in soft tissue: about 1 year
- in bones: 20 years

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For exposure biomarkers, the selection of the appropriate biological matrix requires knowledge of toxicokinetics of the chemical of interest. The levels of the biomarker in different matrices will provide different information about the exposure (e.g. recent or chronic exposure). Information on persistence in the body (either the parent compound or its metabolites) determines a time-variable concentration profile that is associated with temporal patterns of exposure and elimination kinetics. As a general rule, biomarkers of exposure to compounds that remain stable in the human body (e.g. persistent organic pollutants, metals) are measurements of the original compound concentrations in biomatrix. For chemicals that are metabolized rapidly (e.g. organophosphate pesticides and phthalates), a metabolite of the original compound, or more than one, is often used as a biomarker of exposure; these metabolites are generally measured in urine.

Although potentially there are a high number of matrices that can be used, blood and urine are the most common ones, followed by hair and breastmilk.

Sources

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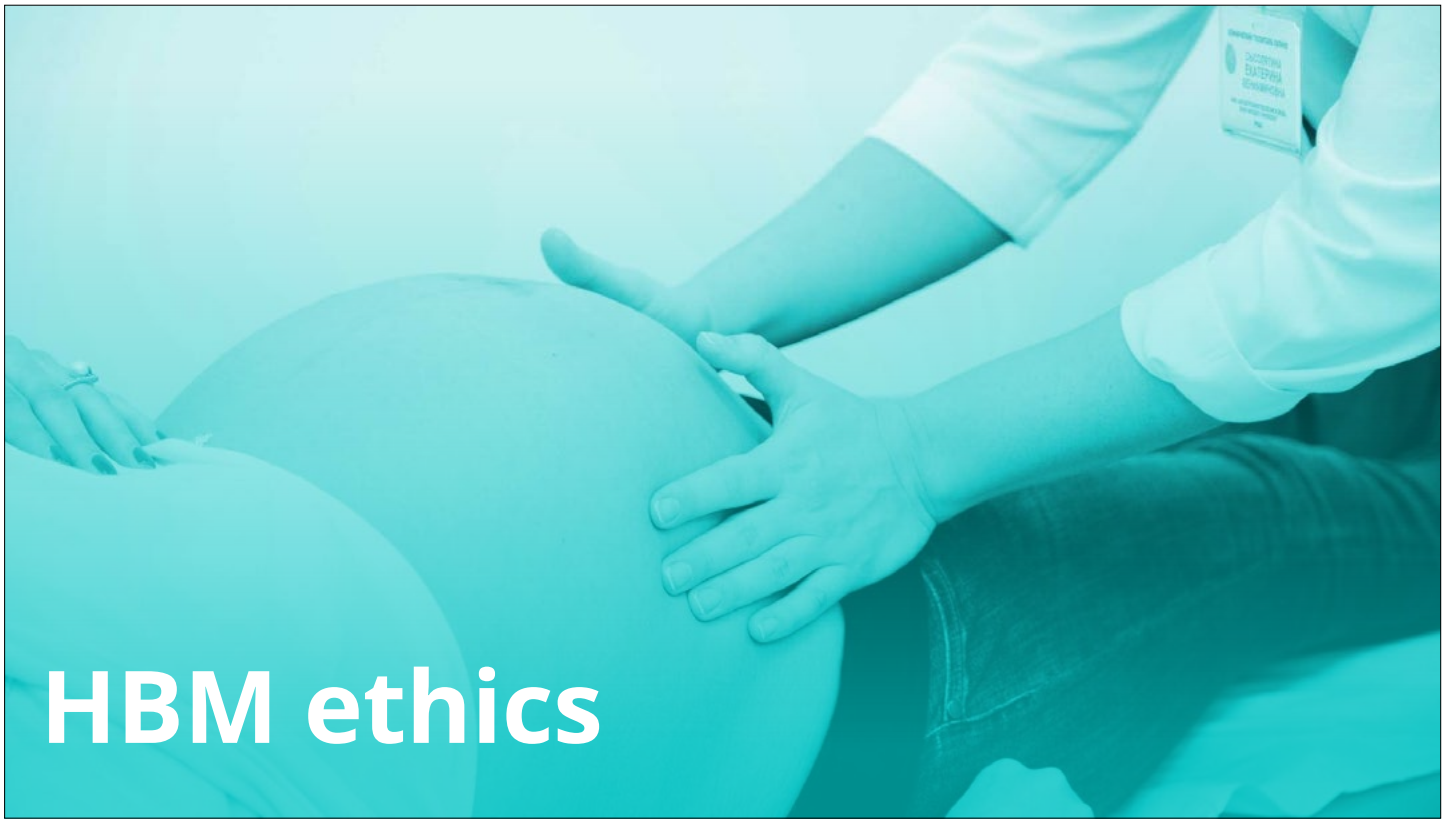

Notes: HBM: human biomonitoring.

Research ethics

basic principles

(I)

Equity: public health ethics is centrally concerned with the idea of equity

- research conducted in low-resource settings
- equitable distribution of benefits, burden and risk of research

Justice: refers to the ethical obligation to treat each person in accordance with what is morally right and proper

Good governance: although good governance is not an ethical principle but rather a political aspiration, it is subject to a number of ethical considerations

Governance mechanisms:
these must be accountable and open to public scrutiny to ensure at the ethical challenges posed by public health actions are addressed systematically and fairly

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All research with humans must be carried out in ways that show respect and concern for the rights and welfare of individual participants and the communities in which research is carried out, ensuring that risks are minimized and are reasonable in light of the importance of the research. Research must also be sensitive to issues of justice and fairness: people in low-resource settings receiving equitable benefit from their participation in health-related research and a fair distribution of the benefits and burdens of research. The main criteria to invite groups, communities and individuals in research must be scientific reasons and not compromised social or economic position or their ease of manipulation.

Inclusion and exclusion criteria should not be based upon potentially discriminatory criteria, such as race, ethnicity, economic status, age or sex, unless there is a sound ethical or scientific reason to do so.

In the ethics of research involving human subjects the principle refers primarily to distributive justice, which requires the equitable distribution of both the burdens and the benefits of participation in research. Differences in distribution of burdens and benefits are justifiable

- only if they are based on morally relevant distinctions between people; and
- special provision must be made for the protection of the rights and welfare of vulnerable people.

Sources

International ethical guidelines for epidemiological studies. Geneva: Council for International Organizations of Medical Sciences; 2009 (https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf, accessed 10 November 2022).

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Research ethics

basic principles

(II)

Respect for human rights and for each individual involved

Respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination; and

Protection of people with impaired or diminished autonomy, which requires that those who are dependent or vulnerable be afforded security against harm or abuse

28

Sources

International ethical guidelines for health-related research involving humans. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

International ethical guidelines for epidemiological studies. Geneva: Council for International Organizations of Medical Sciences; 2009 (https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf, accessed 10 November 2022).

Human biomonitoring in artisanal and small-scale gold mining: ethical and scientific principles. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/339848, accessed 10 November 2022).

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Research ethics

basic principles

(III)

- **Caring** for participants' health needs
- **Community engagement** for participants' health needs
- **Reimbursement and compensation** for participants (according to national regulations)
- **Treatment and compensation** for research-related harm (according to national regulations)
- **Specific requirements** for involving vulnerable people, children, adolescents and pregnant and breastfeeding women
- **Confidentiality**
- **Exclusion/declaring** conflict of interest
- **Contribution effectively** to national or local capacity

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When participants' health needs during and after research cannot be met by the local health infrastructure or the participant's pre-existing health insurance, the researcher and sponsor must make prior arrangements for adequate care for participants with local health authorities, members of the communities from which people are drawn or nongovernmental organizations such as health advocacy groups. Research participants should be reasonably reimbursed for costs directly incurred during the research (travel, compensations). It should be noted that national regulations influence ethics arrangements. For example, reimbursement and compensation for research participants and treatment and compensation for research-related harm are not regulated legally in some countries.

An important aspect of storing human biological material is confidentiality guarantee to the donor. The information resulting from analysis of the material could, if disclosed to third parties, cause harm, stigma or distress. Those responsible for research must arrange to protect the confidentiality of such information by, for example, providing only anonymized or coded data to researchers and limiting access of the material of third parties.

Sources

Human biomonitoring in artisanal and small-scale gold mining: ethical and scientific principles. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/339848, accessed 10 November 2022).

International ethical guidelines for health-related research involving humans. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

Legal and ethics policy documents. In: European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5bdd50874&appId=PPGMS, accessed 15 May 2023).

Specific ethical considerations: involvement of pregnant women and children

A parent or a legally authorized representative of the child or adolescent has given permission

The agreement (assent) of the child or adolescent has been obtained in keeping with the child's or adolescent's capacity, after having been provided with adequate information about the research tailored to the child's or adolescent's level of maturity

Person informing the child or young person about participation must be able to communicate information according to the age and maturity of the potential participant

Older children should be included in the information process

If a participant aged 15—17 years wishes, they must receive written information about the study

Pregnant women should be involved only when research with non-pregnant individuals is impossible; justification of their involvement is needed

30

When vulnerable individuals and groups are considered for recruitment in research, researchers and research ethics committees must ensure that specific protections are in place to safeguard the rights and welfare of these individuals and groups.

When the social value of the research for pregnant or breastfeeding women, their fetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-breastfeeding women, a research ethics committee may permit a minor increase above minimal risk. Short-term and long-term follow-up of the fetus and the child may be required in research involving pregnant and breastfeeding women, depending upon the study intervention and its potential risks.

Children are clearly unable to consent for research themselves. Parents or other legal guardians decide for them. Consent from the parents should not imply that an intervention can be made against the will of the child.

Sources

International ethical guidelines for health-related research involving humans. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

Knudsen LE, Tolonen H, Scheepers PTJ, Loots I, Vorkamp K, Hajeb P et al. Implementation and coordination of an ethics framework in HBM4EU – Experiences and reflections. Int J Hyg Environ Health. 2023;248:114098. doi: 10.1016/j.ijheh.2022.114098.

Mapping key ethics points in HBM study

Study design	Study planning and conducting	Analysis, assessment, interpretation	Communication
Scientific and social value	Specific requirements of vulnerable groups	Confidentiality and data-sharing requirements	Communication of results
Research ethics basic principles	Informed consent	Withdrawal conditions	Providing advice
Submitting to research ethics committee	Community involvement	Biobanking (extended informed consent)	Treatment (if needed)
Confidentiality	Compensation and treatment in case of harm (according to national regulations)		Risk reduction measures

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Ethics is an integral part of research from the very beginning to the very end of all HBM studies.

Notes: HBM: human biomonitoring.

Sources

International ethical guidelines for health-related research involving humans. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

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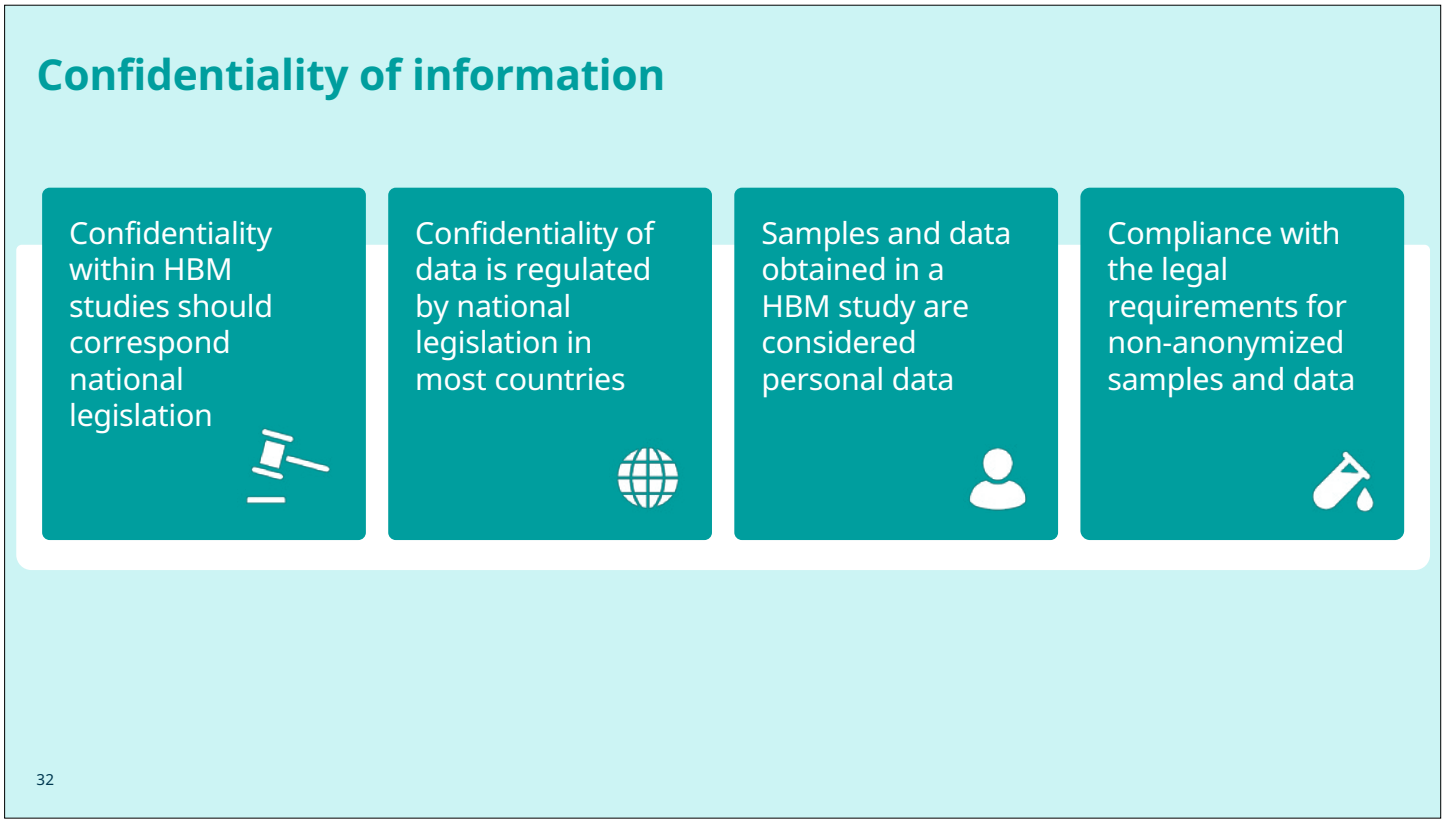


Personal and health information of study participants has to be managed in compliance with the ethical principles and relevant national regulations.

For example, in the EU the GDPR regulates the processing of personal data — any information relating to an identified or identifiable natural person ("data subject") — whereas the Data Protection Directive imposes the practice of informed consent, including the right to know one's own results, and requires notification of the national data protection authority.

There are certain categories of data in terms of confidentiality:

- non-anonymized data refers to pseudonymized data, which are single measurement data for which indirect re-identification of data subjects is possible;
- anonymized data are measurement data for which re-identification of data subjects is completely impossible; de-identification is not possible by combining variables or by matching with any other data; and
- aggregated data merge information of multiple patients or survey participants and the collected information cannot be retraced to the individual data.

Notes: EU: European Union; GDPR: General Data Protection Regulation; HBM: human biomonitoring.

Sources

General data protection regulation (EU) 2016/679. Brussels: European Commission; 2016 (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016R0679, accessed 15 May 2023).

Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data. Brussels: European Commission; 2003 (https://eur-lex.europa.eu/eli/dir/1995/46/oj, accessed 10 November 2022).

International ethical guidelines for health-related research involving humans, fourth edition. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

Legal and ethics policy documents. In: European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5bdd50874&appId=PPGMS, accessed 15 May 2023).

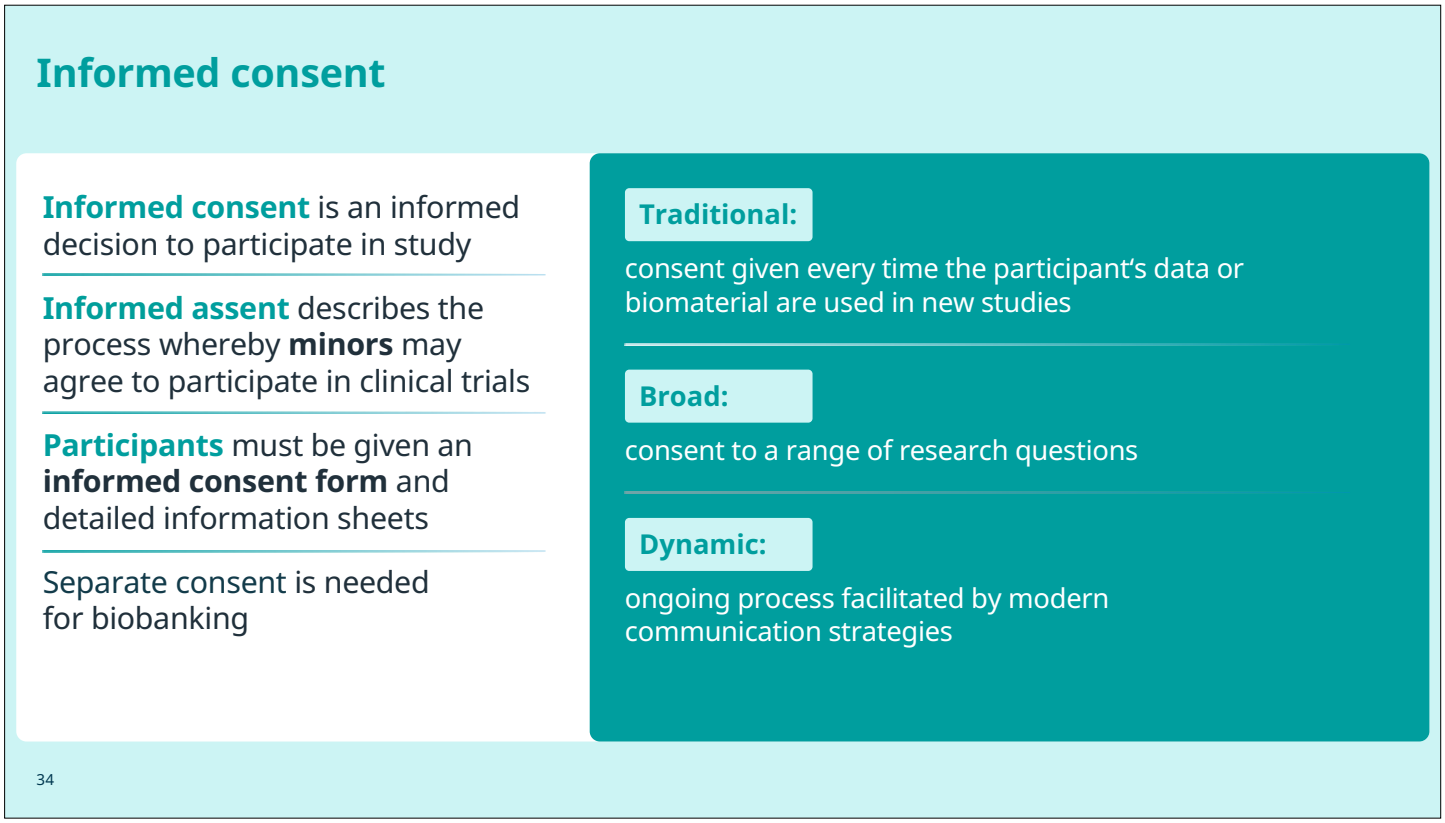
The submission for ethical approval to the relevant (national/local/etc) ethics committee should correspond to national regulation(s) even if international (e.g. WHO) committee approval has been obtained. The investigator is responsible for ensuring that the materials submitted to an ethical review committee include a declaration of any potential conflicts of interest affecting the study.

Sources

Human biomonitoring in artisanal and small-scale gold mining: ethical and scientific principles. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/339848, accessed 10 November 2022).

International ethical guidelines for health-related research involving humans, fourth edition. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

Standards and operational guidance for ethics review of health-related research with human participants. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/handle/10665/44783, accessed 10 November 2022).



Informed consent is an informed decision to participate in research taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.

Sources

Knudsen LE, Tolonen H, Scheepers PTJ, Loots I, Vorkamp K, Hajeb P et al. Implementation and coordination of an ethics framework in HBM4EU – Experiences and reflections. Int J Hyg Environ Health. 2023;248:114098. doi: 10.1016/j.ijheh.2022.114098.

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 ((https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May).

International ethical guidelines for health-related research involving humans, fourth edition. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

International ethical guidelines for epidemiological studies. Geneva: Council for International Organizations of Medical Sciences; 2009 (https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf, accessed 10 November 2022).

Consent form content

- Nature and aims of the study
- Background information on the topic (in plain language)
- Description of what participation means in practice (when, where, who, what)
- Possible risks, inconveniences or discomforts that could be expected to result from participation
- Potential benefits for participants (if relevant, as there might not be any direct benefits)
- Cost (for participants)
- Contact details of the institution coordinating the study
- Information about what will happen to the result
- Explanation that participation is always voluntary and that participants can withdraw at any time
- Explanation about how privacy and confidentiality of information/data will be maintained over the time
- Description of biological material storage in a biobank (if applicable) and possible uses of biological material in the future
- Timeline of the study and when the communication of results can be anticipated

35

Participants must be given an informed consent form and detailed information sheets written in a language and in terms that are fully understandable.

A withdrawal form should be prepared to give to any survey subject who decides to withdraw from the survey. Survey participants may withdraw at any time; they will be asked to confirm their withdrawal with a signature.

Sources

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 ((https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May).

Investigator duties

- To guarantee an optimal protection of the rights and dignity of every study participant
- To ensure that a study adheres to the legal and ethical framework
- To obtain approval from an independent ethics research committee
- To refrain from unjustified deception, undue influence, or intimidation
- To seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of participation and has had sufficient opportunity to consider whether to participate
- When individual consent is required, obtain from each prospective subject a signed form
- To renew the informed consent of each subject if there are significant changes in the conditions
- The principal investigator has a non-delegable duty to ensure that all personnel working on the study comply with research ethics requirements
- Sponsors have a duty to ensure that these obligations are fulfilled

36

Sources

International ethical guidelines for health-related research involving humans, fourth edition. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

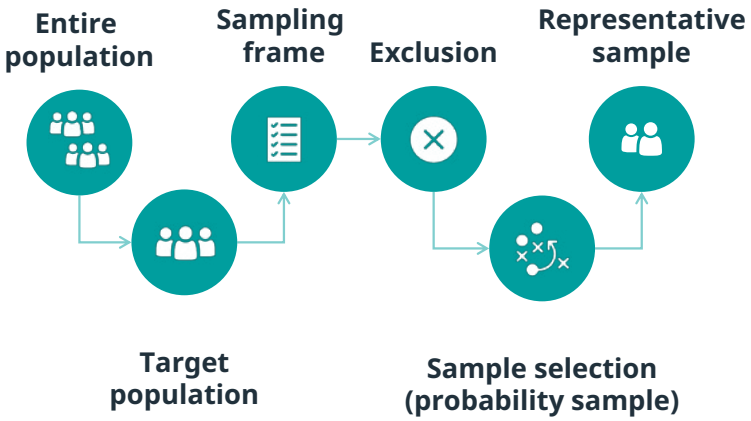
International ethical guidelines for epidemiological studies. Geneva: Council for International Organizations of Medical Sciences; 2009 (https://cioms.ch/wp-content/uploads/2017/01/International_Ethical_Guidelines_LR.pdf, accessed 10 November 2022).

Sampling size

Choosing a representative sampling size

The expected response/participation rate is used to adjust the number of people invited to achieve the sample size

For example, for an expected response rate of 60%, 360 people need to be invited to get the needed sample of 216 people



38

Sources

Description of national programmes. In: European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5babccc1c&appId=PPGMS, accessed 15 May 2023).

Estimation of sampling size: approach example

Sample should be representative!

Size varies depending on statistical power, cost, staff, study facilities, selected approach

Calculating sampling size:

$$N = \frac{Z^2 \times p \times (1 - p)}{e^2}$$

Where

Z is the *Z* score representing the desired level of confidence/probability of error
p is the estimated prevalence of outcome of interest in the population
e is the margin of error/precision of the estimate

Desired confidence level	Z-score
80%	1.28
85%	1.44
90%	1.65
95%	1.96
99%	2.58

Example:
estimated prevalence (*p*) = 10%
precision of the estimate (*e*) = 4%
95% confidence level (*Z*) = 1.96

$1.96^2 \times 0.1 \times (1-0.1)/0.04^2 = 216$

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The sample size chosen is likely to be based on various factors, including, among others, costs, statistical power, staff and study facilities. But it should be representative for a population or population group. The sampling process can be random or judgemental. Randomization is a more expensive and time-consuming process but provides a broader picture of exposures among the population. A judgemental approach is applied if only the individuals at higher risk of being exposed to certain chemical are selected for study.

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

Vogel N, Conrad A, Apel P, Rucic E, Kolossa-Gehring M. Human biomonitoring reference values: differences and similarities between approaches for identifying unusually high exposure of pollutants in humans. Int J Hyg Environ Health. 2019;222(1):30-33. doi: 10.1016/j.ijheh.2018.08.002.

Estimation of sampling size: HBM4EU approach

$$n = Deff \times \frac{2f(\alpha,P)\sigma^2}{(\mu_1 - \mu_2)^2}$$

Where

n — the number per group

$f(\alpha,P)$ 7.9 for α = 0.05 and a power of 80% (β = 0.20)

σ — standard deviation

$\mu_1 - \mu_2$ — difference to be detected

$Deff$ — captures the effect of not using a simple random sampling

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In the HBM4EU programme, when calculating sampling numbers for the different domains, representative sampling takes into account feasibility and practical aspects but will not take into account the variability in the biomarker concentrations among individuals. When the variation is known or can be predicted, the sample size formula for comparing the means for two groups using a *t*-test for independent samples can be used to estimate the needed sample size for the comparison of pollutant concentrations in specific groups. The numbers that will ensure representativeness among areas of an HBM survey might not allow statistical significance when comparing groups.

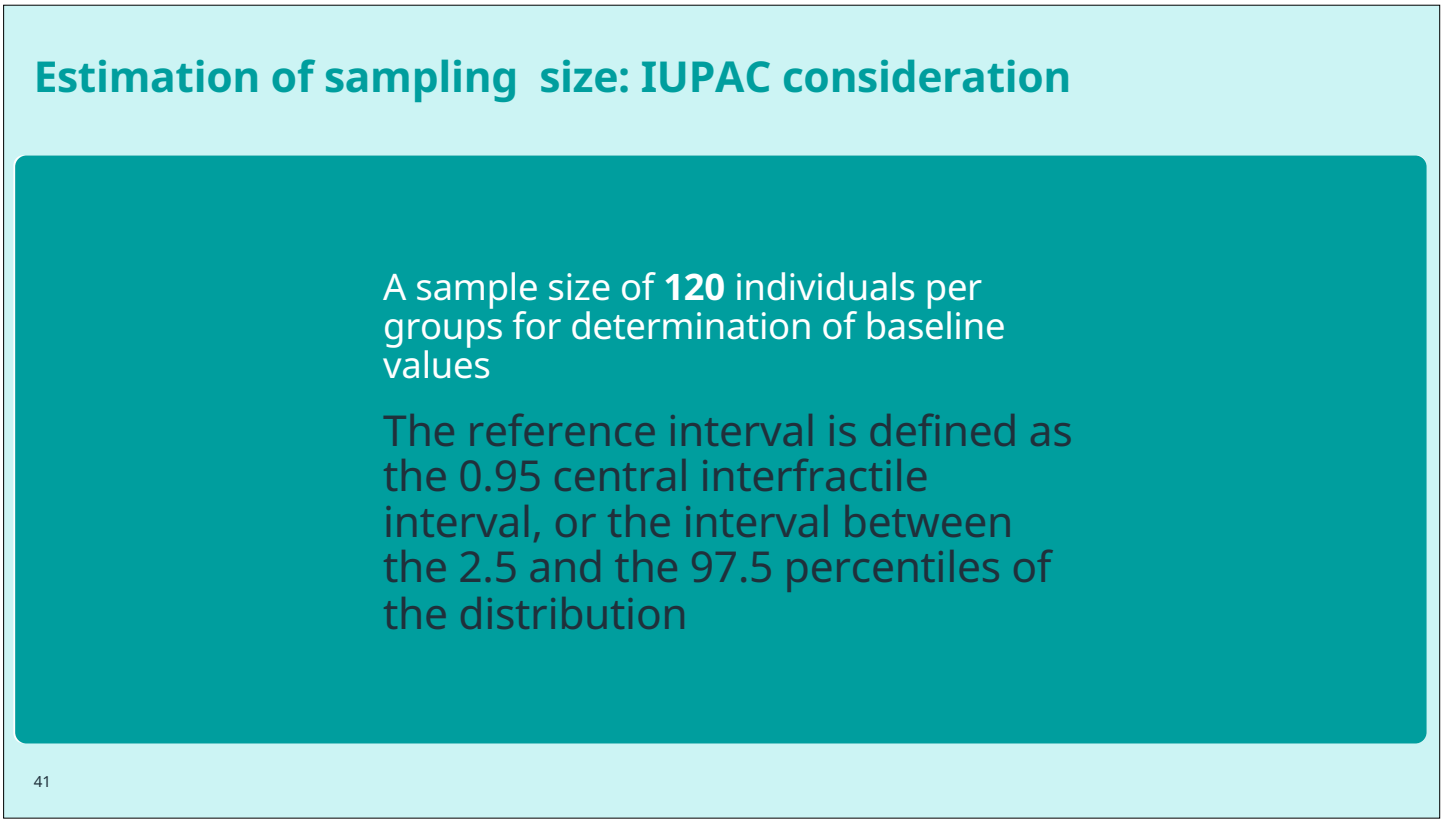
The formula given on the slide can be used to compare two groups. The formula is applied to data that have undergone ln-transformation to take into account the skewed distribution. The mean and standard deviation in the formula refers to the ln-transformed data. By working on the ln-transformed data, the analysis is equivalent to comparing the geometric means of the pollutant (i.e. the untransformed data) between two groups.

What is In-transformed data? Data transformation is a process that changes derived data into a new value via a mathematical equation so that the data appear to more closely meet the assumptions of a statistical inference procedure that is to be applied or to improve the interpretability of the data.

Notes: HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative.

Sources

Description of national programmes. In: European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5babccc1c&appId=PPGMS, accessed 15 May 2023).



A simplistic approach recommended for cross-sectional surveys is to use a minimum of 120 randomly selected individuals per population group to allow for the estimation of group-specific reference values with sufficient precision and meaningful comparison of population groups.

Notes: IUPAC: International Union of Pure and Applied Chemistry.

Sources

Poulsen OM, Holst E, Christensen JM. Calculation and application of coverage intervals for biological reference values. Pure Appl Chem. 1997;67(7):1601-11. doi: 10.1351/pac199769071601.

Becker K, UBA-Team. Study design and fieldwork: SOPs train the trainers module 1: fieldwork, Berlin, June 2011. Dessau-Roßlau: German Environment Agency; 2011 (https://www.yumpu.com/en/document/view/37871977/study-design-and-field-work-kerstin-becker, accessed 10 November 2022).

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

Vogel N, Conrad A, Apel P, Rucic E, Kolossa-Gehring M. Human biomonitoring reference values: differences and similarities between approaches for identifying unusually high exposure of pollutants in humans. Int J Hyg Environ Health. 2019;222(1):30-33. doi: 10.1016/j.ijheh.2018.08.002.

Community involvement and communication strategy

Community involvement

Proactive and sustainable engagement with communities at the earliest opportunity

A way of showing respect for them and the traditions and norms that they share

Increasing trust and confidence

Valuable for the contribution it can make to the successful conduct of research

A means of ensuring the relevance of proposed research to the affected community, as well as its acceptance by the community

Helps to ensure the ethical and social value and outcome of proposed research

Is particularly important when the research involves minorities or marginalized groups, including individuals with diseases, in order to address any potential discrimination

A means of ensuring roles and responsibilities

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Community consists not only of people living in the geographical area where research is to be carried out, but also of different sectors of society that have a stake in the proposed research (participants, including patients and consumer organizations, community leaders and representatives, relevant nongovernmental organizations and advocacy groups, regulatory authorities, government agencies and community advisory boards), as well as subpopulations from which research participants will be recruited.

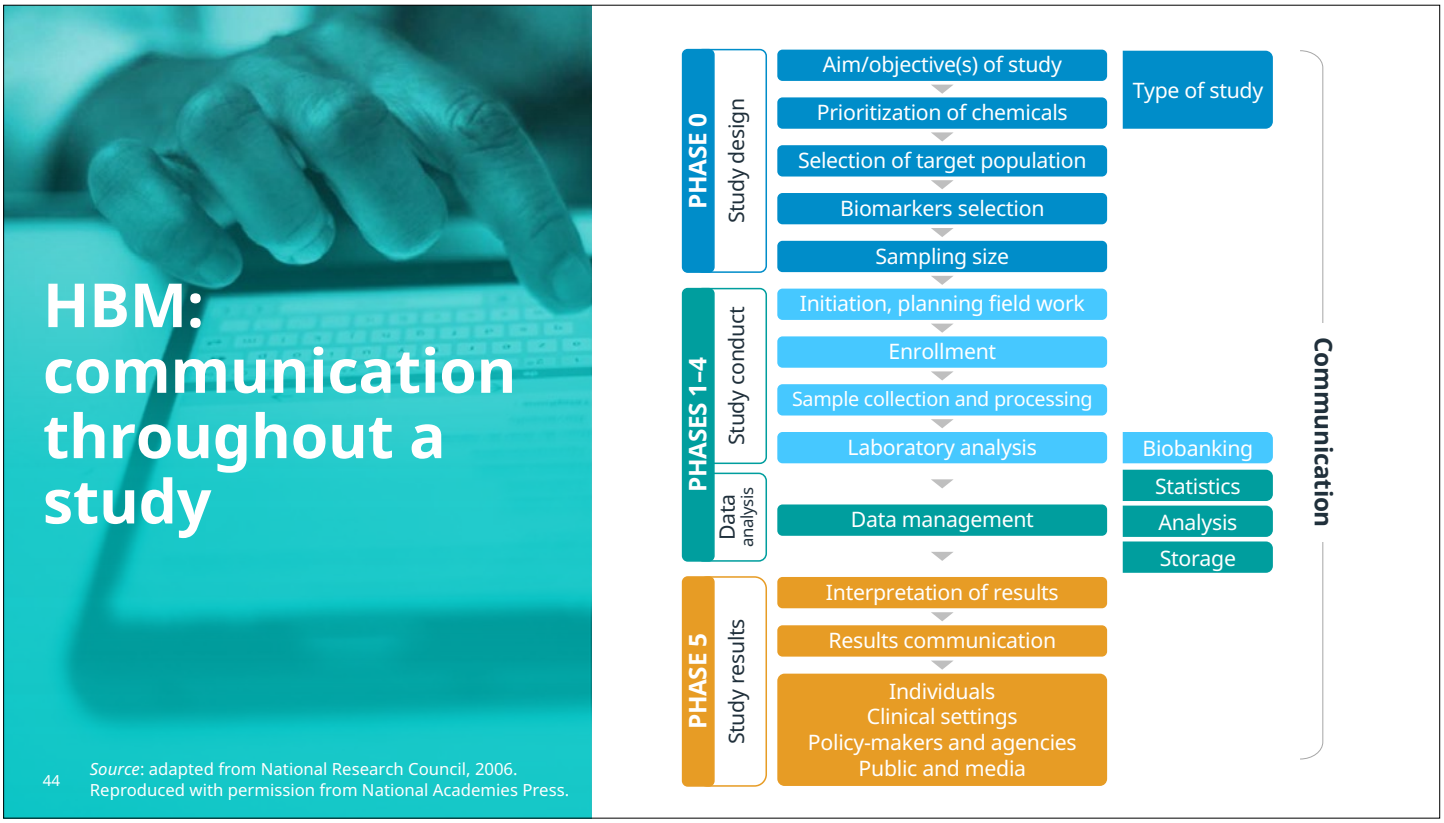
Before a study is initiated, the community from which participants will be recruited should, when feasible, be consulted about the research priorities, preferred trial designs and willingness to be involved in the preparation and conduct of the study. This will help to promote smooth study functioning and contribute to the community's capacity to understand the research process. Failure to engage with the community can compromise the social value of the research, as well as threaten the recruitment and retention of participants. Community engagement should be an ongoing process, with an established forum for communication between researchers and community members.

Any disagreements that may arise regarding the design or conduct of the research must be subject to negotiation between community leaders and the researchers.

Sources

International ethical guidelines for health-related research involving humans, fourth edition. Geneva: Council for International Organizations of Medical Sciences; 2016 (https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, accessed 10 November 2022).

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/334181, accessed 10 November 2022).



Three periods of extensive communication campaigns are identified:

- prior to and at the onset of the sampling period
- during the survey
- at the results dissemination stage.

Notes: HBM: human biomonitoring.

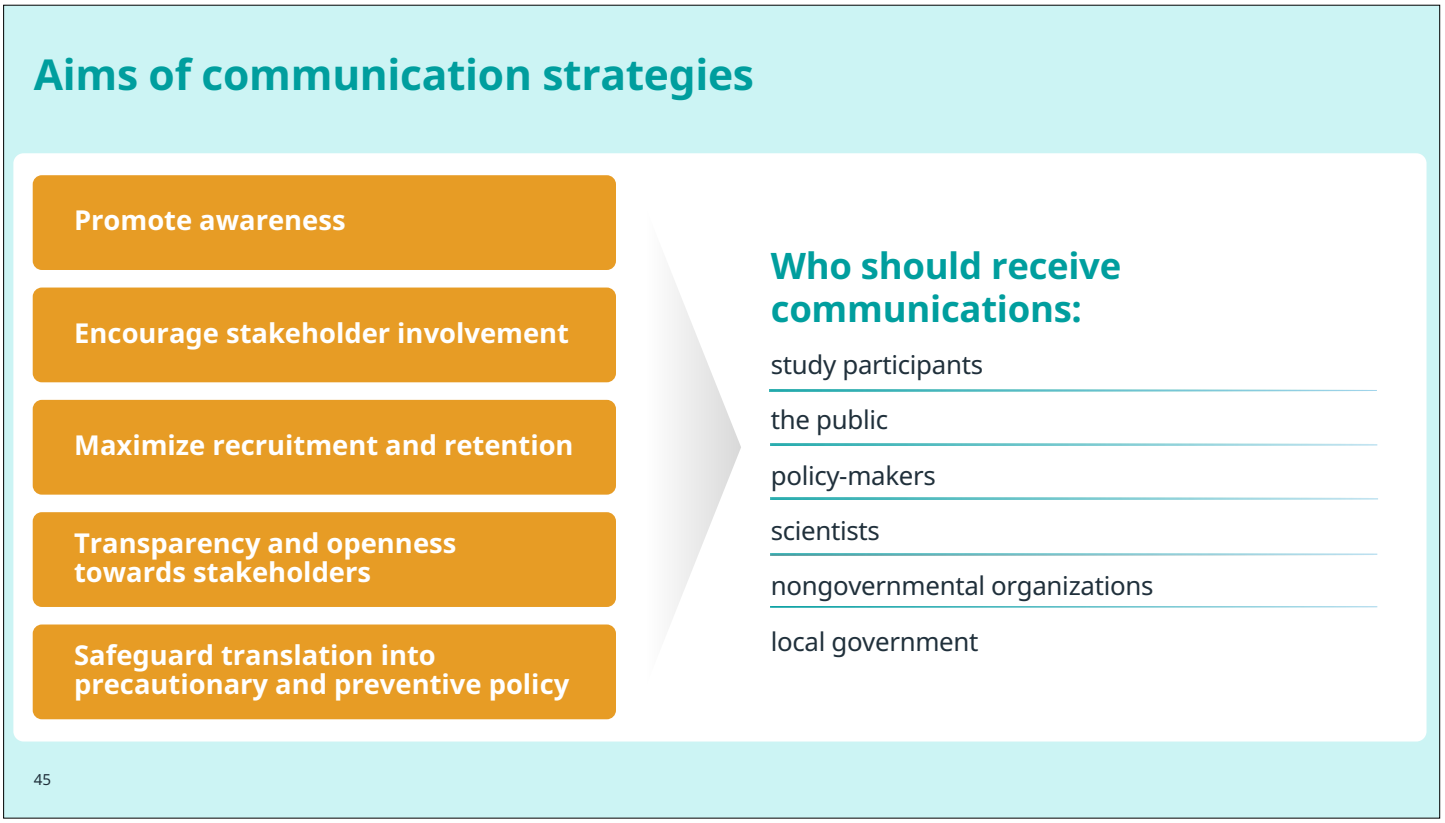
Sources

Fiddicke U, Becker K, Schwedler G, Seiwert M, Joas R, Joas A et al. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.

Committee on Human Biomonitoring for Environmental Toxicants, National Research Council. Human biomonitoring for environmental chemicals. Washington (DC): National Academies Press; 2006 (https://www.nap.edu/catalog/11700/human-biomonitoring-for-environmental-chemicals, accessed 10 November 2022).

Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May2023).

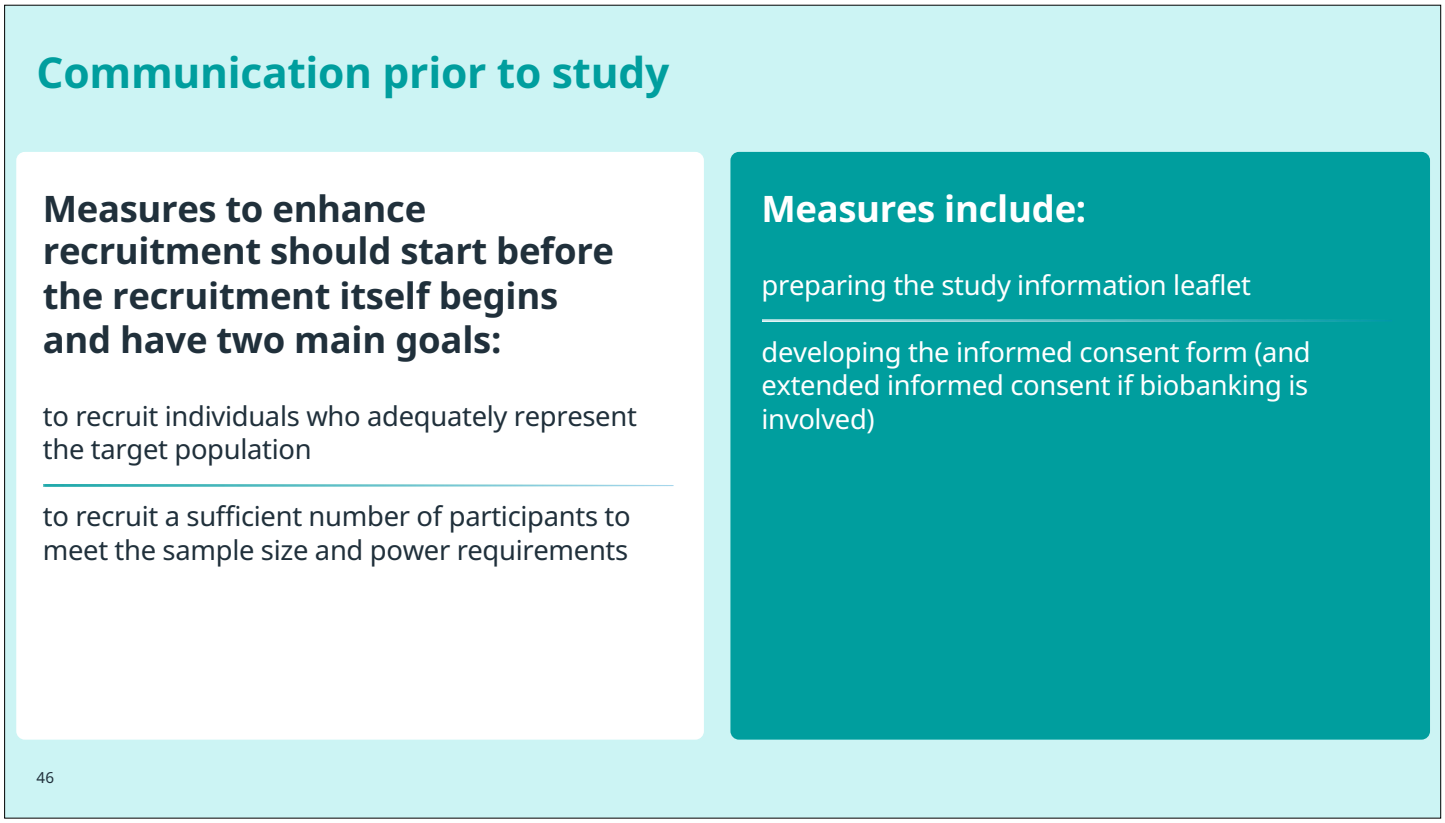


In addition to the survey participants, the survey leaders have to provide targeted information to the public, policy-makers and public health professionals. Effective communication can help to stimulate preventive action at the population and individual levels. At the same time, it is important to avoid inducing anxiety in survey participants when corrective actions are not warranted at the individual level.

Sources

Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May2023).



The initial campaign should start as soon as the survey protocol is ready, and the priority target group is policy-makers.

The survey information leaflet, prepared before initiating campaign, is one format to use to communicate about the survey. Links to the survey website with a description of the survey, answers to FAQs, information on sources of funding and contact details of the survey coordinator should be available for participants.

The information leaflet should provide a brief summary of the survey and its aims in plain language understandable for a non-professional audience. It should clearly explain what participation means in practice: how long it takes, where it takes place and what it involves.

Notes: FAQs: frequently asked questions.

Sources

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 ((https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May2023).

Communication during study

Purpose:

to react quickly and effectively to any upcoming questions

to facilitate communication

to receive and answer questions and queries, as well as to develop FAQs

Pay attention:

field staff should receive basic communication skills and other training before the study starts

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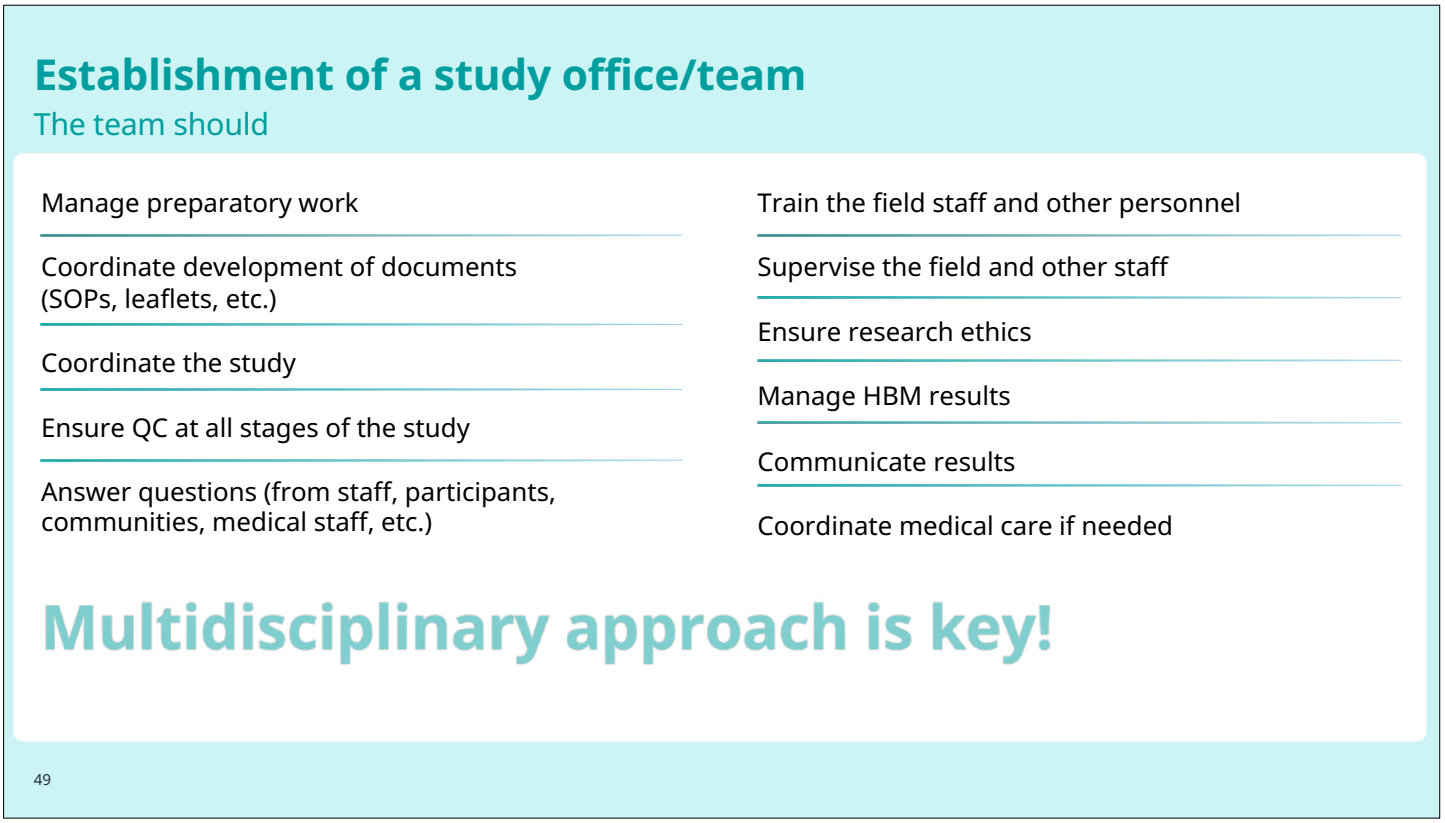
Notes: FAQs: frequently asked questions.

Sources

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May2023).

Field work



The study office/team is a central unit for conducting fieldwork and responsible for the management of recruitment and sampling. HBM studies require involvement of specialists with a variety of expertise: epidemiologists, chemists, toxicologists, health-care workers, social workers and communication specialists, among others.

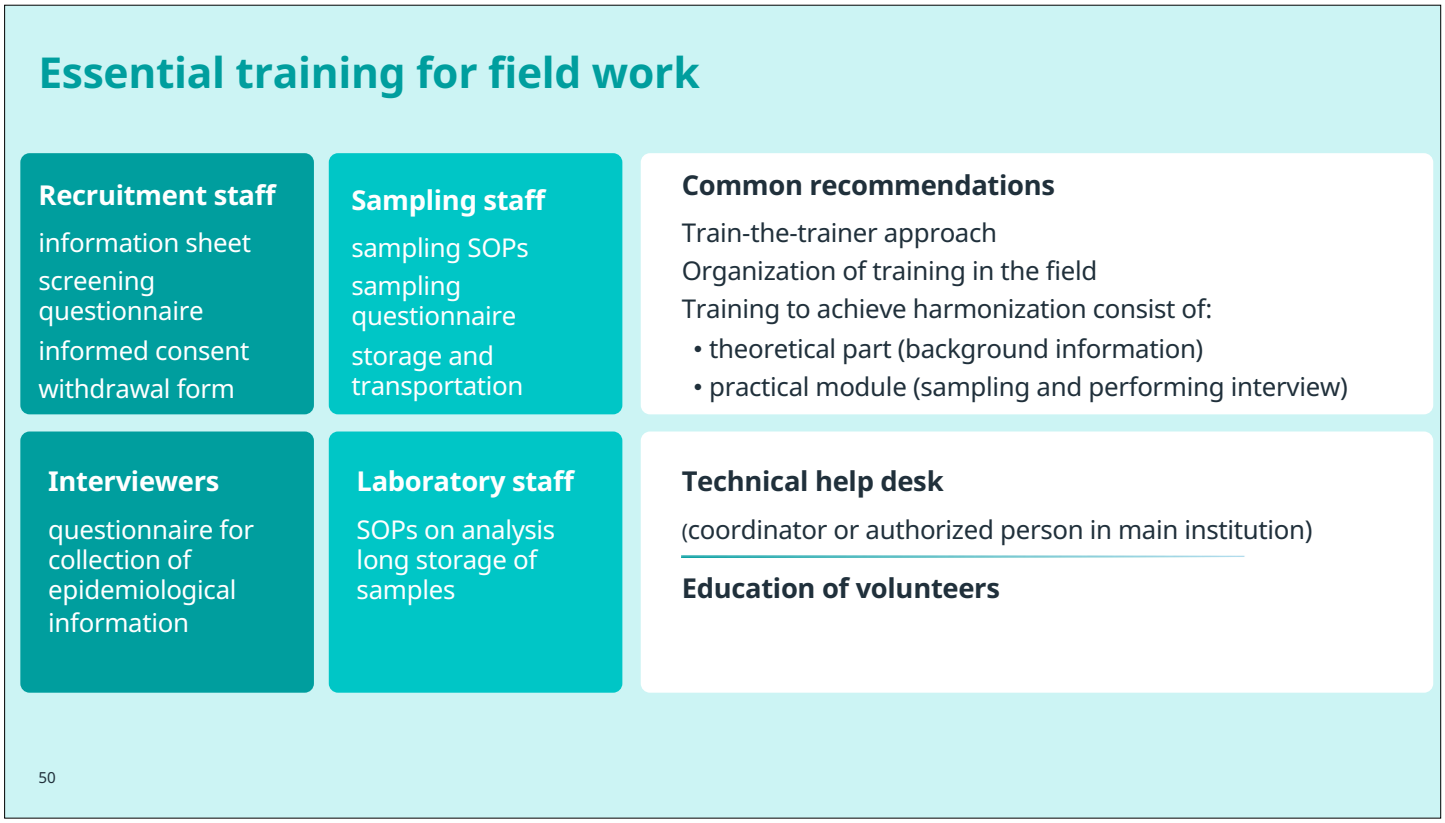
Notes: HBM: human biomonitoring; SOP: standard operating procedure; QC: quality control.

Sources

Fiddicke U, Becker K, Schwedler G, Seiwert M. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 ((https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May2023).

Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).



Training needs to consist of theoretical background information on the study objectives and a practical module.

Qualified field staff for conducting the study should fulfil the following criteria:

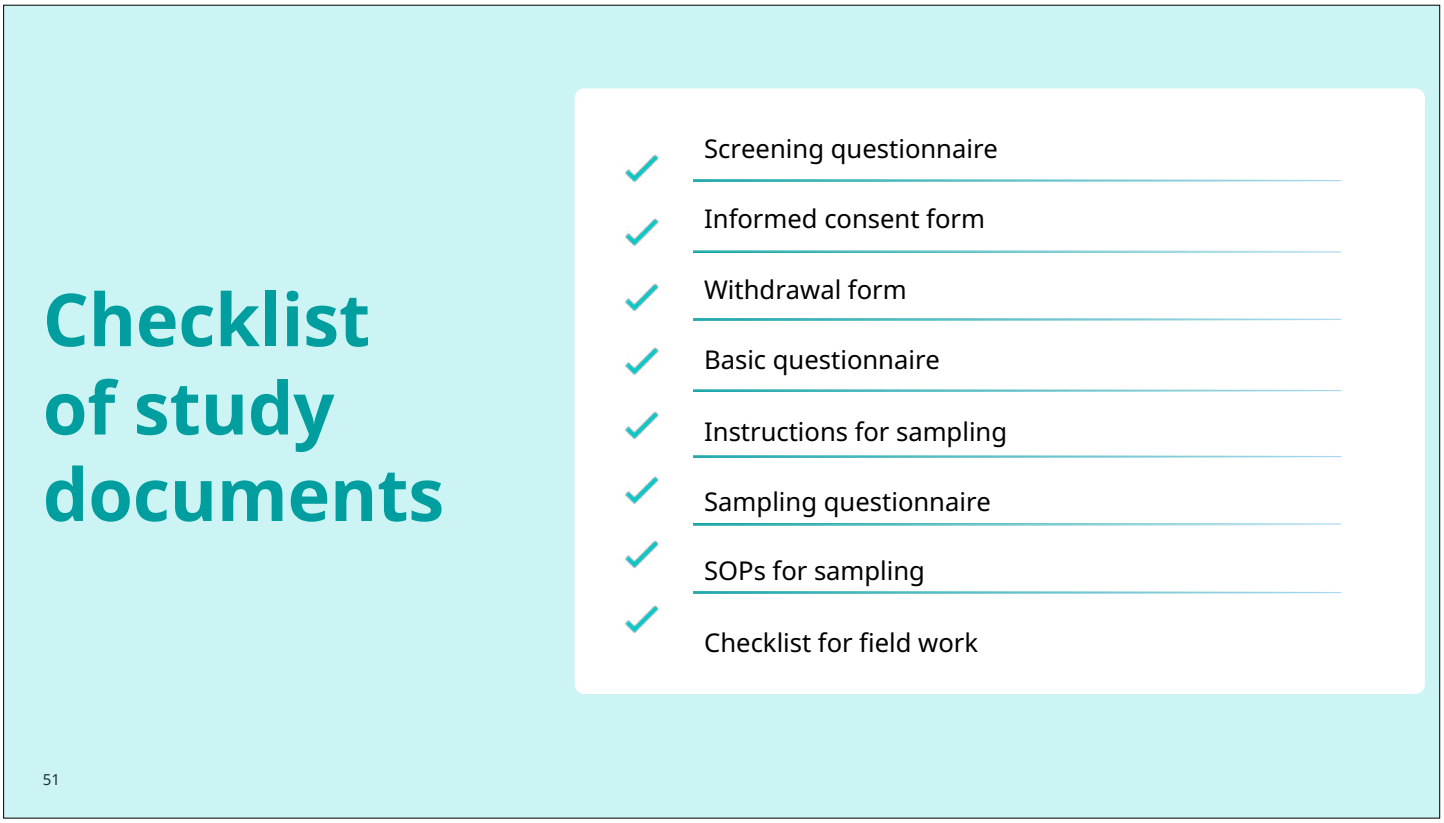
- be well trained to understand what is the aim the study and consequentially of each question;
- be experienced in dealing with people and do not hold reservations about people of different social classes or ethical origins;
- should not get too „personal“ with participants and should not comment on their answers;
- have local knowledge on the sampling area; and
- have experience in interview conduct.

Notes: SOP: standard operating procedure.

Sources

Fiddicke U, Becker K, Schwedler G, Seiwert M. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.

Human biomonitoring for Europe (HBM4EU) [website]. Dessau-Roßlau: German Environment Agency; 2022 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).



Notes: SOP: standard operating procedure.

Sources

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021;232:113684. doi: 10.1016/j.ijheh.2020.113684.

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).

European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 ((https://cordis.europa.eu/project/id/733032/results, accessed 15 May 2023).

Questionnaires

Questionnaires are important for interpretation of results

Design should be based as much as possible on standard questions; newly designed questionnaires should be tested in the target population

Interviews conducted by study personnel generally provide a higher quality of data than self-administered questionnaires

Routinely collected medical data should be obtained when possible

Linking data between chemical concentrations with Q data*

Questionnaires should be:

- **Translated to national language(s) if needed**
- **Adopted to national/local context**
- **Tested before study (at least 5–10 people during pilot testing)**

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* A form of regression analysis in which the relationship between an outcome or dependent variable and one or more predictors or independent variables is analysed

Questionnaires in HBM studies/surveys are used to collect necessary information for the interpretation of biomarkers; this includes data on personal characteristics (e.g. anthropometric data, ethnic origin, education level, socioeconomic status), potential exposure sources (e.g. occupational, residential environment), health-related data (e.g. complaints, diseases), lifestyle and so on. Questionnaires should be tested in a small group (5—7 people) from the target population before the start of sampling.

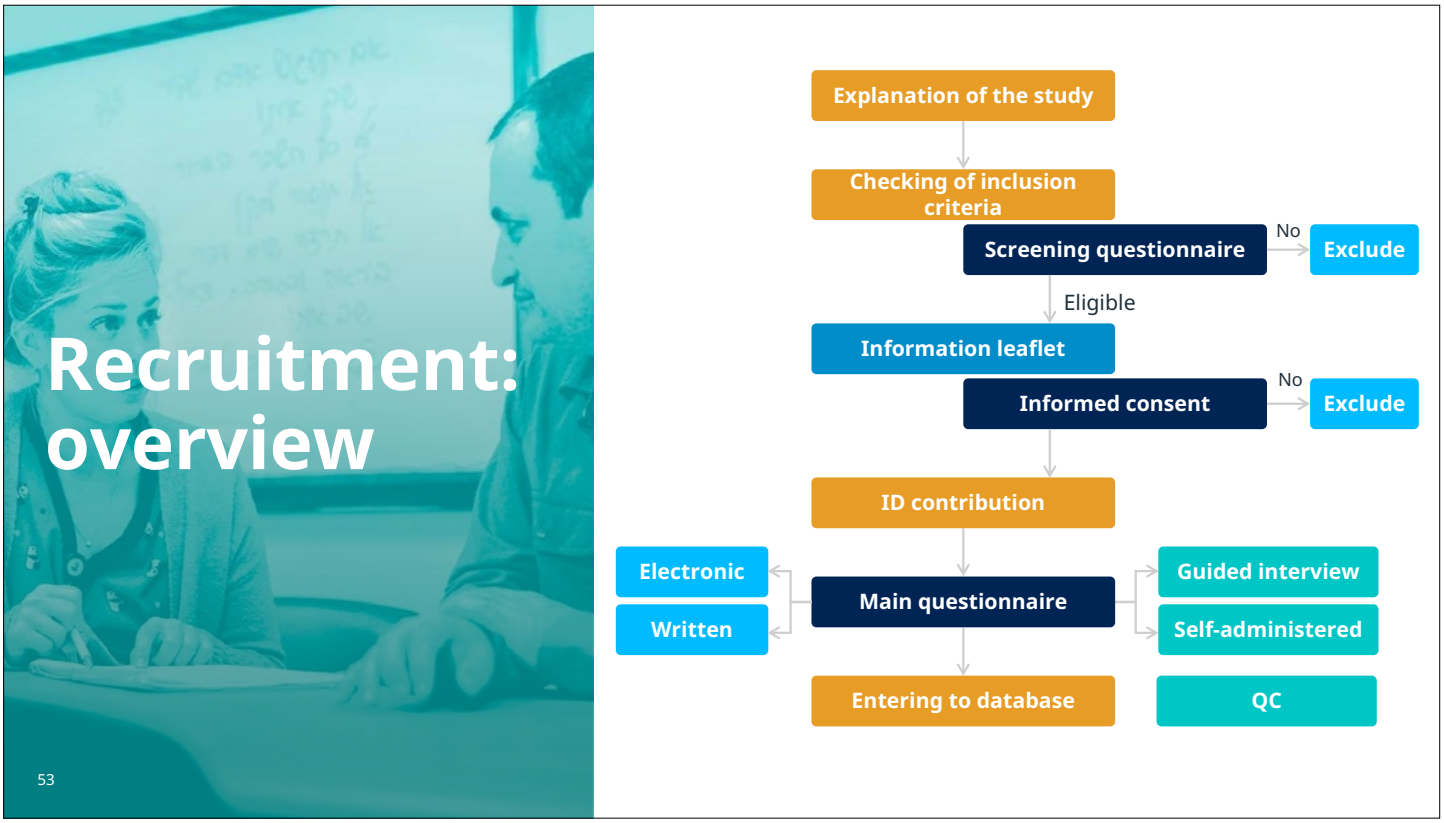
Notes: HBM: human biomonitoring.

Sources

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).

1st-prioritisation report on survey design: study protocols, SOPs and guidelines, tailored and transferred questionnaires for recruitment and sampling. In: Deliverables. European Human Biomonitoring Initiative [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5de975e76&appId=PPGMS, accessed 15 May 2023).

Kim Pack L, Gilles L, Cops J, Tolonen H, van Kamp I, Esteban-López M et. al. A step towards harmonising Human Biomonitoring study setup on European level: Materials provided and lessons learnt in HBM4EU. Int J Hyg Environ Health. 2023;249:114118. doi: 10.1016/j.ijheh.2023.114118.



The flow of recruitment is as follows.

The interviewer politely introduces him/herself and provides a short explanation of the study.

The inclusion criteria are checked for the participant to ensure eligibility using a screening questionnaire. If the inclusion criteria are met, the participant is given an information leaflet. Otherwise the participant is withdrawn from the study.

After the participant is sufficiently informed about the study, he or she signs the consent for participation. If this is not done, the participant is withdrawn from the study.

After signing the informed consent, the participant is given an unique identity code, which is used for all collected samples and data in the study database. The participant is then interviewed using the epidemiological questionnaire. Alternatively, a questionnaire can be filled out by the participant (self-administered), but this is not recommended. Interviews conducted by sstudy personnel generally provide higher quality of data than self-administered questionnaires. Routinely collected medical data should also be obtained when possible.

After providing basic information, the participant undergoes the sampling.

Notes: QC: quality control.

Sources

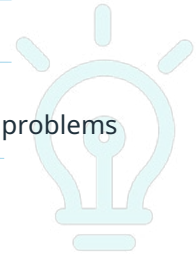
Fiddicke U, Becker K, Schwedler G, Seiwert M. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.

1st-prioritisation report on survey design: study protocols, SOPs and guidelines, tailored and transferred questionnaires for recruitment and sampling. In: Deliverables. European Human Biomonitoring Initiative [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5de975e76&appId=PPGMS, accessed 15 May 2023).

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).

Recruitment: main considerations

- Open and inclusive communication on study: purposes, benefits, risks, etc.
- Communication using plain language
- Inclusive forms of participation
- Individual needs of volunteers (e.g. timing of sampling if not contradicted with the SOPs)
- Timing of recruitment (not too early and not too late)
- Discussion and exchange of experiences among study participants
- Participants' experiences and feedback should be studied (interviews, surveys, etc.), e.g. participants withdrawing should be asked to state a reason for dropping out to identify problems
- Inclusion/exclusion criteria should be applied



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Existing motivational drivers can be studied prior to the main campaign to adjust the communication material for recruitment; for example, interview possible candidates from the target audience on why they would participate and how they could benefit (e.g. if the participants› main wish is to learn about how they are exposed and how to reduce their exposure, this should be included in the recruitment material as well as in the communication of results).

Inclusive forms of participation can further increase their involvement by enabling the participants to take part in all phases of the study from formulating the research question to analysing and disseminating the results.

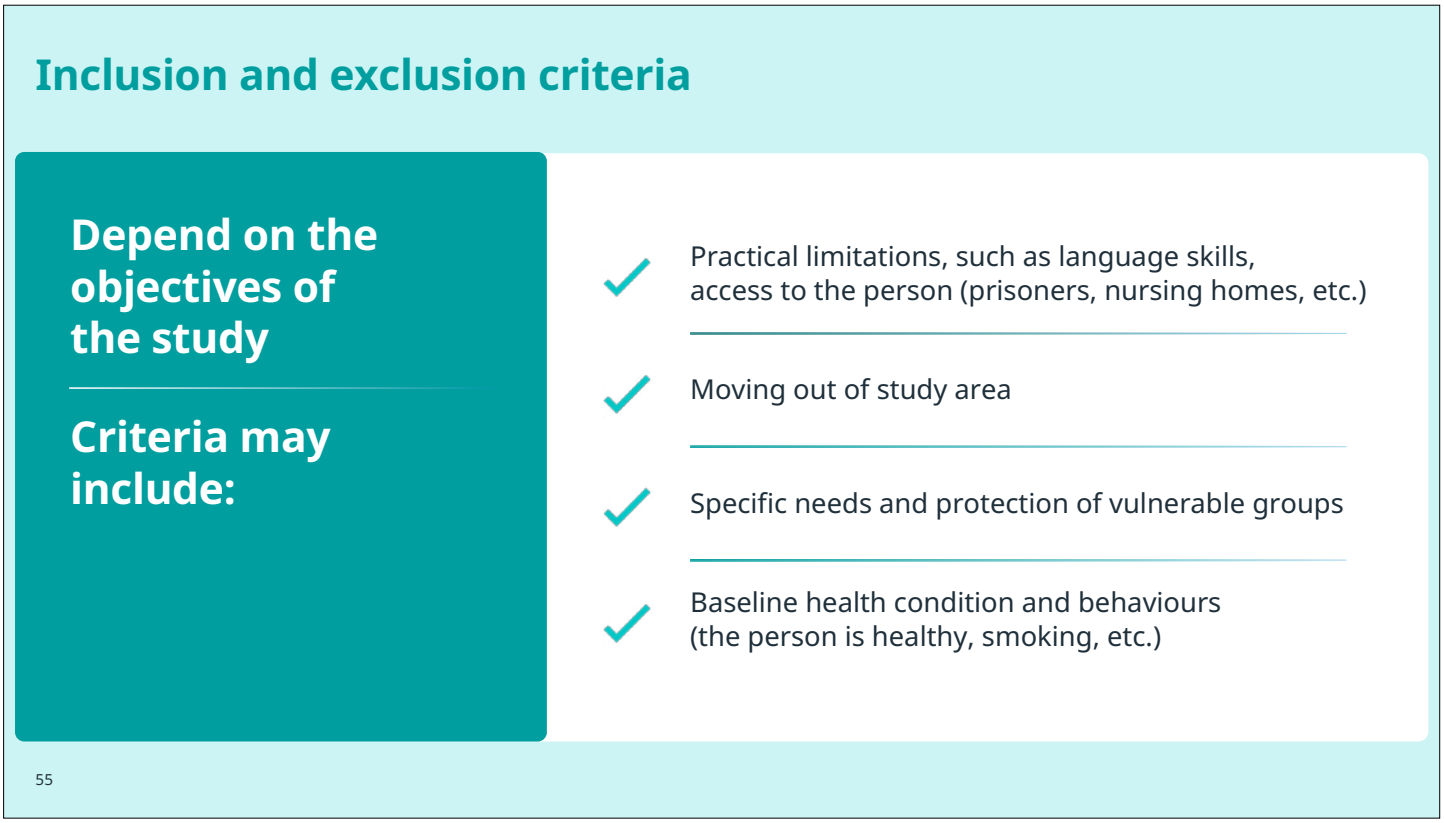
Participants can be offered a place to discuss and exchange their experiences with other participants in a safe environment that enables them to stay anonymous.

Further evaluation and impact assessment of HBM through participatory evaluation or other means can increase its impact on public health and environmental policy.

Notes: HBM: human biomonitoring; SOP: standard operating procedure.

Sources

Robinson J A, Kocman D, Speyer O, Gerasopoulos E. Meeting volunteer expectations: a review of volunteer motivations in citizen science and best practices for their retention through implementation of functional features in CS tools. J Environ Plan Management. 2021;64(12):2089-113. doi: 10.1080/09640568.2020.1853507.

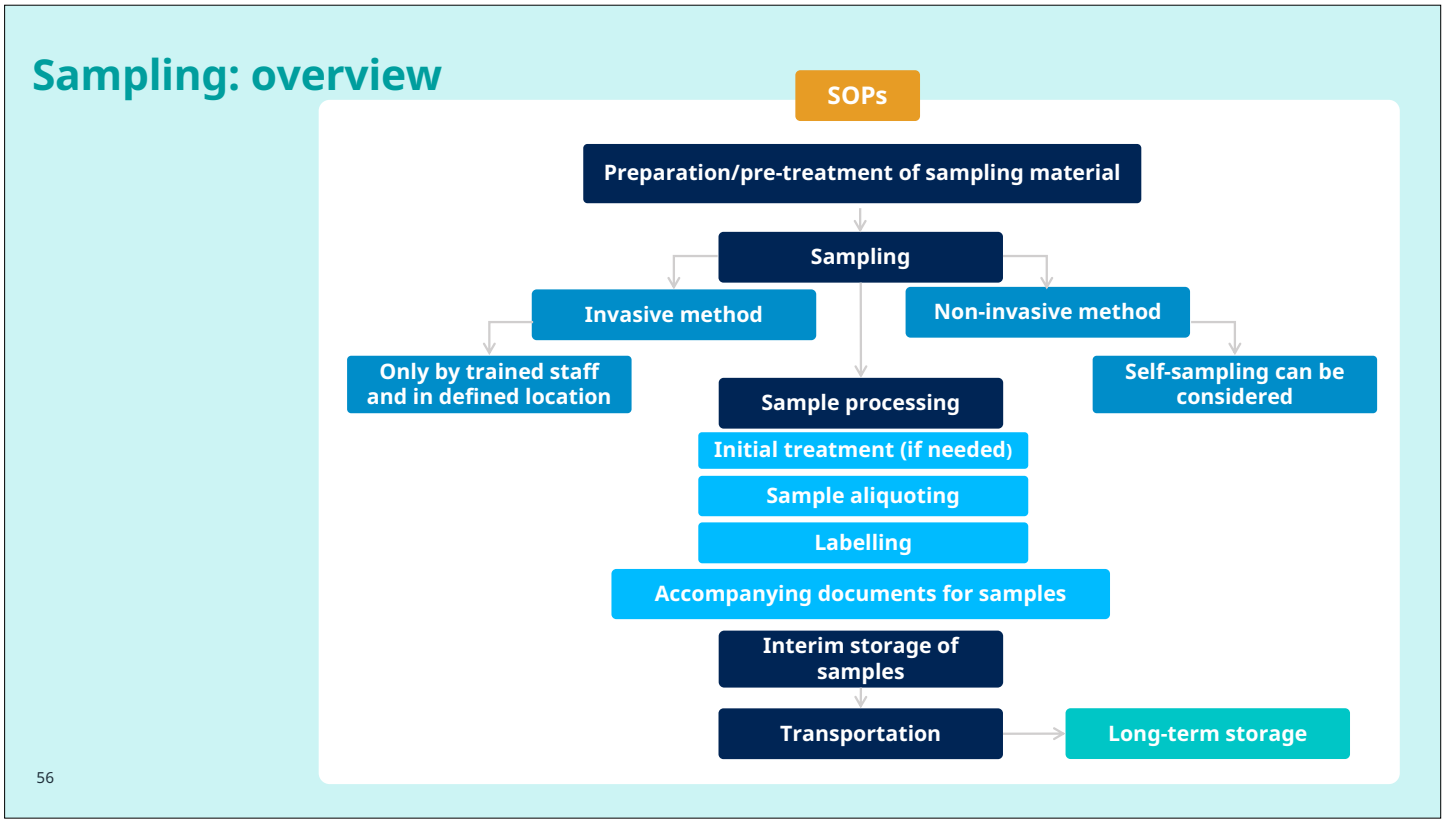


For the recruitment of the target population, inclusion and exclusion criteria (setting out eligibilty) need to be identified in accordance with the study objectives before sample participants are selected and study started.

Sources

Tolonen H, National Institute for Health and Welfare (THL), Finland. Taking a representative sample for all age groups: presentation at HBM4EU training school, June 2018, Ljubljana, Slovenia. Dessau-Roßlau: German Environment Agency; 2018 (https://www.hbm4eu.eu/?mdocs-file=4483, accessed 10 November 2022).

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).



Detailed information on biological specimens collection should be defined in a standard operating procedure that is separately developed for each biomatrix. This should be prepared by the study office/ team and strictly followed during the study conduct.

The SOPs can include:

- detailed instructions for sampling;
- the questionnaires that need to be filled in for each sample collection – time of collection, basic characteristics of the sample (e.g. volume), and information relevant for the chemicals in the specific sample; and
- instructions for aliquoting of the sample, storage and transport.

Notes: SOP: standard operating procedure.

Sources

Fiddicke U, Becker K, Schwedler G, Seiwert M. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.

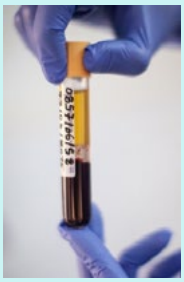
Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).

1st-prioritisation report on survey design: study protocols, SOPs and guidelines, tailored and transferred questionnaires for recruitment and sampling. In: Deliverables. European Human Biomonitoring Initiative [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5de975e76&appId=PPGMS, accessed 15 May 2023).

Sampling: main considerations (I)

What must be defined prior to sampling?

- SOPs
- Method of taking sample
- Transportation
- Aliquoting of samples (up to 100)
- Archiving
- Long-term/unlimited time archiving



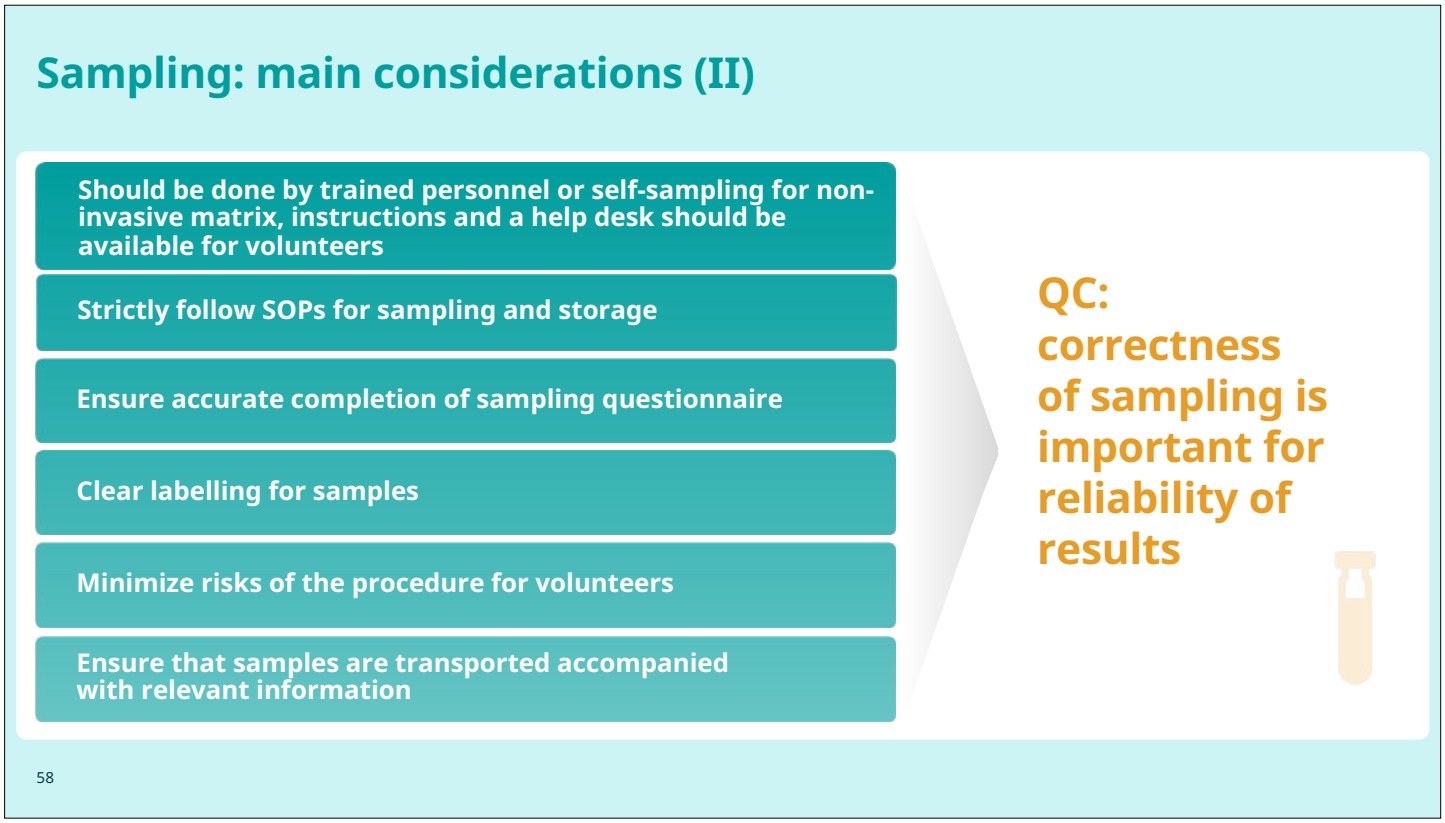
57

Notes: SOP: standard operating procedure.

Sources

Esteban M, Castano A. SOP3: Procedure for obtaining human samples. Zenodo. 2018:7 doi: 10.5281/zenodo.6304202.

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).



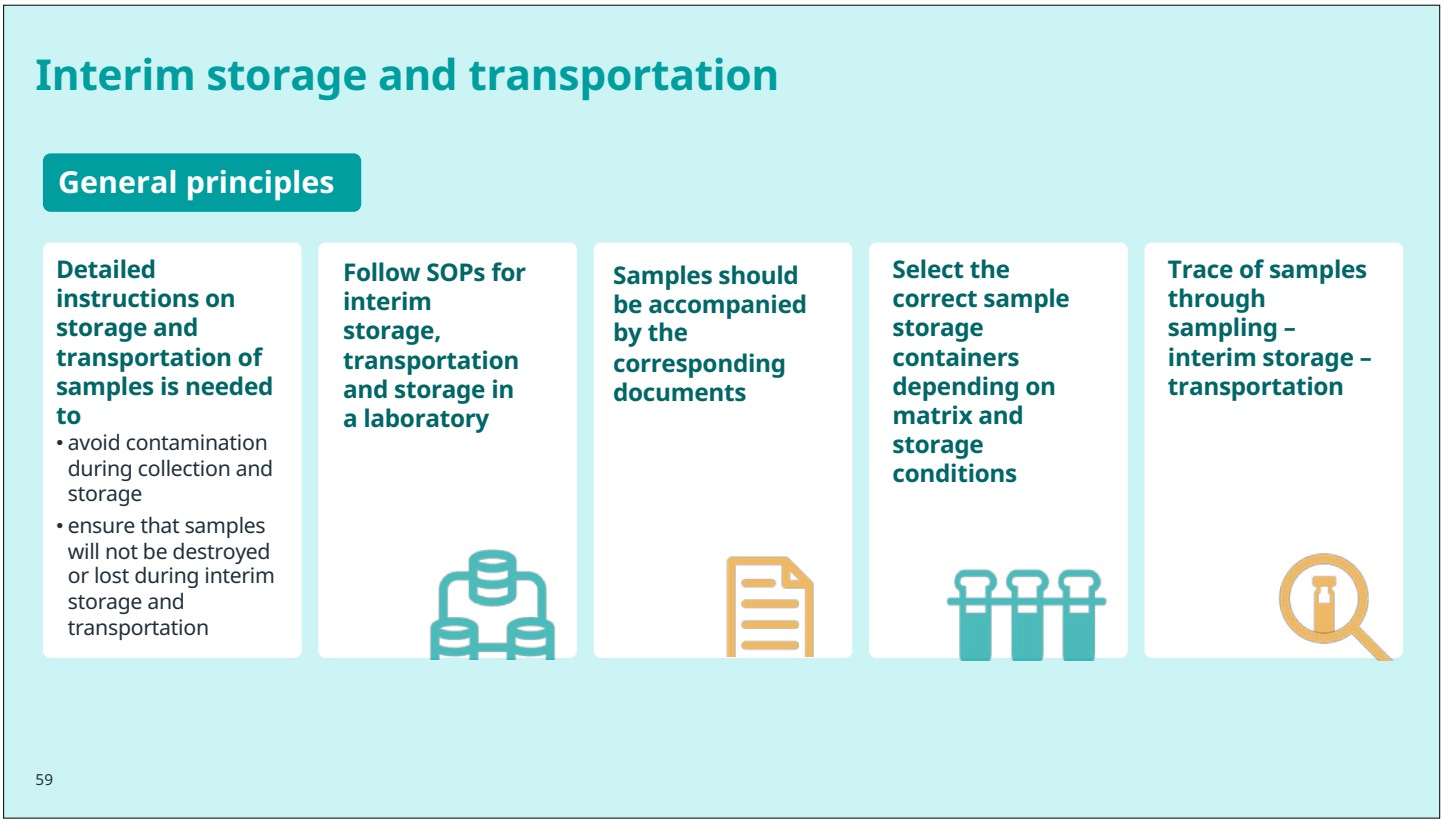
Notes: SOP: standard operating procedure; QC: quality control.

Sources

Fiddicke U, Becker K, Schwedler G, Seiwert M. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).

1st-prioritisation report on survey design: study protocols, SOPs and guidelines, tailored and transferred questionnaires for recruitment and sampling. In: Deliverables. European Human Biomonitoring Initiative [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5de975e76&appId=PPGMS, accessed 15 May 2023).



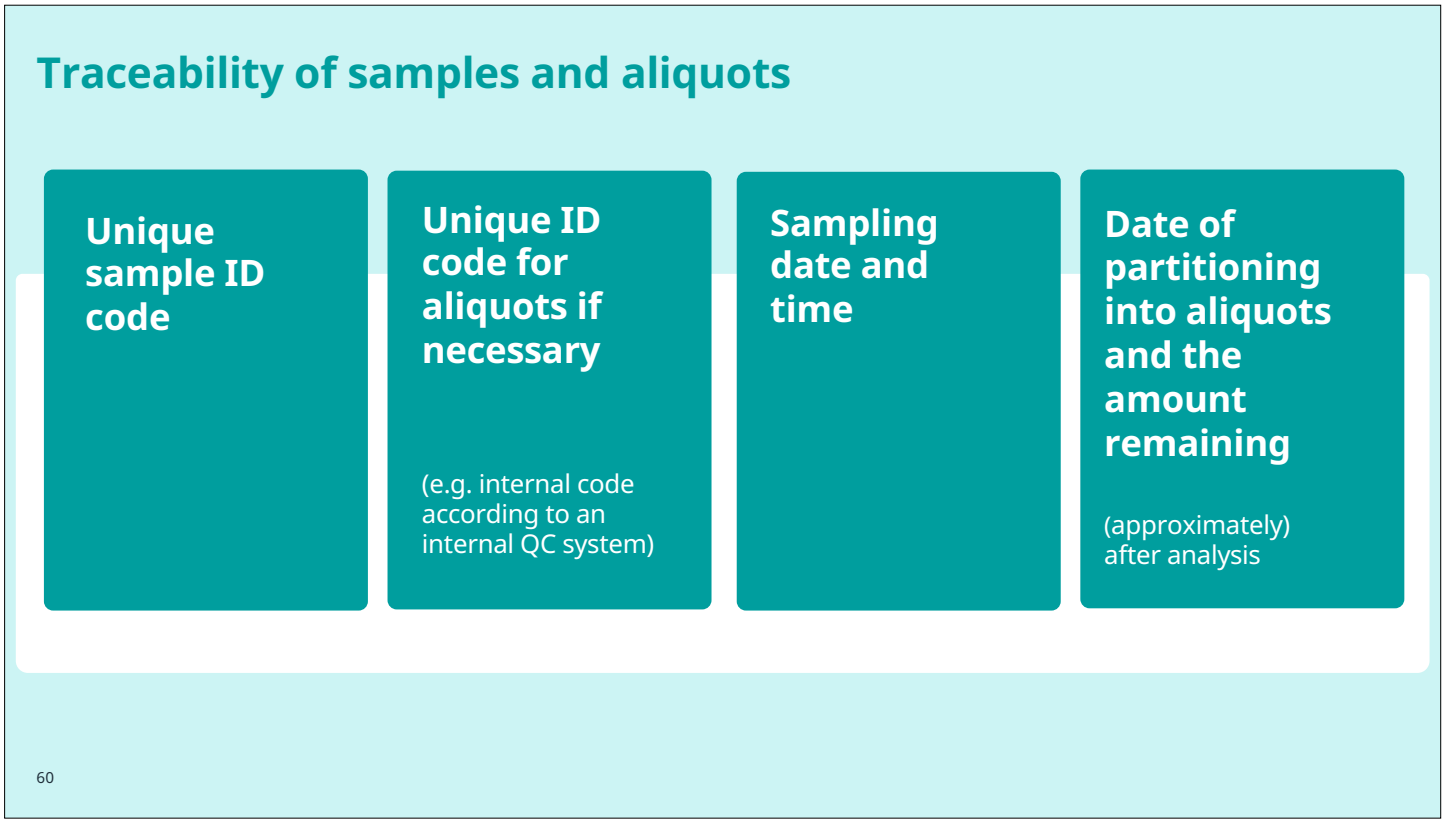
Selection of the sample collection/storage containers and tubes should be based upon the sample type to be stored and the substance to be measured:

- sample type: urine vs serum or blood
- substance to be tested: organic vs inorganic.

Notes: SOP: standard operating procedure.

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).



Notes: QC: quality control.

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

Blood samples: general requirements

Whole blood and **plasma** samples: tubes with anticoagulant

Serum samples: tubes with no additives

Collection of pooled samples is sometimes an option

Short-term storage: 2—8 °C until arrival at the laboratory

Registration of the samples in the laboratory and reconciliation with the shipping manifesto provided by the sender

Plasma: centrifugation and plasma removal is needed at the latest within 24 hours from sampling

Sample aliquoting: polypropylene tubes (1—2 mL)

Storage: freezer at or below –20 °C until analysis; contamination during storage should be avoided

Biobanking (long-term storage): –80 °C; preferable at –150 °C

61

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

Urine samples: general requirements

Different of sample: first morning spot urine, random spot urine, 24-hour urine

Collection of spot urine: 120 mL polypropylene vessel with a screw cap
Collection of 24-hour or pooled urine samples can be an option

Short-term storage: at 4 °C until arrival at the laboratory

Registration of the samples in the laboratory and reconciliation with the shipping manifesto provided by the sender

Sample aliquoting: polypropylene tubes (1, 2, 5 or 10 mL)

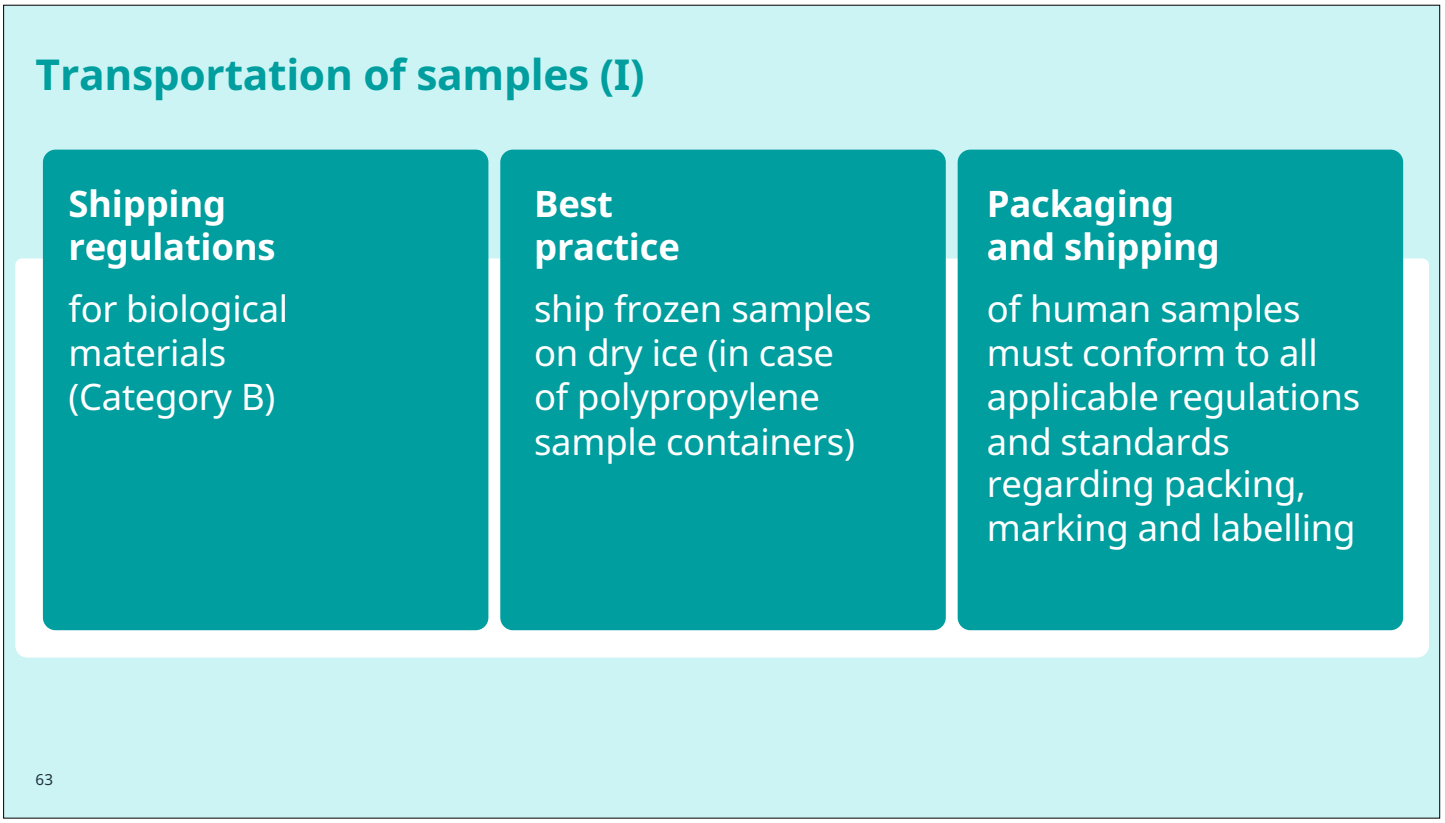
Storage: freezer at or below –20 °C until analysis;
contamination during storage should be avoided

Biobanking (long-term storage): –80 °C; preferably at –150 °C

62

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).



All biological material must be transported in compliance with the relevant shipping regulations for biological material (Category B). Transportation regulations might depend on the national rules.

Sources

Guidance on regulations for the transport of infectious substances 2015–2016. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/149288, accessed 10 November 2022).

Dangerous goods regulations and other publications. Montreal: International Air Transport Association; 2022 (http://www.iata.org/publications/dgr/Pages/index.aspx, accessed 10 November 2022).

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

Transportation of samples (II)

1. Before preparing the packing, ensure all vessels are safely closed and labelled with an ID-number

2. Place urine vessels and/or blood tubes in the respective box-rack

3. Each box-rack must be placed in a bag with absorbent material

4. Remove the adhesive protector, press the bag to eliminate the air and seal it

5. Place the accompanying documents inside the plastic bag

64 *Source*: WHO, 2018. WHO, 2016.

Sources

Guidance on regulations for the transport of infectious substances 2015–2016. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/149288, accessed 10 November 2022).

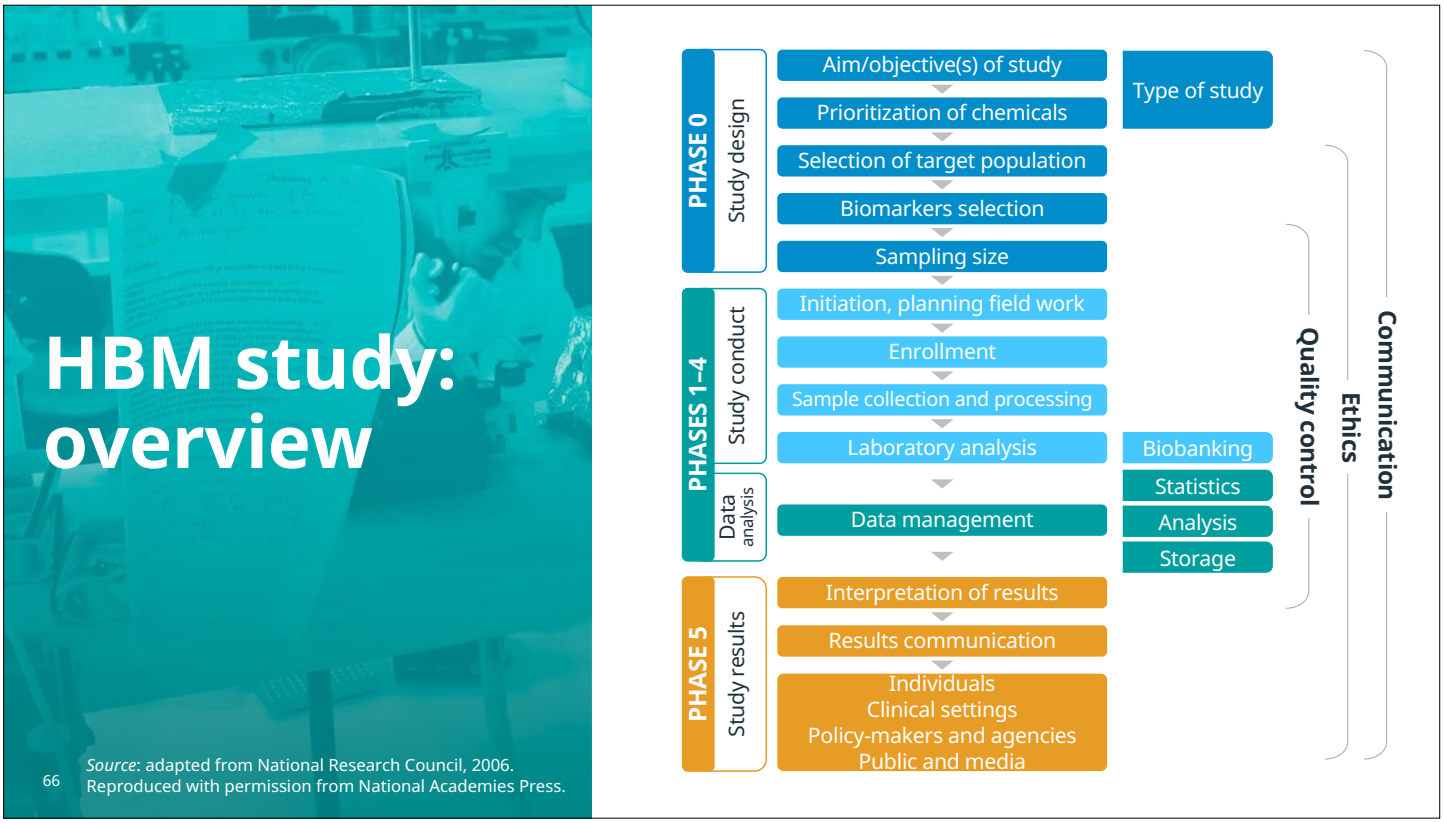
Dangerous goods regulations and other publications. Montreal: International Air Transport Association; 2022 (http://www.iata.org/publications/dgr/Pages/index.aspx, accessed 10 November 2022).

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

Esteban López M, Navarro C, Castaño A. Sampling procedure for hair, control at pre-analytical phase, storage and transport of samples: training workshop for national coordinators and laboratory analysts in the frame of the UNEP/WHO project, Ljubljana, Slovenia. World Health Organization; 2016.

Phased approach to planning and conducting HBM study

Notes: HBM: human biomonitoring.

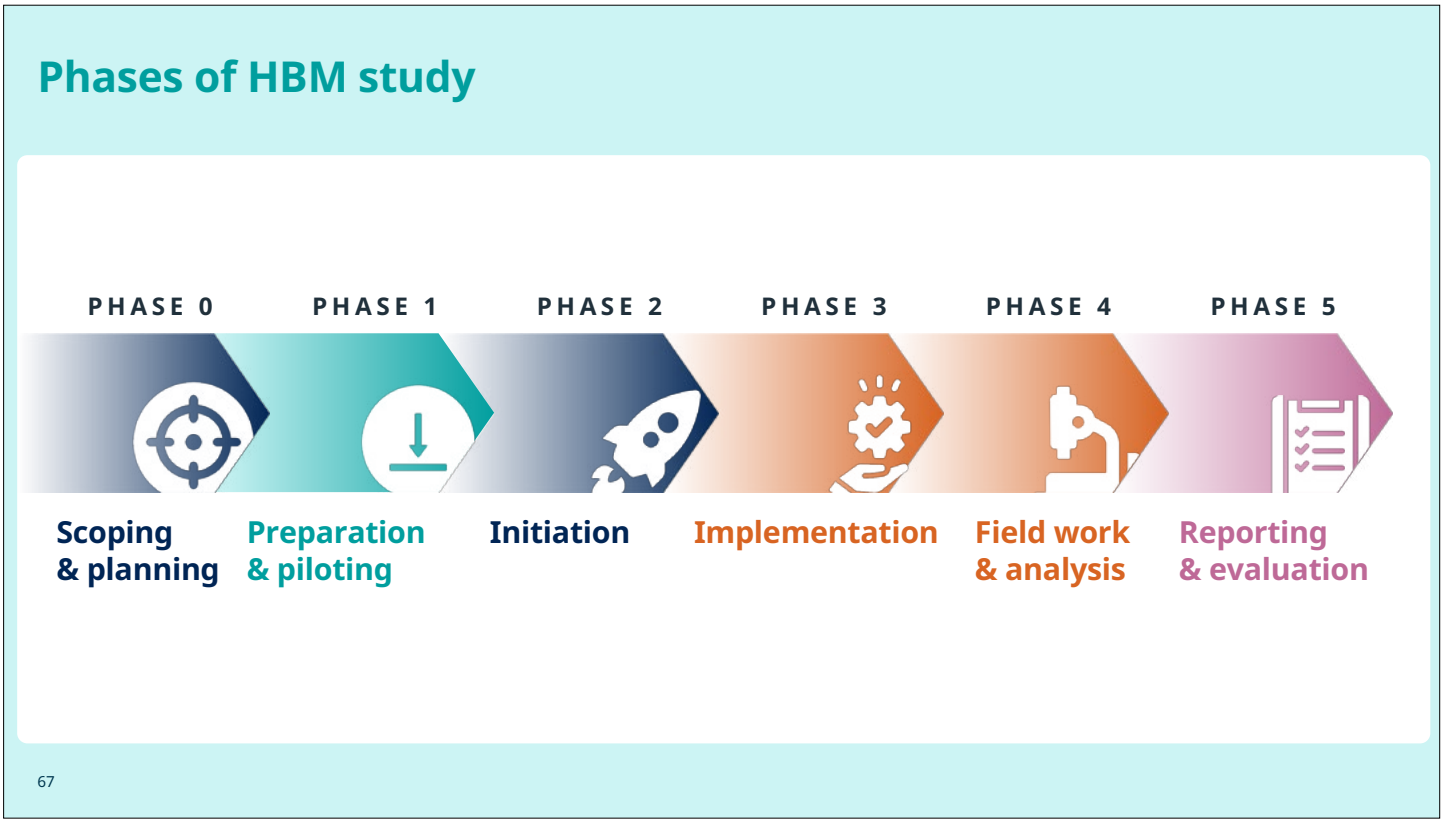


Whatever approach to planning and conducting a study is taken (phases or stages or steps) the procedures, tasks, actions are very similar. Demonstration of phased approach in the next slides highlight similarities in planning and conducting HBM surveys.

Notes: HBM: human biomonitoring.

Source

Committee on Human Biomonitoring for Environmental Toxicants, National Research Council. Human biomonitoring for environmental chemicals. Washington (DC): National Academies Press; 2006 (https://www.nap.edu/catalog/11700/human-biomonitoring-for-environmental-chemicals, accessed 10 November 2022).



A phased approach was applied for HBM4EU study.

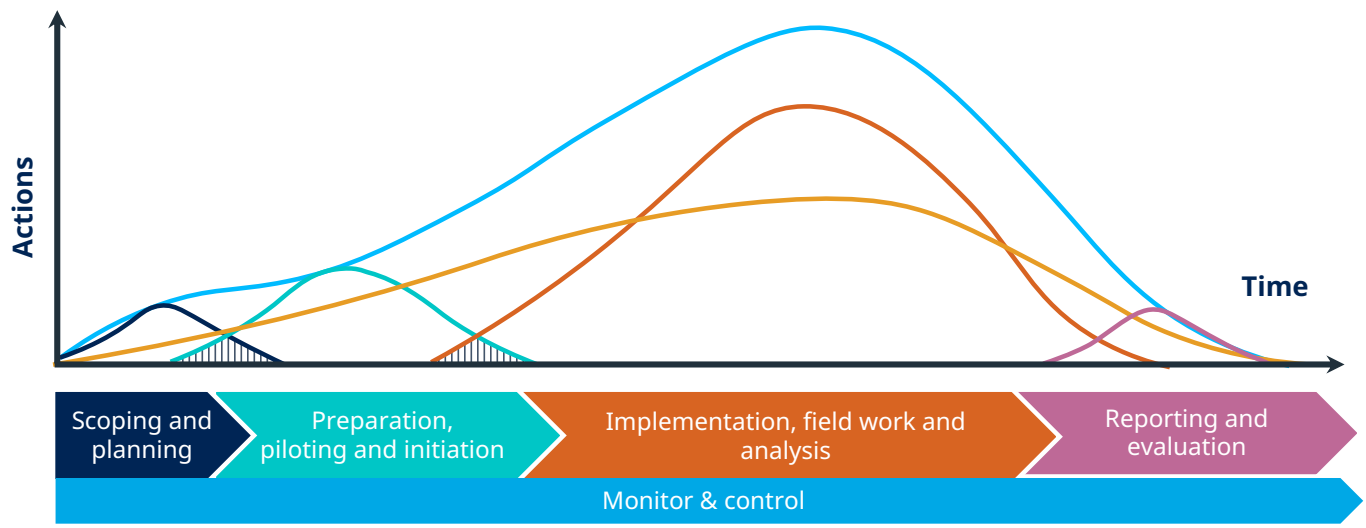
Research subjects, target population, selection of participants, communication with stakeholders, biological analyses, data management, policy advice, and legal and ethical considerations are aspects that should be considered.

Notes: HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative.

Sources

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021 Mar;232:113684. doi: 10.1016/j.ijheh.2020.113684.

Overlapping of phases



68

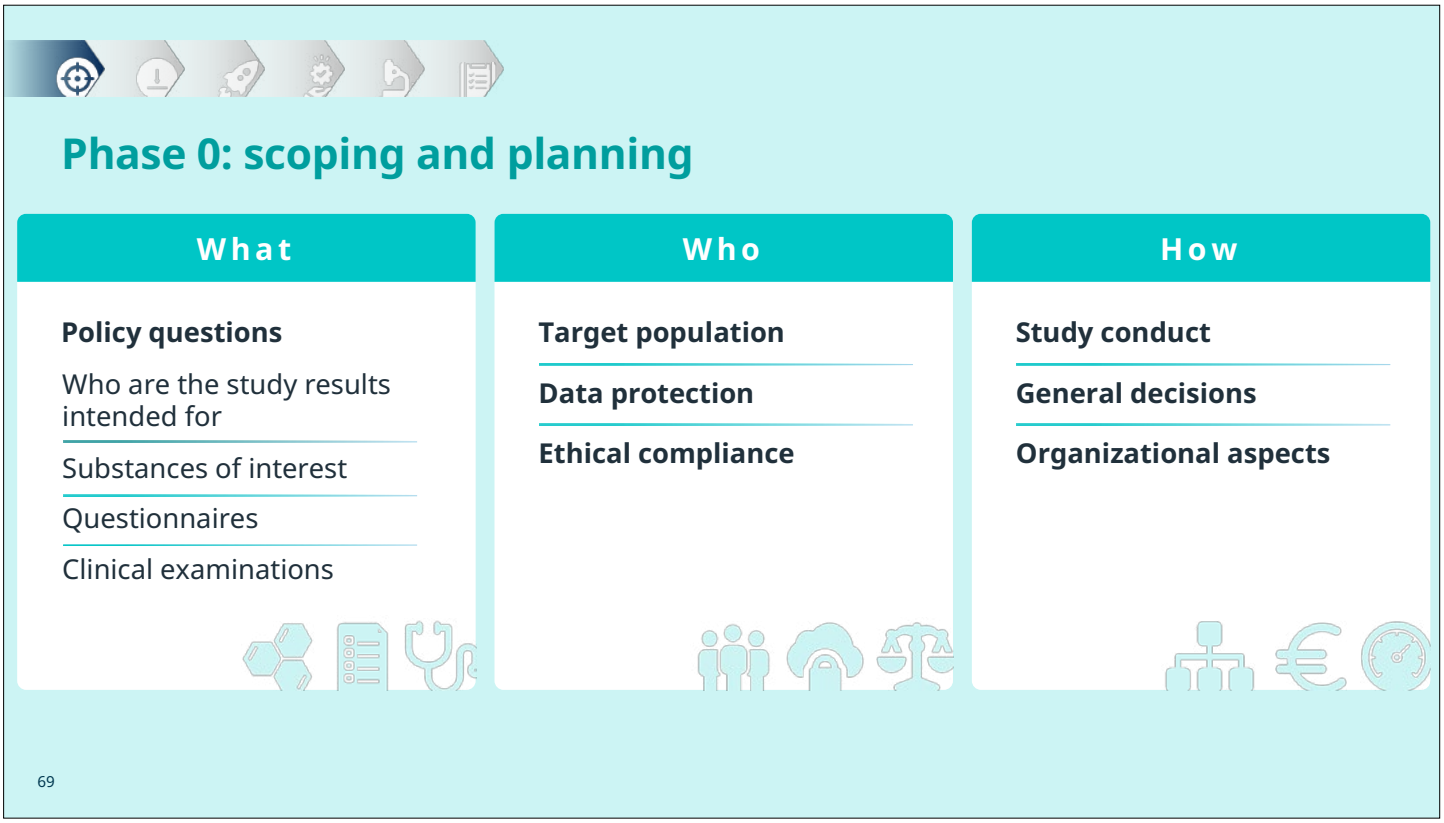
Phases are described in a chronological order, and this may give rise to an impression that one phase should be finalized before the next one can start. However, an overlapping of some parts of phases is common in HBM studies.

Notes: HBM: human biomonitoring.

Sources

European Commission, Digit, Centre of Excellence in Project Management. The PM2 project management methodology: guide 3.0. Brussels: European Commission; 2018 (https://op.europa.eu/en/publication-detail/-/publication/ac3e118a-cb6e-11e8-9424-01aa75ed71a1, accessed 10 November 2022).

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021;232:113684. doi: 10.1016/j.ijheh.2020.113684.



At Phase 0 the researcher and the team should answer questions What, Who and How.

What?

This includes:

- identifying the scope and hypothesis of the study; and
- the planned research programme, including substances of interest and instruments (sampling, clinical examinations and questionnaires).

When determining the substances of interest, the following criteria should be taken into account:

- biomarkers (LOQ in the target population, time frame for sample collection);
- analytical method (LOQ, certified reference material and standards, costs, etc.);
- sample volume (for single analysis, repetitions and biobanking);
- sample collection and storing (material, volume, preservatives, control for background contamination, stability for biobanking including labels, QA/QC aspects),
- processing of samples - during fieldwork, conservation and shipment, reception in laboratory, and aliquoting process; and
- qualified laboratories for the analyses.

Choice of format and application of questionnaires will depend on the study format:

- epidemiological questionnaire and specific questions that cover the previous 24–72 hours for past urine collection for substances with short half-lives;
- supporting questionnaires for recruitment (eligibility check, availability, history of contact), for sampling (period of sampling, recent exposure related to the target biomarker and so on), non-respondents and satisfaction;
- method chosen for application (face-to-face interview, telephone interview, self-administered, paper and pencil, web-based formats).

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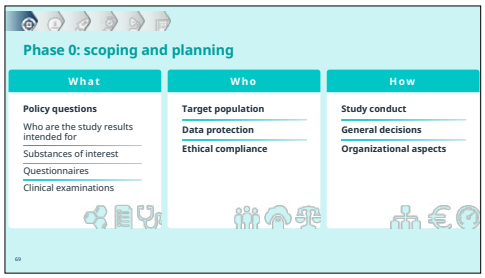

Who?

The “Who” question will identify the target population, set the sampling size and select invitees.

- Target population: general/subgroups and eligibility.
- Degree and direction of representativeness: national, regional, local, according to sex and socioeconomic status, oversampling of a subgroup.
- Ethics.
- Organizational aspects of data protection and data management.
- The recipients of the study results as this may help to plan communications and outreach activities: government, community, the public, specific interest groups, etc.

How?

Answering the “How” will specify organizational structure of the study including distribution of responsibilities and resources. Decisions on the following aspects need to be made:

- Study design: cross-sectional, cohort etc.
- Sampling frame: how will participants be contacted?
- Timing and duration of the fieldwork: season, how many seasons?
- Involvement of individual participants in the study and any repeated involvement
- Manner to apply selected instruments (e.g. questionnaires)
- Collection and drop-off of samples, additional physical measurements
- Places where study will be conducted: hospital, participant homes, schools, etc.
- Incentives for participants: what kind is acceptable?
- Information on individual and general study results
- QA of the whole programme and single steps
- Pilot study: which instruments and processes should be tested.

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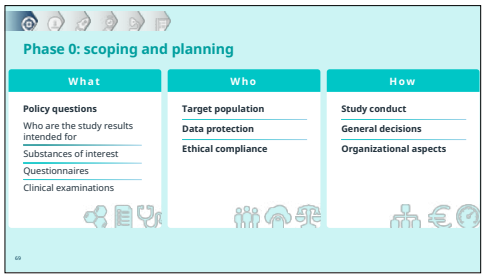


Organizational aspects

- Structure: study owner, principal investigator, project manager, managing team etc.
- Budget: allocation of material, financial and human resources
- Personnel and responsibilities: preparation of all written documents including study protocol, standard operating procedures for each instrument that is applied or developed, data management and communication materials
- Personnel for the fieldwork: nurses, professional interviewers, etc.
- Subcontracting: for fieldwork, laboratories.

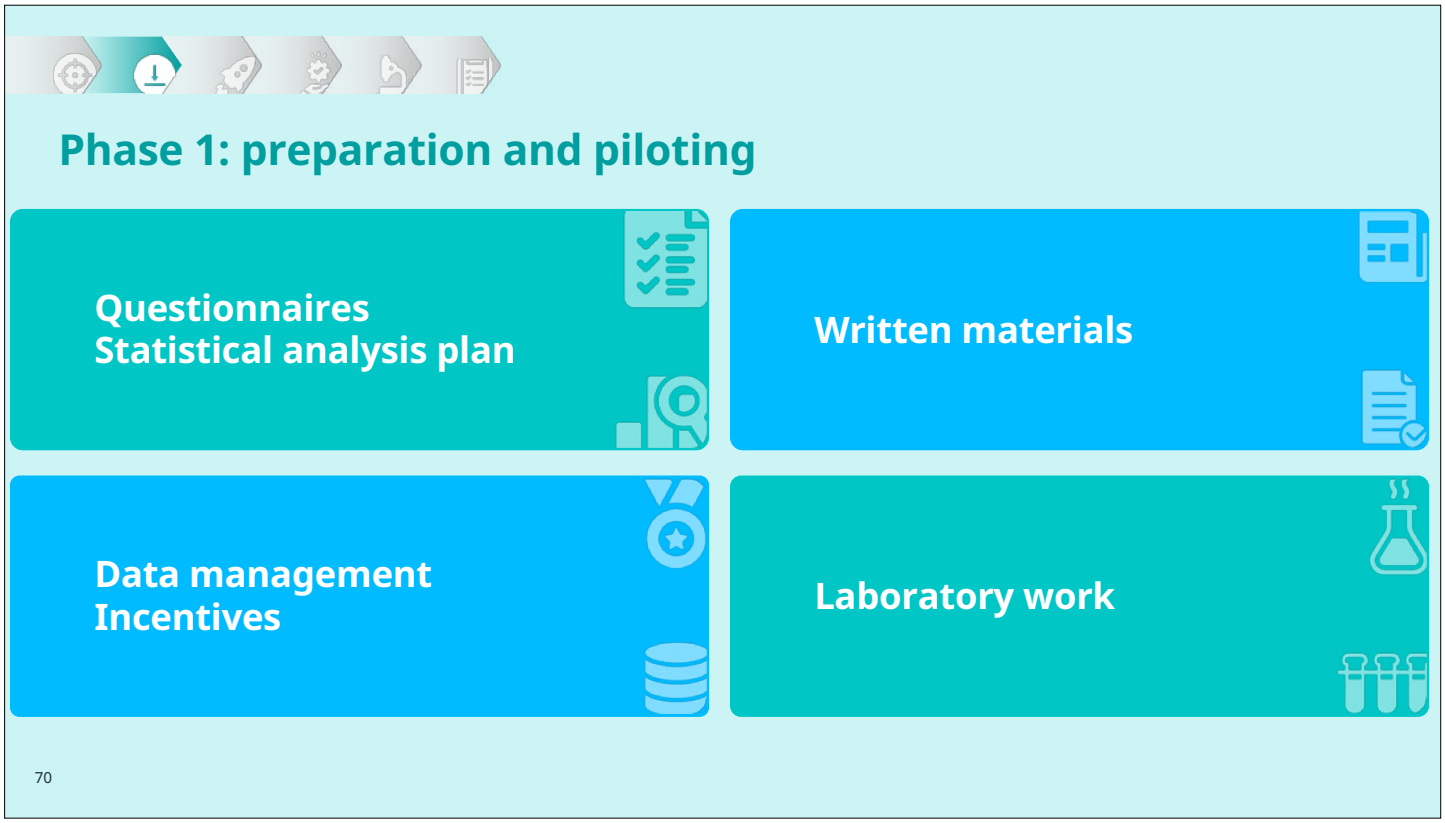
Notes: LOQ: limit of quantification; QA/QC: quality assurance/quality control.

Sources

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021 Mar;232:113684. doi: 10.1016/j.ijheh.2020.113684.

Exley K, Cano N, Aerts D, Biot P, Casteleyn L, Kolossa-Gehring M et al. Communication in a human biomonitoring study: focus group work, public engagement and lessons learnt in 17 European countries. Environ Res. 2015;141:31–41. doi: 10.1016/j.envres.2014.12.003.

Kim Pack L, Gilles L, Cops J, Tolonen H, van Kamp I, Esteban-López M et. al. A step towards harmonising Human Biomonitoring study setup on European level: Materials provided and lessons learnt in HBM4EU. Int J Hyg Environ Health. 2023;249:114118. doi: 10.1016/j.ijheh.2023.114118.



The following aspects should be developed in the preparation phase.

Questionnaires and statistical analysis plan

- If possible, use validated questionnaires.
- Tested with volunteers is recommended to validate them and to assess the time needed for completion of a questionnaire. This is also relevant for determination of the participant burden, which is of interest for ethic committees.
- A statistical analysis plan should justify questions in the questionnaires.

Set up and/or finalization of written materials

- Study protocol, standard operating procedures.
- Ethical and data protection materials necessary for approval by the ethics committee.
- Communication materials for study participants with information about the study (information leaflets, flyers and so on) and for other stakeholder groups (such as the public or policy-makers)
- Instructions for sampling (handling and storage of the samples such as urine samples).
- Interview guide (explaining the questions for interviewers and/or participants).
- The background information for study participants (e.g. frequently asked questions).
- Translations into different languages if necessary.
- Fieldwork manual.

Data management and incentives

- Data management plan.
- Database for the contact details and recruitment.
- Database for questionnaire data and analytical results.
- Incentives (design or purchase them, prepare a reception sheet).

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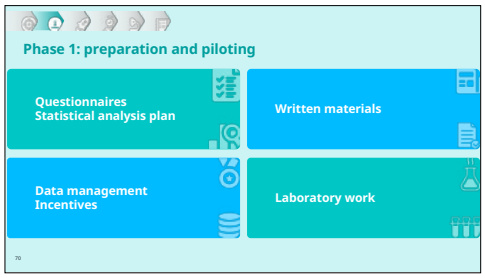
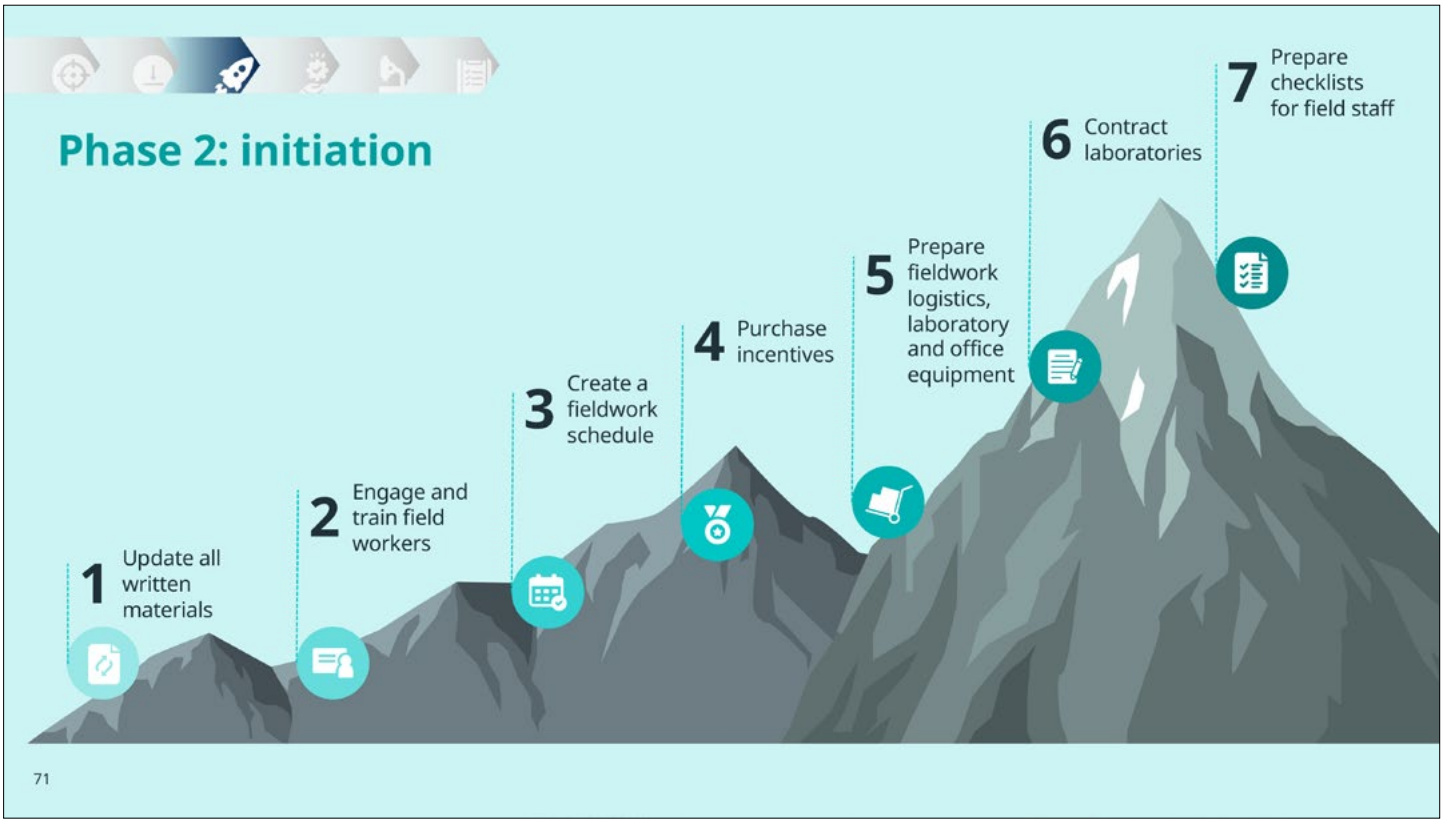


Laboratory work

- Contact and select laboratories.
- Test materials (tubes, vessels, labels) for sample collection on their usability.
- Develop a sample reception protocol for the laboratories that controls the integrity of the packaging and conditions of the samples. General data protection should also be taken into account.
- Create a database of aliquots: include sample ID code, aliquot ID code, sampling date, freezing date, type of sample, remaining aliquots, location in the biobank, and any other relevant material.

Sources

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021;232:113684. doi: 10.1016/j.ijheh.2020.113684.



Phase 2 includes among others purchase of materials; final decisions on the fieldwork, including time schedule, fieldwork logistics; contracting laboratories; and data management.

Training workshops need to be organized for field staff. The fieldworkers should receive hands-on training, copies of SOPs and checkout lists that include all necessary materials and devices for a study visit need to be prepared for field staff.

Notes: SOP: standard operating procedure.

Sources

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021;232:113684. doi: 10.1016/j.ijheh.2020.113684.

Fiddicke U, Becker K, Schwedler G, Seiwert M. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.

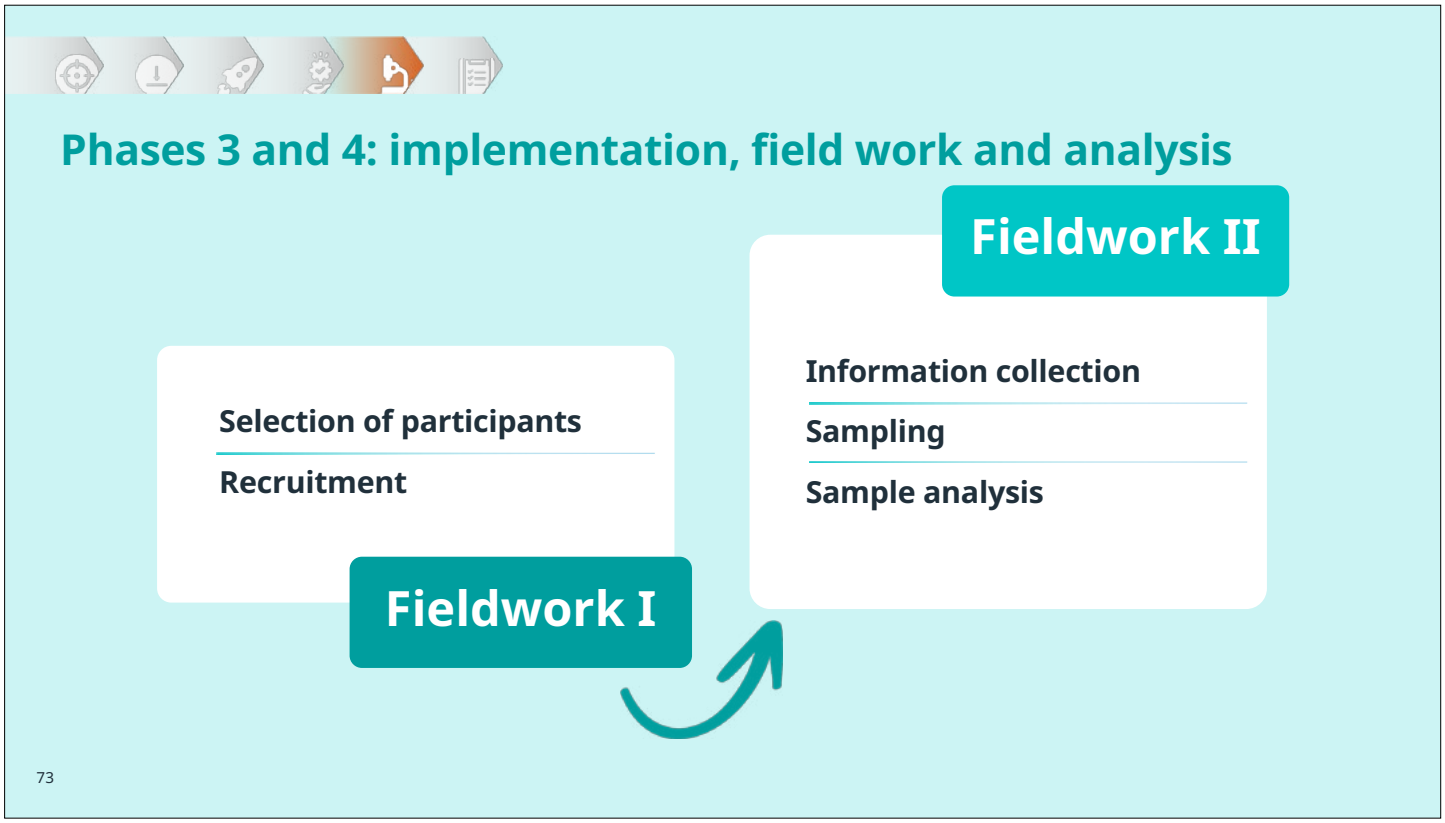
Phase 3 begins with the general recruitment that means:

- Invitations are sent to all people in the target population.
- Confidentiality of data is considered by transferring contact details of individuals into the prepared database and assigning a study-specific ID number to each participant.
- Initiatives to raise awareness for the study are started and communication with target population and the public at the sampling location is initiated to increase the participation rate.
- The study location is prepared for the participants: rooms for examination of participants and for the field staff.

Sources

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021;232:113684. doi: 10.1016/j.ijheh.2020.113684.

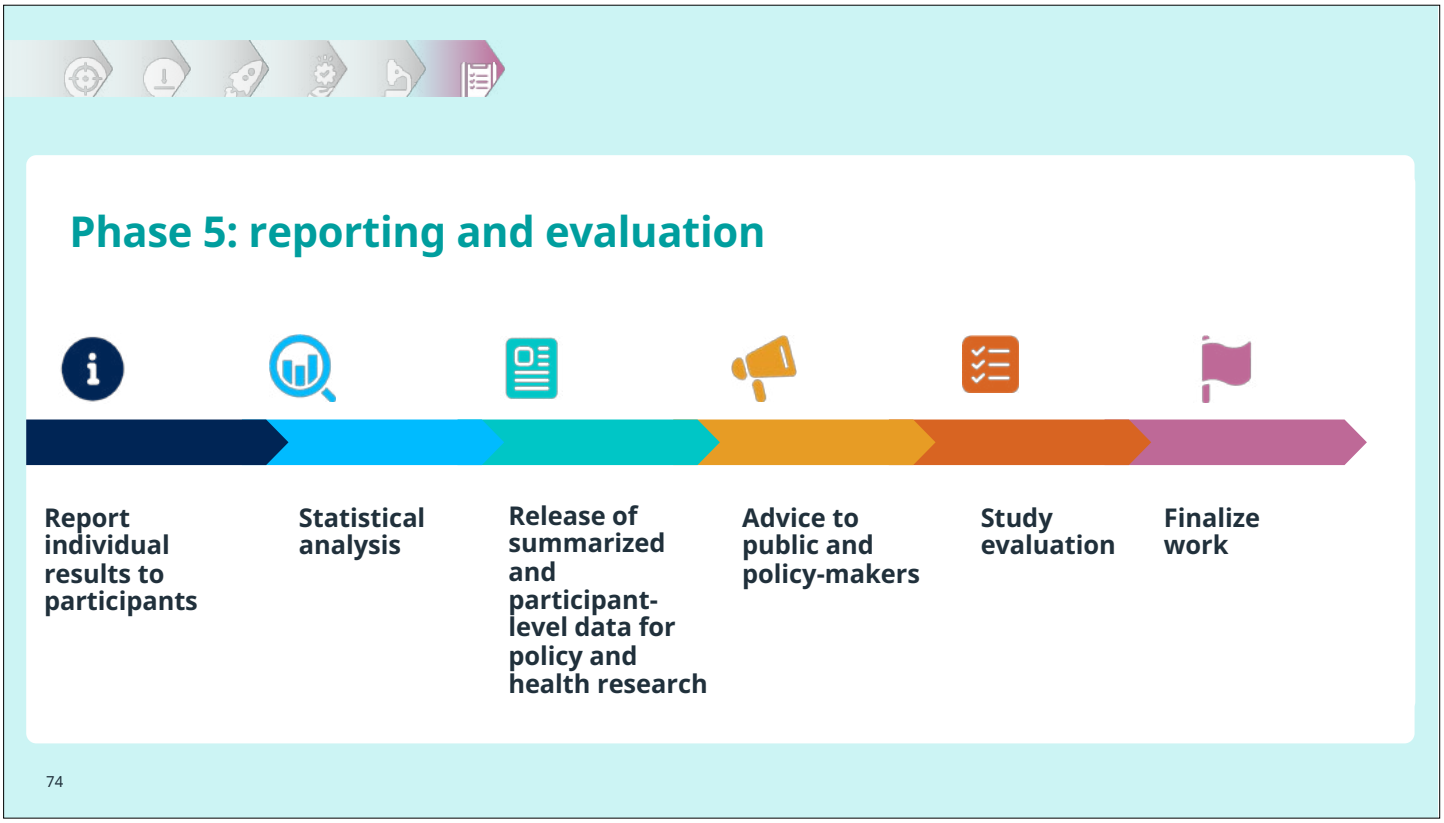
Fiddicke U, Becker K, Schwedler G, Seiwert M. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.



Sources

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021;232:113684. doi: 10.1016/j.ijheh.2020.113684.

Fiddicke U, Becker K, Schwedler G, Seiwert M. Lessons learnt on recruitment and fieldwork from a pilot European human biomonitoring survey. Environmental Research. 2015;141:15-23. doi: 10.1016/j.envres.2014.08.039.



Participants should be given access to their individual results, preferably accompanied by an explanation if their values raise concern. Generally, in this phase the following steps should be considered:

- statistical data analysis according to research questions
- advice to the public and policy-makers
- evaluation and lessons learned
- completion of the survey (results dissemination and communication).

Sources

Fiddicke U, Pack LK, Tolonen H, Sepai O, López ME, Castaño A et al. A phased approach for preparation and organization of human biomonitoring studies. Int J Hyg Environ Health. 2021;232:113684. doi: 10.1016/j.ijheh.2020.113684.

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Health-related Environmental Monitoring, German Environment Agency, Germany

MODULE

5

Laboratory analysis, data management

QA/QC

Biobanking

Data management and analysis

World Health Organization

European Region

QA and QC

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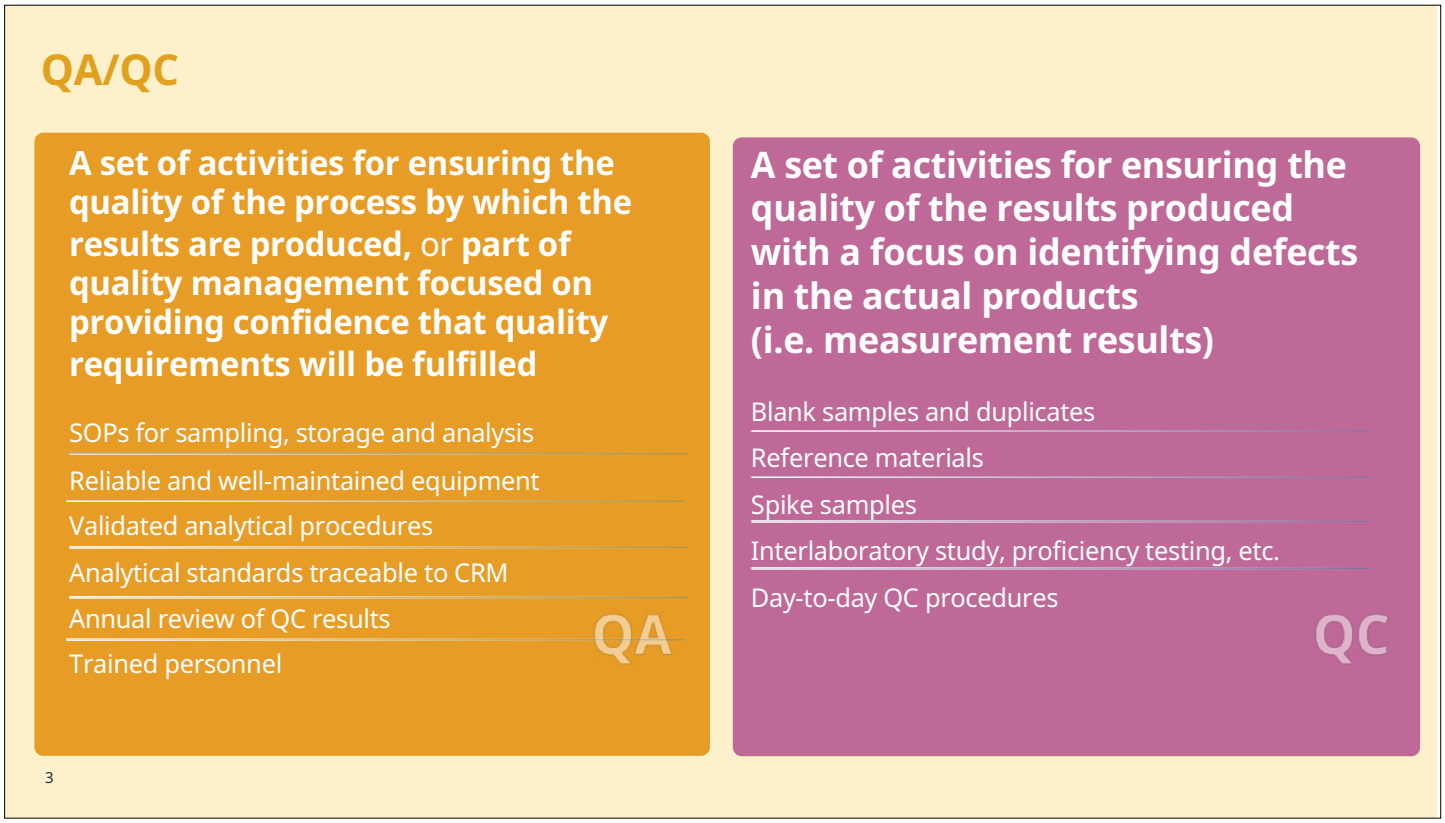

Notes: CRM: certified reference material; QA/QC: quality assurance/quality control; SOPs: standard operating procedures.

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

Barwick V, editor. EURACHEM/CITAC Guide to quality in analytical chemistry: an aid to accreditation, third edition. Gembloux: Eurachem; 2016 (https://www.eurachem.org/images/stories/Guides/pdf/Eurachem_CITAC_QAC_2016_EN.pdf, accessed 16 May 2023).

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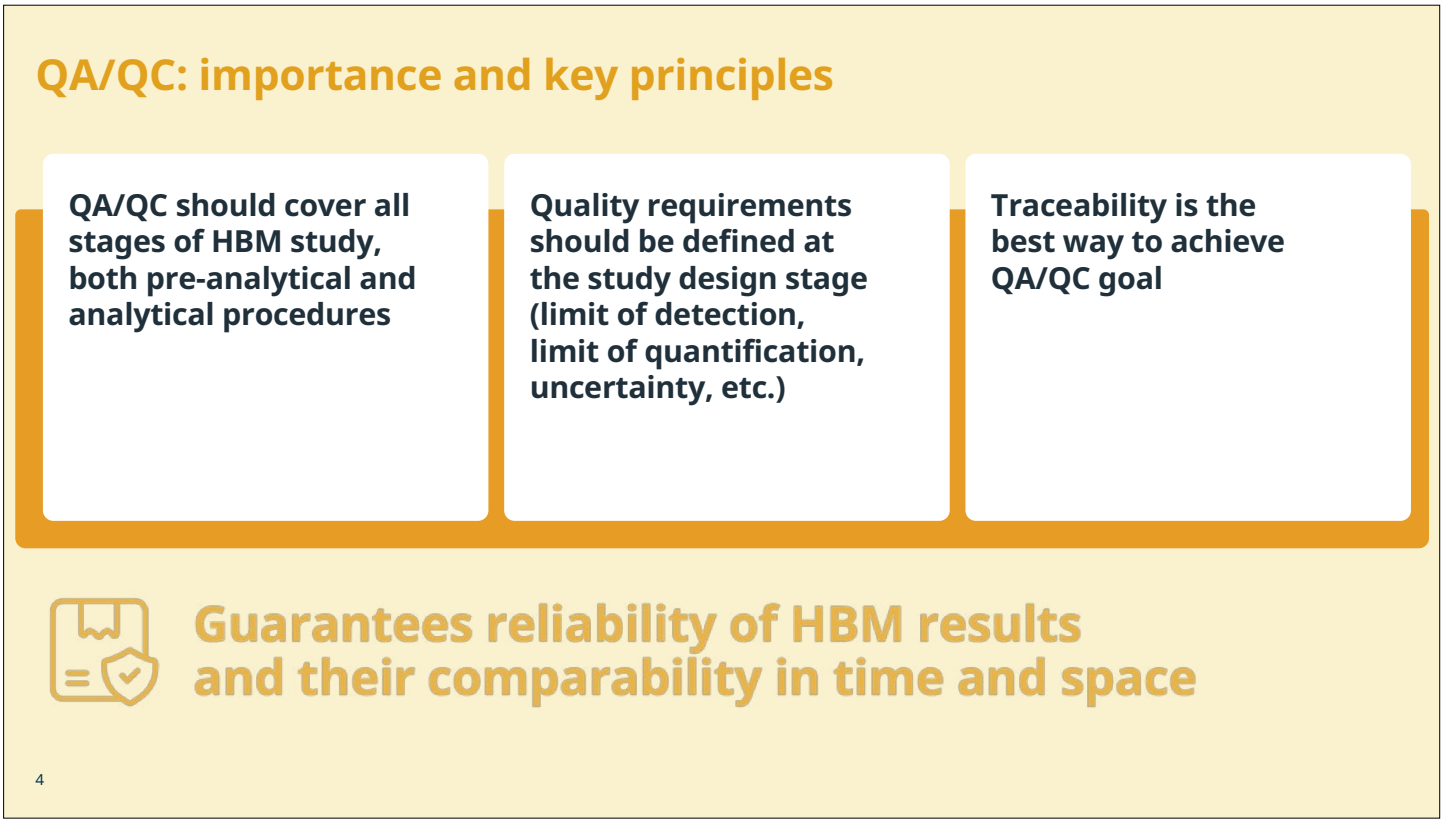

In HBM studies, laboratory analytical performance needs to be considered at the stage of selection of biomarkers and identification of the number of study subjects and the stage of interpretation of analytical results. Measurement traceability (metrological traceability) is a cornerstone of any measurement result.

Notes: HBM: human biomonitoring; QA/QC: quality assurance/ quality control.

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

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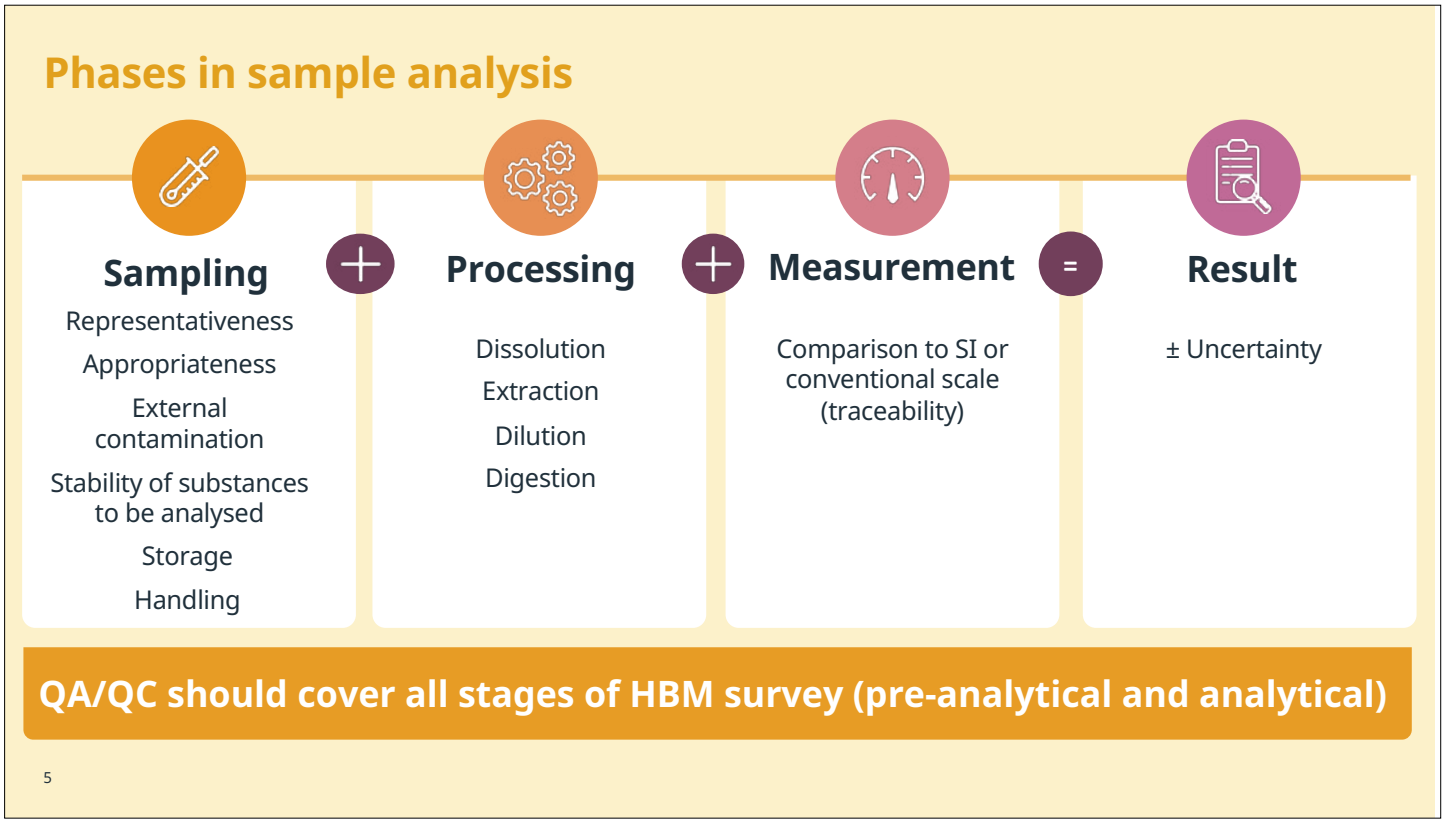

QC measures are critical at the analytical phase to prevent external contamination of samples. Control measures in pre-analytical stages of HBM study (sample collection and processing) are often paid less attention despite being equally, or even more, important from a QC standpoint. All the precautions and control measures taken during chemical analysis are useless if the samples have been contaminated or altered during sampling, transport or processing.

Possible sources of external contamination are:

- exogenous contamination at the sampling location;
- contamination by field or laboratory staff during handling;
- contamination from the sampling equipment or vessels (contamination due to leaching of the components to be analysed from the walls of the vessel employed); or
- concentration in the sample decreased through absorption/adsorption of the components to be analysed into the walls of the vessel employed.

Notes: HBM: human biomonitoring; QA/QC: quality assurance/ quality control; SI: the International System of Units.

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).

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Validation of analytical procedure: basic parameters (I)

Accuracy = precision + trueness

Accuracy describes the measure of exactness of an analytical method

Precision is the measure of the degree of repeatability of an analytical method under normal operation; it shows how close results are to one another

Trueness is closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value

6 *Source*: Accuracy of the measurement of a target grouping according to BIPM and ISO 5725 (Kartoglu; http://epela.net/illustrated/images_big/03.html). Reproduced under CC BY NC SA 4.0 licence (https://creativecommons.org/licenses/by-nc-sa/4.0/).

There are certain characteristics related to validation of analytical procedures.

Precision usually refers to repeatability and/or reproducibility of measurements in an analytical method under normal operation, estimated through the standard deviation of replicate measurements.

Trueness is estimated by:

- using certified reference materials
- using reference materials or in-house materials
- using reference methods
- using results from proficiency testing
- using spiked samples.

Accuracy is closeness of agreement between a measured quantity value and a "true" quantity value of a measurand.

Two more parameters are important for analysis and interpretation of results.

LOD is the lowest amount of the analyte that can be detected by the method at a specified level of confidence. It is usually calculated as the value in a blank sample +3 times the standard deviation of 10 measurements of a blank sample.

LOQ is the lowest concentration of analyte that can be determined with an acceptable level of uncertainty and can, therefore, be set arbitrarily as the required lower end of the method working range. It is usually calculated as the value in a blank sample +10 times the standard deviation of 10 measurements of a blank sample.

Notes: LOD: the limit of detection; LOQ: the limit of quantification.

Sources

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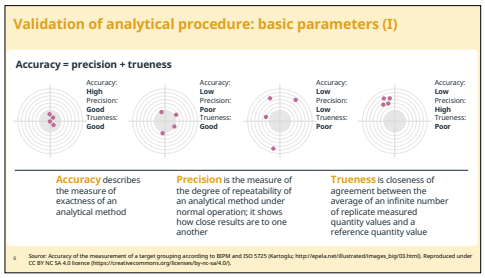

4 Source: Accuracy of the measurement of a target grouping according to BIPM and ISO 5725 (Kartoglu, http://epela.net/illustrated/images_big/03.html). Reproduced under CC BY NC SA 4.0 licence (https://creativecommons.org/licenses/by-nc-sa/4.0/).

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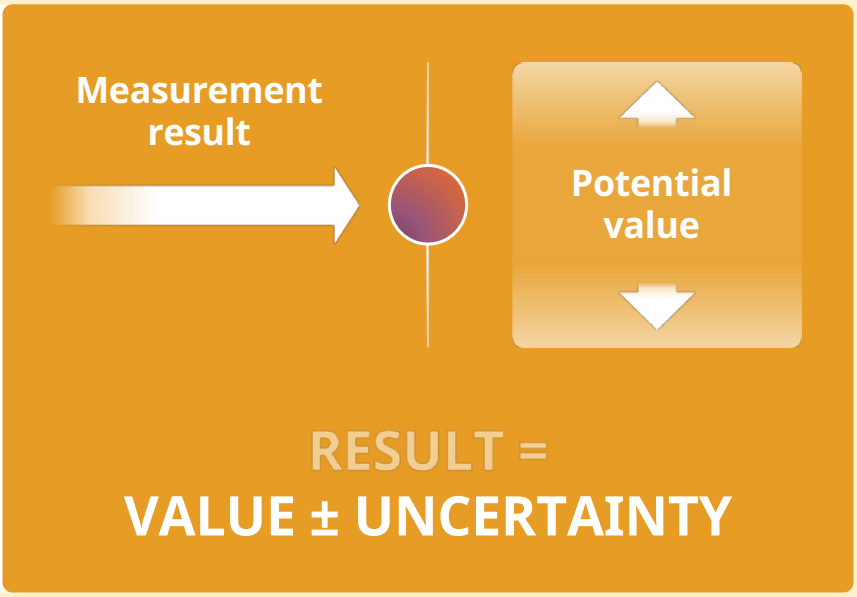
Validation of analytical procedure: basic parameters (II)

Measurement uncertainty is a parameter, associated with the result of a measurement, that characterizes the dispersion of the values that could reasonably be attributed to the measurand

The result of a measurement is only an approximation or estimate of the value of the measurand and, therefore, is complete only when accompanied by a statement of the uncertainty of that estimate



7

An estimation of the difference between the measured value and the true value is one of the most complex elements of method validation. A measurement begins with an appropriate specification of the measurand, the method of measurement and the measurement procedure.

There are different expressions for uncertainty:

- standard uncertainty: uncertainty of the result of a measurement expressed as a standard deviation;
- type A evaluation of uncertainty: method of evaluation of uncertainty by the statistical analysis of series of observations;
- type B evaluation of uncertainty: method of evaluation of uncertainty by means other than the statistical analysis of series of observations;
- combined standard uncertainty: standard uncertainty of the result of a measurement when that result is obtained from the values of several other quantities;
- expanded uncertainty: quantity defining an interval about the result of a measurement that may be expected to encompass a large fraction of the distribution of values that could reasonably be attributed to the measurand; and
- coverage factor: a numerical factor used as a multiplier of the combined standard uncertainty in order to obtain an expanded uncertainty.

Sources

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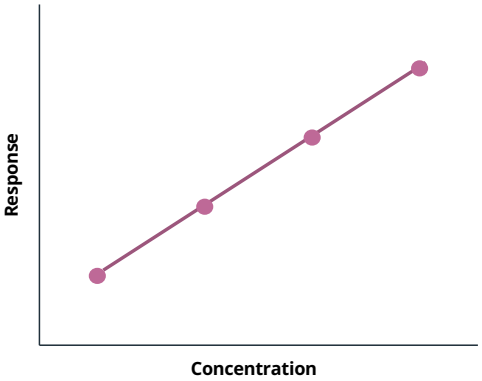
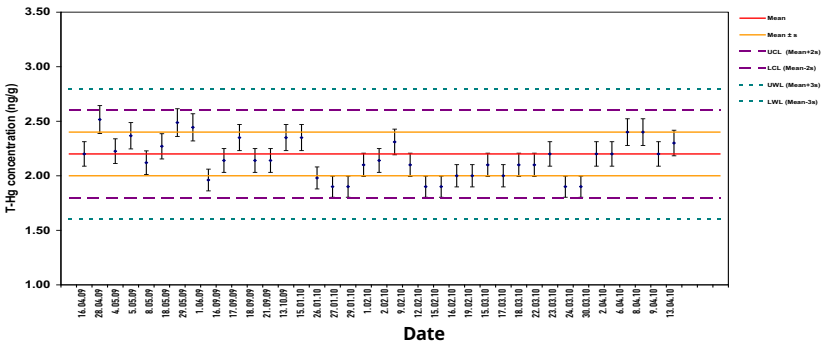
Standards and reference materials

Used for calibration and assessment of a measurement procedure (validation) and QC

Used for a single purpose in a given measurement (e.g. cannot be used for both calibration and validation of results in the same procedure)





Calibration
Use of calibration standards, certified standards

Validation
Use of reference material in daily practice (QC chart)

8 *Source*: WHO, 2018.

Laboratories involved in HBM should use appropriate measurement standards and other material for calibration and control of their measurement processes (different terms are used, sometimes interchangeably: standards, RM, CRM, certified standards, calibration standards, working standards, primary standards).

RM. This is material that is sufficiently homogeneous and stable with respect to one or more specified properties and that has been established to be suitable for its intended use in a measurement process. Appropriate RMs can provide valuable information, within the limits of the uncertainty of the RM's certified value(s) and the uncertainty of the method being validated. RMs must be within the scope of the method in terms of matrix type, analyte concentration and so on, and ideally a number of RMs covering the full range of the method should be tested. The uncertainty associated with an RM should be no greater than one third of that of the sample measurement.

CRM. This is a reference material characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that states the value of the specified property, its associated uncertainty and its metrological traceability.

Purity of an RM. A pure substance is used as RM for calibration of the measurement stage of a method. The uncertainty associated with RM purity will contribute to the total uncertainty of the measurement. For example, an RM certified as 99.9% pure, with an expanded uncertainty (k = 2) of 0.1% will contribute an uncertainty component of 0.1% to the overall measurement uncertainty budget.

Laboratories need to demonstrate that their use of measurement standards is indeed both appropriate and sufficient.

Notes: CRM: certified reference material; HBM: human biomonitoring; LCL: lower control limit; LWL: lower warning limit; QC: quality control; RM: reference material; s: uncertainty; UCL: upper control limit; T-Hg: total mercury; UWL: upper warning limit.

Sources

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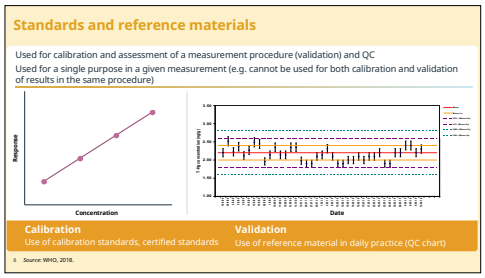

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Interlaboratory comparison

The organization, performance and evaluation of measurements or tests on the same or similar items by two or more laboratories in accordance with predetermined conditions, in order to:

- confirm the laboratory competence and check the ability of the laboratory to deliver reliable results (proficiency testing)
- identify problems in laboratories and initiate actions for improvement
- find out whether a certain analytical method performs well and is fit for its intended purposes
- guarantee comparability of analytical results from different laboratories

Can be organized at

national or international level

Laboratories involved in official control activities are required to

provide evidence for their competence in carrying out testing (to be accredited)

9

Interlaboratory comparison is an assessment of the organization, performance and evaluation of tests on the same or similar test items by two or more laboratories in accordance with predetermined conditions for laboratory testing performance.

The proficiency test is an evaluation of participant laboratory performance against pre-established criteria by means of interlaboratory comparisons.

Purposes for proficiency testing in interlaboratory comparisons also include:

- evaluation of the performance of laboratories for specific tests or measurements
- provision of additional confidence to laboratory customers
- identification of interlaboratory differences
- education of participating laboratories based on the outcomes of such comparisons
- validation of uncertainty claims.

Sources

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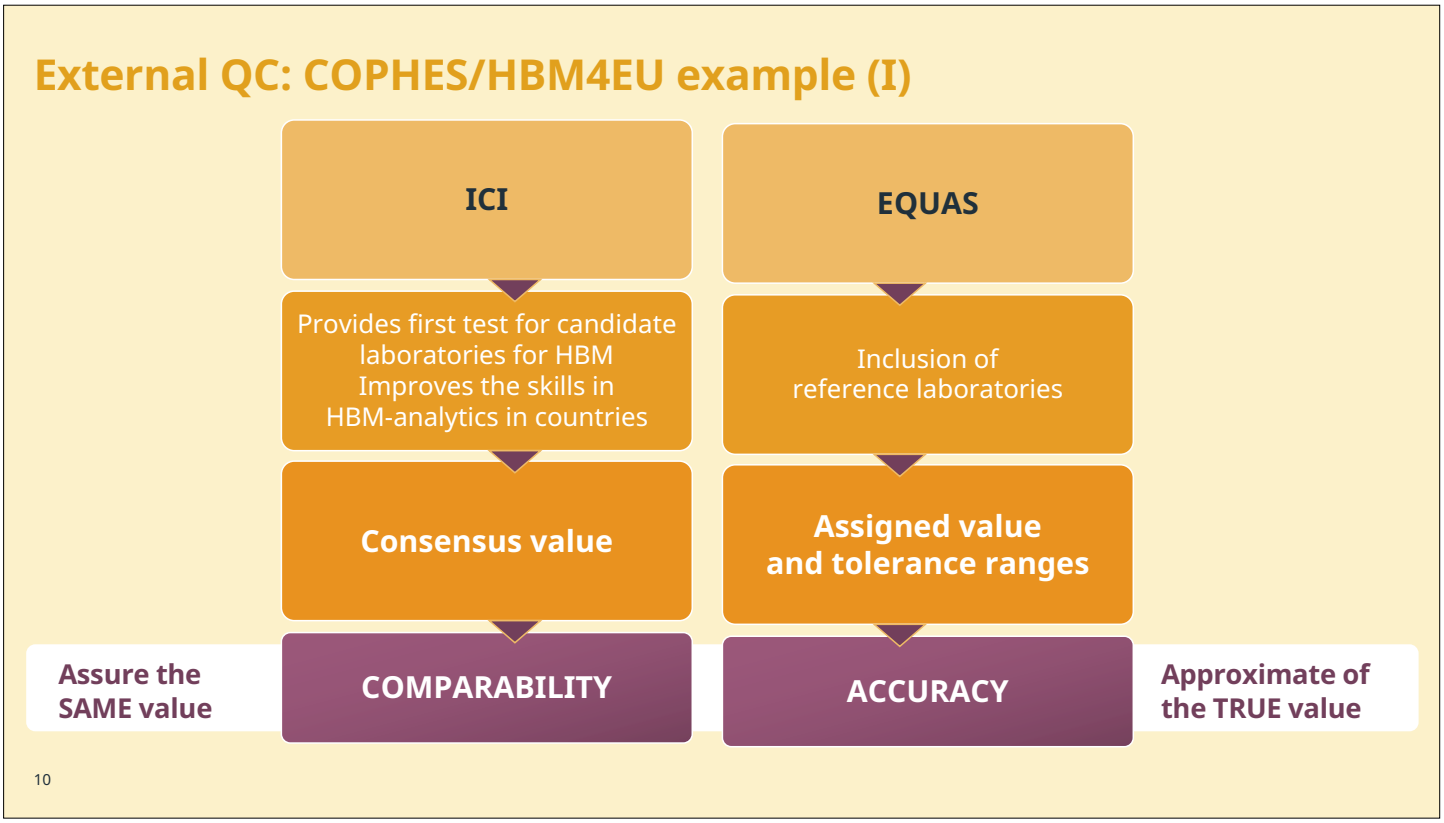

External QC is one of the basic requirements in QA/QC procedures. The analytical laboratory should participate in sample exchanges and certification programmes.

The QA programme for each selected biomonitoring parameter should include at least three proficiency tests:

- one ICI and two EQUAS test; or
- two ICI's and one EQUAS test/run.

The sequence can be expanded by additional runs if a poor or unsatisfactory comparability is found in the runs executed.

Notes: COPHES: Consortium to Perform Human Biomonitoring on a European Scale; EQUAS: external Quality Assessment Scheme; HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative; ICI: intercomparison investigation; QA/QC: quality assurance/quality control.

Sources

The quality assurance/quality control scheme in HBM4EU projects. In: European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5b62ef261&appId=PPGMS, accessed on 16 May 2023).

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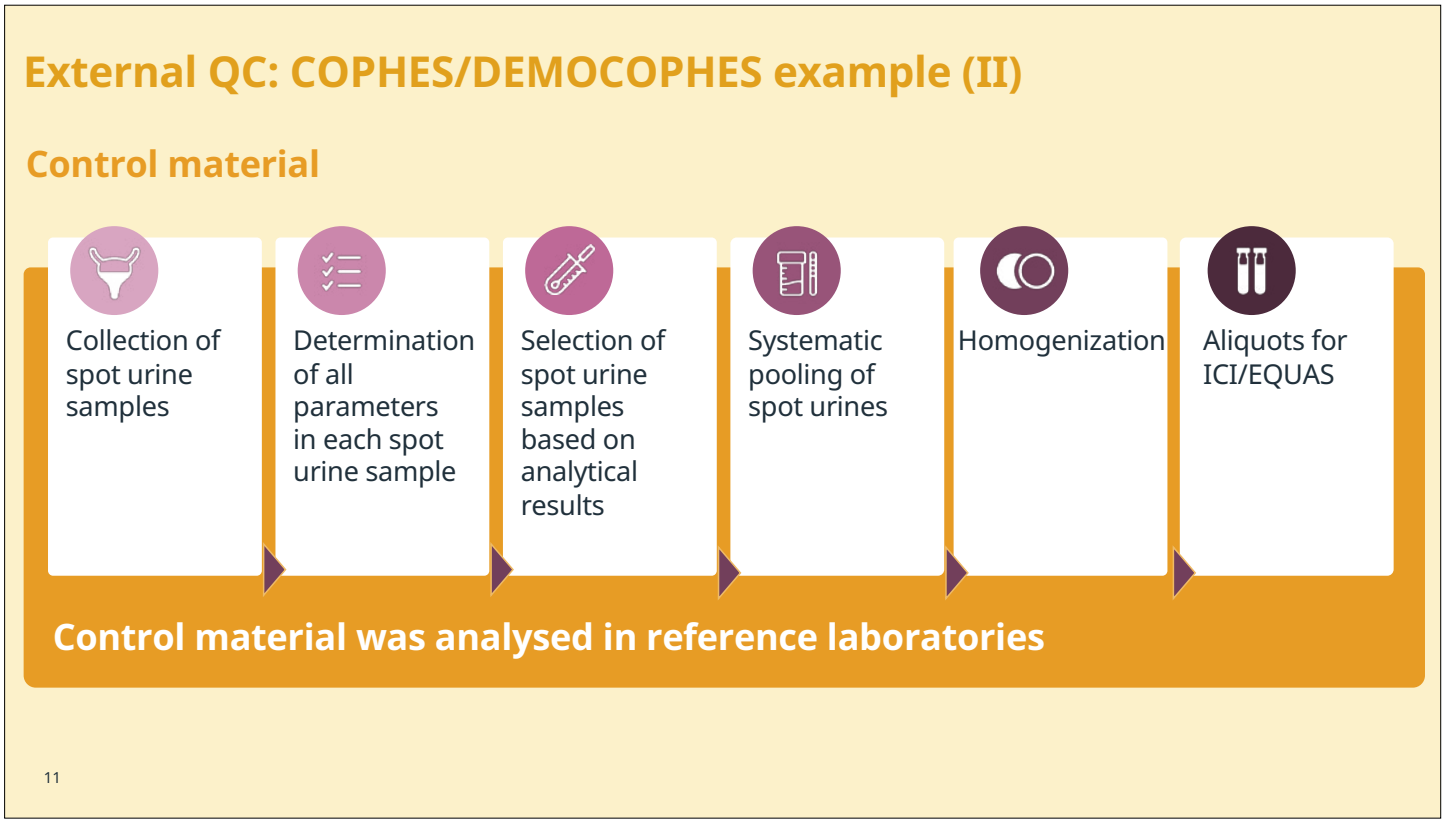

Materials for ICI and EQUAS tests are produced by the ICI/EQUAS organizers or must be purchased by them.

To ensure evident information for QA of HBM analyses, the materials for the ICI/EQUAS runs should be prepared based on human materials or adequate surrogates. However, the use of native biological materials implies unknown or unpredictable native background levels of the HBM parameter.

The control material is extensively tested for stability and homogeneity of the materials that have to be tested before distribution to the laboratories that participate in the ICI/EQUAS application. Each ICI/EQUAS material should be sent in triplicate with hidden attribution to the exercise participants.

Notes: COPHES: Consortium to Perform Human Biomonitoring; DEMOCOPHES: Demonstration of a Study to Coordinate and Perform Human Biomonitoring on a European Scale; EQUAS: external Quality Assessment Scheme; HBM: human biomonitoring; ICI: intercomparison investigation; QA: quality assurance.

Sources

The quality assurance/quality control scheme in HBM4EU projects. In: European Human Biomonitoring Initiative. Deliverables [website]. Brussels: European Commission; 2023 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5b62ef261&appId=PPGMS, accessed on 16 May 2023).

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Traceability of samples: the pathway of sampling–interim storage–transportation–laboratory

Accompany documents include:

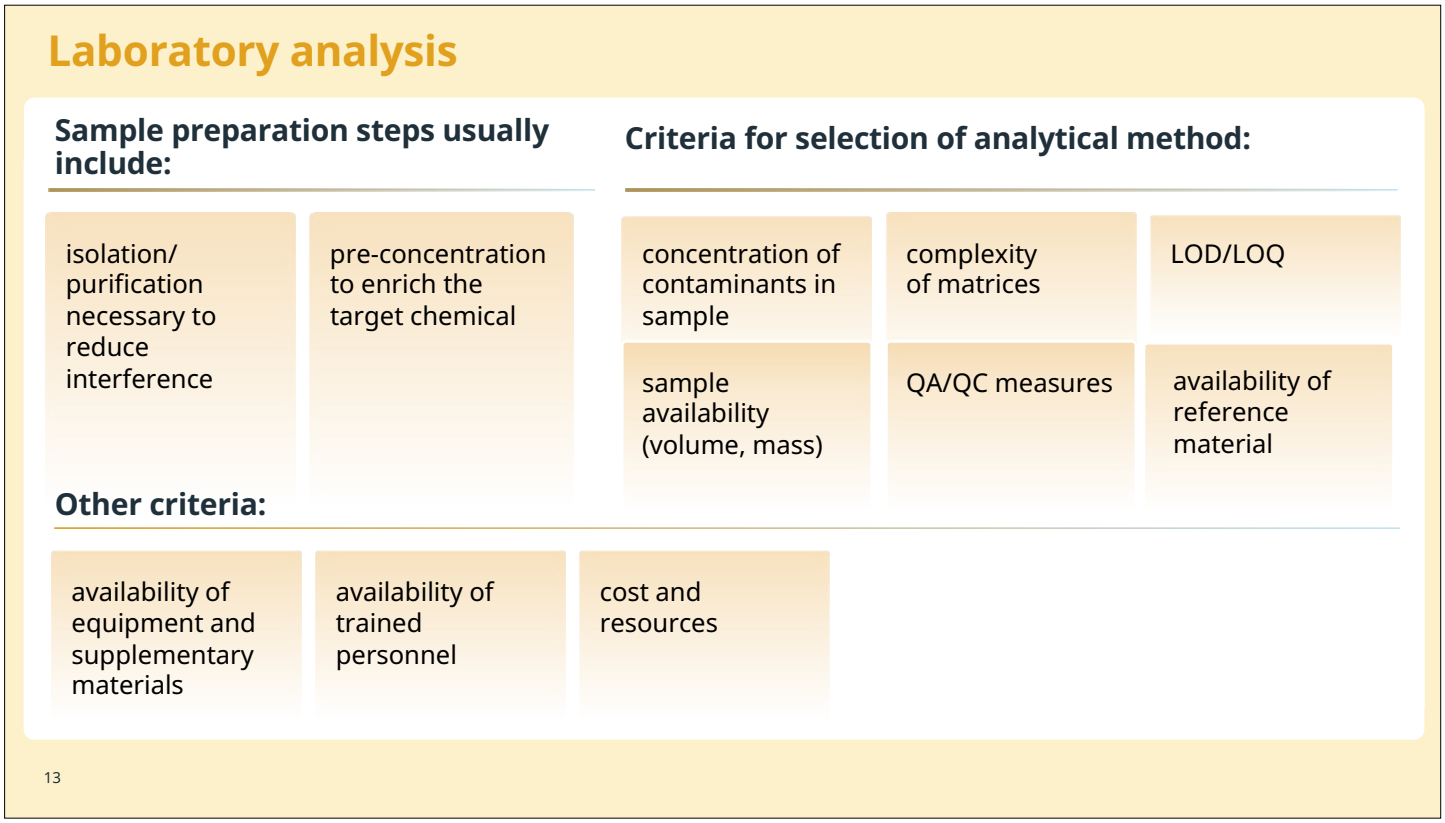
- **sampling questionnaire**
- information on **interim storage condition**
- information on **transportation conditions**
- aliquoting of sample

Labelling of samples

12

Sources

WHO Regional Office for Europe & United Nations Environment Programme. Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 13 May 2023).



Notes: LOD: the limit of detection; LOQ: the limit of quantification; QA/QC: quality assurance/quality control.

Sources

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Normalization of biomarkers
if needed

Question	Urine	Blood
Why?	To make results independent of urinary dilution (water intake)	Individuals with higher lipid concentrations tend to have proportionally higher concentrations of lipid-soluble contaminants
What?	Important for urine to avoid variations during a day and between people	A correction for blood lipid content should be considered in case of lipid-soluble contaminants (e.g. brominated flame retardants, per/poly-fluoroalkyl substances)
How?	Creatinine excretion (g/L or mmol/L) Osmolality (Osm/kg or mOsm/kg) SG (ratio of densities)	Estimation of total lipids in blood: • enzymatic method • gravimetric method

14

In some cases, the concentrations of biomarkers measured in the biological samples should be adjusted after the chemical determinations. Measurements performed in urine samples are influenced by the urinary dilution level. Therefore, the concentrations of chemicals in urine are usually normalized for dilution (the ratio of the density of a substance in urine to the density of a reference substance in distilled water) using creatinine-based normalization or SG, the latter being more reliable. Creatinine levels in urine vary depending on sex, age, body mass index, fat-free mass and race/ethnicity, and this method is not suitable for children.

For lipophilic compounds, such as dioxins, variability in serum lipid concentrations can be accounted for by expressing results as “concentration of chemical per gram of serum lipids”.

Notes: SG: specific gravity.

Sources

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Storage of biological samples (in laboratory)

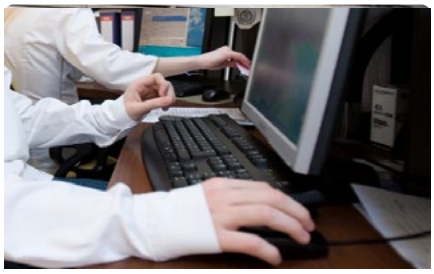
Standardized storage conditions

Preservation of high-quality/homogenized sample

Traceability of individual aliquots

Transparent sample record: from source, sampling, treatment and storage history

Linkage to other collected data



15

In case that longer archiving is needed then consideration in a biobank might be more viable/safer in order to prevent cross-contamination but also correct preservation of the sample and broader access to its use.

Sources

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Biobanking

What is a biobank?

- Obtains biological materials for future use of these materials in research
- Storage tool: physical (building with facilities and samples), with data and logistic/management infrastructure for environmental and/or biological and human samples (specimens)
- Supports many types of contemporary research (exposomics, RA, trends analysis, etc.)
- Important resource in medical research but also wider (nature sciences)
- Biobanking is a tool supporting HBM expansion and further use of data
- Applicable in exposome research
- Supports interdisciplinary collaboration and establishment of international infrastructures (e.g. BBMRI and ISBER)
- Biobanking is overseen by government agencies or research organizations
- Undergoes harmonization: best practices and guidelines (scientific, ethical, technical and legal)

17

A biobank is a biorepository that stores biological samples (usually human) and/or other specimens (environmental, biological) for use in research and evidence-informed decision-making. Biobanking is important for understanding of exposure, trends, risks and of factors affecting human health.

Biobanking needs a special facility for archiving samples over a long term. It is aiming to support not only the present but also future monitoring activities and the banking activity is expected to have a wider scope.

Selection and collection of samples for biobanking should be designed carefully so that a minimum set of archived samples will provide an unbiased view of the levels of pollutants in humans and the environment.

Notes: BBMRI: Biobanking and Biomolecular Research Infrastructure; HBM: human biomonitoring; ISBER: International Society for Biological and Environmental Repositorie; RA: risk assessment.

Sources

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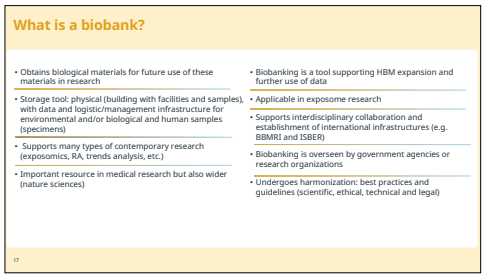

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Biobanking

Ethical issues

- Permission is needed to store material in a biobank from an ethical committee and the donor
- Consent for a particular use or a broad consent for unspecified future use must be obtained from the donor when the material is entered into the biobank
- When biological materials and related data (e.g. health or employment records) are stored, institutions must have a governance system to obtain authorization for future use of these materials in research
- Researchers must not adversely affect the rights and welfare of the donors from whom materials were collected
- Custodians of biological materials must arrange protection for the confidentiality of information linked to the materials by sharing only anonymized or coded data with researchers and limiting access by third parties. Key to the code must remain with the custodian

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The protocol for every study using stored human biological materials and related data must be submitted to a research ethics committee, which must ensure that the proposed use of the materials falls within the scope specifically agreed to by the donor, if the donor has given broad informed consent for future research. Donors or their legal representatives should be able to withdraw consent for maintenance and use of biological material stored in a biobank.

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What is stored in a biobank?

Samples for banking may be classified into:

human samples (different biological matrices)

biota samples (e.g short-lived organisms in lower trophic level, such as fishes; long-lived, higher-trophic level organisms, typically top predators like fish-eating birds other terrestrial, marine and limnic species (plants and animals)

environmental specimens and samples (e.g. soils, sediments, vegetation, passive compounds providing monitoring data)

19 biobank interior, © RECETOX archive 2021

Biobanks can contain more than just biological samples (unless the bank is specified for medical, clinical or radiological purposes).

Sources

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Biobank: examples

Swedish Museum of Natural History and the **National Aquatic Biological Specimen Bank/National Wildlife Specimen Bank** in Canada started as research projects and archive specimens

back to late 1960s/ early 1970s

The United States' **National Biomonitoring Specimen Bank** and Germany's **Federal Environmental Specimen Bank** were created as a pilot bilateral programme in the mid 1970s and shifted to a long-term programme

Japan has two environmental specimen banks archiving specimens back to 1960s: **es-BANK** (Environmental Specimen Bank in Ehime University), National Institute for Environmental Studies' **Environmental Time Capsule**

From the 1980s onwards, many other countries creating biobanks:

- Yangtze ESB and Kadoorie Biobank
- IFREMER and ANDRA
- ESB
- Antarctic Environmental Specimen Bank, Mediterranean Marine Mammal Tissue Bank
- Nordic ESB
- National Institute of Environmental Research
- ISCIII National Human Biobank; Biscay Bay Environmental Biospecimen Bank
- Fish Biobank, United Kingdom Biobank
- International Agency for Research on Cancer's IBB (>5 million human samples)

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The slide gives examples of biobanks but this is not an exhaustive list. Biobanks started as research projects in the late 1960s and early 1970s and archive specimens. There are many environmental specimen banks that also include human samples, some of which have been operated for HBM of chemical exposure.

Notes: ANDRA: French National Radioactive Waste Management; ESB: environmental specimen bank; IBB: biobank of International Agency for Research on Cancer; IFREMER: national Institute for Ocean Science Research (France); ISCIII: Carlos III Health Institute (Spain).

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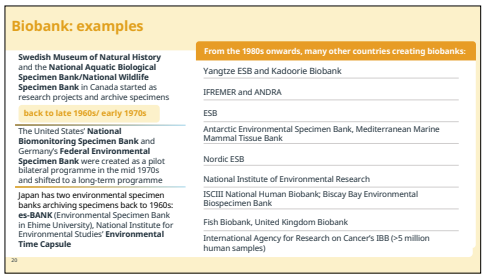

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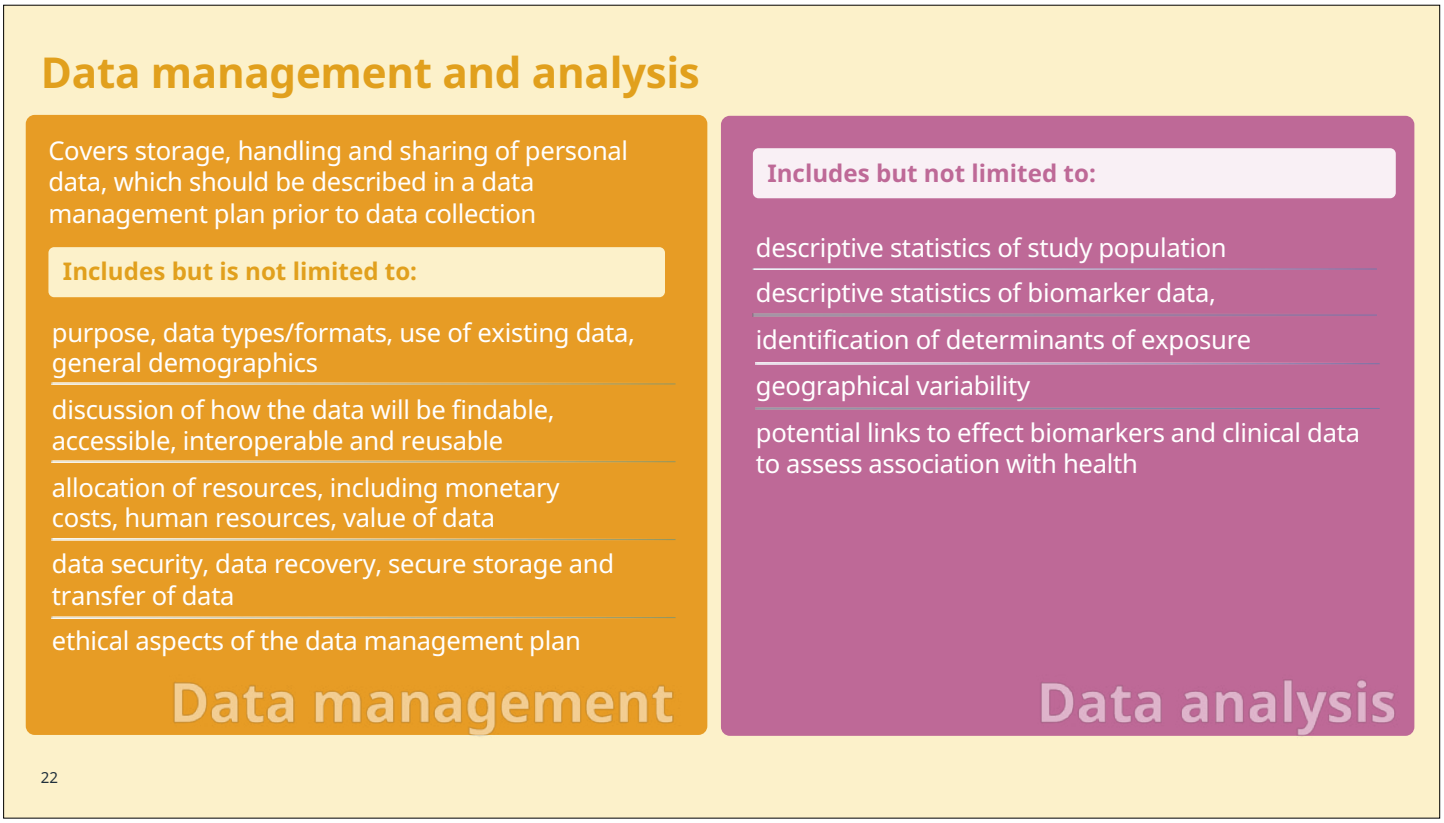
Data management and analysis

https://dreambroker.com/channel/674dr9pv/vflbozyn

Greet Schoeters

Professor Emeritus
University of Antwerp, Belgium



Data analysis includes management and analysis of the data obtained throughout the study from measurements of selected chemicals in the collected specimens and accompanying data obtained from questionnaires. Analysis of the data has the potential to identify major sources of exposure, geographical trends and risk factors and trends over time if there are several rounds of data collection. When connected with environmental monitoring data, multiple exposure sources can be quantified more accurately. Data analysis should allow to identify high exposure subgroups and to assess the risk for adverse health outcomes by comparison with health-based guidance values.

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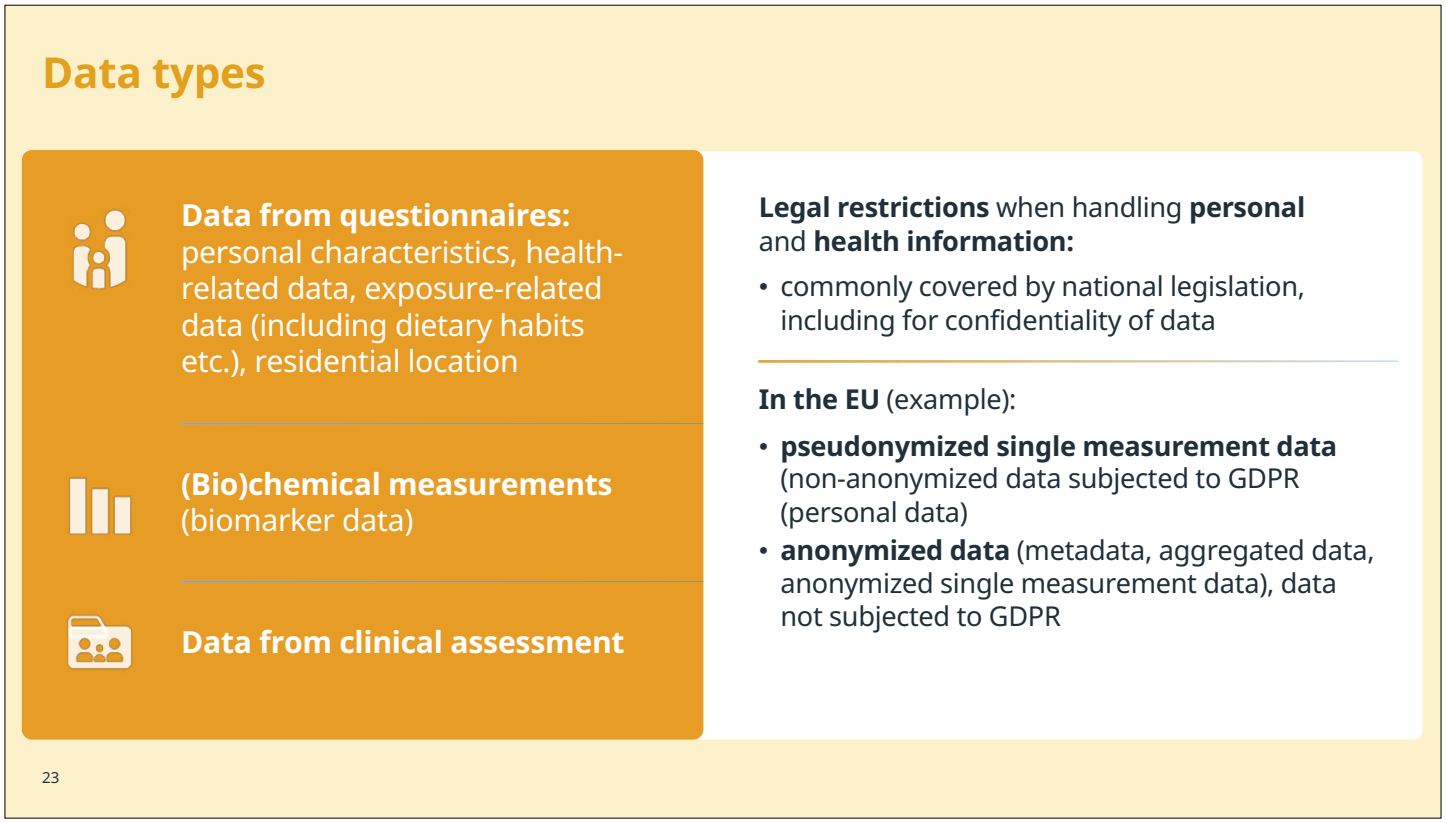

Commonly, data types in HBM include:

- data from questionnaires;
- chemical, biochemical or molecular measurements from collected specimens (blood, urine, hair, etc.);
- data from clinical assessment, including any type of assessment performed by a physician (e.g. physiological, cognitive and anthropometric measures)

Confidentiality and personal data protection are basic principles of data management.

For example, in the EU, data management is regulated by GDPR. Most of the data used in HBM is psedonymized. As defines in GDPR: “Personal data is any information relating to an identified or identifiable natural person (‘data subject”)”.

Pseudonymization means the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Anonymized data do not relate to an identified or identifiable natural person.

Metadata are data that define and describe other data, a series of structured information common to all the single measurement entries held in one data collection.

Aggregated data form a dataset of descriptive statistics calculated from single measurement data.

Notes: EU: European Union; GDPR: General Data Protection Regulation; HBM: human biomonitoring.

Sources

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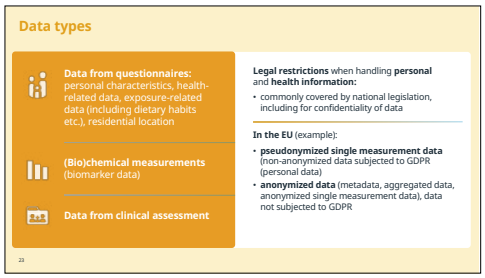

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Biomarker analysis

ID	HM_HG	HM_HG_Q	UM_CRT	UM_HG	UM_HG_Q	CB_HG	CB_HG_Q
xx001	0.181	> LOQ	1350	0.52	> LOQ	0.56	> LOQ
xx002	0.520	> LOQ	550	0.09	> LOQ	1.45	> LOQ
xx003	0.391	> LOQ	1150	0.24	> LOQ	0.86	> LOQ
xx004	0.336	> LOQ	1380	0.22	> LOQ	1.92	> LOQ
xx005	0.894	> LOQ	450	0.03	< LOQ	5.45	< LOQ
xx006	0.435	> LOQ	920	0.17	> LOQ	2.35	> LOQ
xx007	0.448	> LOQ	660	0.33	> LOQ	3.89	> LOQ
...	...	...	...	...	...	...	...

A data file with measurements of Hg in different matrix

Values below LOD or LOQ should be replaced by:

a fixed value, e.g. LOD/2 or LOD/√2, or

a single value (replacement with a specific number, e.g. between 0 and LOD), or

multiple imputation (similar to single imputation, but multiple datasets are imputed)

Two laboratory QC limits are commonly utilized to evaluate biomarker data:

LOD

the lowest analyte concentration likely to be reliably distinguished from the blank and at which detection is feasible

LOQ

the lowest concentration at which the analyte can be reliably detected where some predefined goals for bias and imprecision are met (usually determined by the laboratory conducting testing, LOQ ≥ LOD)

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The slide gives an example of a data file containing measurements of mercury in different biological specimens. Each raw entry represents one study subject coded by an unique ID number. Each column or raw entry represents a set of measurements of one parameter in the study subjects. Parameter (variable) name should also be unique and explained in a codebook.

Before statistical analyses are performed, certain treatments of data need to be done.

For the biomarker data, LOD or LOQ is usually given by the laboratory. Samples below LOD/LOQ can be dealt with by:

- complete case analysis, where observations with values below the LOD/LOQ are simply eliminated; this introduces bias by eliminating low values and is not recommended;
- replacement by fixed value, where every value below the LOD/LOQ is replaced by a constant such as LOQ/2 or LOQ/√2;
- single imputation provides the dataset with a specific number (e.g. between 0 and LOD) in place of the missing data points by analysing the other responses and looking for the most likely value that corresponds to that individual and then selecting one of those possible responses at random and placing it in the dataset; and
- multiple imputation, which is like single imputation but more complex as it imputes more than one dataset, setting the imputed values to fall between the interval (0 to LOD) to try to come up with a variance/confidence interval that can be used to better understand the differences between imputed datasets.

In cases where very few data points are missing, single imputation may be the simpler option and solve the issue without many serious errors.

Notes: CM-HG: mercury concentration in cord blood; CM-HG-Q: missing data on mercury concentration in cord blood; Hg: mercury; HM-HG: mercury concentration in maternal hair; HM-HG-Q: missing data on mercury concentration in maternal hair; LOD: the limit of detection; LOQ: the limit of quantification; QC: quality control; UM-CRT: mercury concentration in maternal urine adjusted to creatinine; UM-HG: mercury concentration in maternal urine; UM-HG-Q: missing data on mercury concentration in maternal urine

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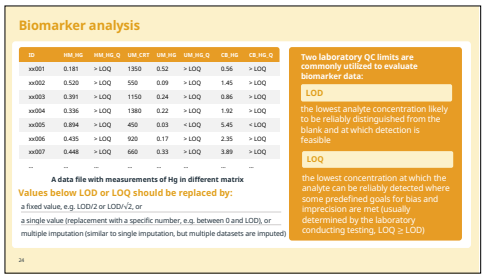

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Questionnaire data

Mercury exposure example

Data should be stored in a way to allow data handling and statistical analysis

ID	Xx001	Xx002	Xx003	Xx004	xx005	xx006	xx007	...
Location	1	...	...	...	...	...	...	...
Date_ interview	01/01/2017	...	...	...	...	...	...	...
date_ mother_birth	12/5/1986	...	...	...	...	...	...	...
date_ child_birth	30/12/2016	...	...	...	...	...	...	...
child_ gender	1	...	...	...	...	...	...	...
mother_ weight_kg	63	...	...	...	...	...	...	...
mother_ height_ cm	163	...	...	...	...	...	...	...
birth_ weight_ g	3995	...	...	...	...	...	...	...
education_ mother	5	...	...	...	...	...	...	...
source_ water	1	...	...	...	...	...	...	...
amalgam	1	...	...	...	...	...	...	...
No_ amalgam	4	...	...	...	...	...	...	...
Freq_seafood	5	...	...	...	...	...	...	...

Recoding categories

Combining variables

Categorizing continuous variables

Calculations

Treatment of missing data:

- multiple imputation
- maximum likelihood

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On the slide example, each raw data point represents one study subject coded by an unique ID number. Each column represents an information obtained through the questionnaire (one answer), which has unique name and is coded in a way to allow statistical analysis (e.g. 1 = male, 2 = female). Codes are provided in a codebook (discussed next).

Certain treatment of data may be needed before performing statistical analysis of questionnaire information. This includes recoding of categories and combining, categorizing and creating new variables, depending on the research questions posed (e.g. by age groups, according to specific variables, and so on).

To prevent loss of information or introduction of potential selection biases, most of the proposed analyses would need to impute missing data. This minimizes the loss of observations from the analysis and generally leads to less-biased results.

Two methods can be recommended to deal with missing data: multiple imputation (discussed in the earlier slide) and FIML. FIML is one of the best (and easiest) methods for dealing with missing data; it always produces the same result (does not introduce random variation) and it only requires a single model (so avoids any incompatibility of analysis and imputation models).

Notes: FIML: full information maximum likelihood.

Sources

Vrijheid M, Montazeri P, Rambaud L, Vogel N, Vlaanderen J, Remy S et al. HBM4EU deliverable D10.5: statistical analysis plan. Dessau-Roßlau: German Environment Agency; 2019 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5c2052c36&appId=PPGMS,, accessed 10 November 2022).

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Statistical analysis: descriptive analysis

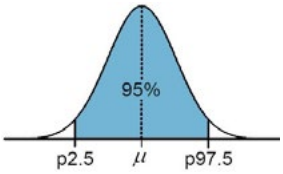
General population characteristics (age, sex, smoking, BMI, etc.)

Continuous variables:

- *N – sample size*
- Median, P25–P75 - *the value below 25%, 50%, 75%*
- Minimum–Maximum – *lowest and highest value of a variable*

Categorical/dichotomous:

- *N (%)*



Biomarkers data

- *N*
- *N* <LOD or N <LOQ – *number(%) of subjects with value above LOQ or LOD*
- Values below LOD or LOQ should be replaced by:
  - a fixed value, e.g. LOD/2 or LOD/√2
  - single (replacement with a specific number, e.g. between 0 and LOD)
  - multiple imputation (similar to single imputation, but multiple datasets are imputed) **(the preferred option)**
- Percentiles – the value of a variable below which a certain percent of observations fall (P5, P10, P25, P50, P75, P90, P95)
- AM ± SD
- GM and 95% CI
- RVs: P95 and 95% CI

26

Notes: AM: arithmetic mean; BMI: body mass index; CI: confidence interval; GM: geometric mean; LOD: the limit of detection; LOQ: the limit of quantification; RVs: reference values; SD: standard deviation.

Sources

Vrijheid M, Montazeri P, Rambaud L, Vogel N, Vlaanderen J, Remy S et al. HBM4EU deliverable D10.5: statistical analysis plan. Dessau-Roßlau: German Environment Agency; 2019 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5c2052c36&appId=PPGMS, accessed 10 November 2022).

Allison PD. Missing data techniques for structural equation models. J Abnormal Psych. 2003;112:545-57, https://doi.org/10.1037/0021-843x.112.4.545.

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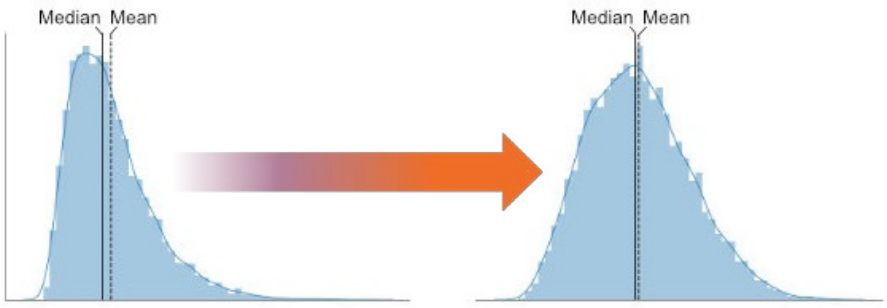
Data handling: transformation

Right-skewed data

Logarithmic transformation

Transforming non-normal data



Transforming right-skewed data to normal distribution

27

Typically, the biomarker data for toxic chemicals are right-skewed. Therefore, logarithmic transformation of data is usually performed to achieve normal distribution. It is required for proper interpretation of the output statistic of the statistical test applied.

Mostly, natural logarithms are used for log transformation. The figure on the slide illustrates that the arithmetic mean value should only be calculated if the raw data are normally distributed. With logarithmic transfomed data, the geometric mean is calculated. The geometric mean has an advantage over the arithmetic mean in that it is less affected by extreme values in a skewed distribution.

Source

Vrijheid M, Montazeri P, Rambaud L, Vogel N, Vlaanderen J, Remy S et al. HBM4EU deliverable D10.5: statistical analysis plan. Dessau-Roßlau: German Environment Agency; 2019 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5c2052c36&appId=PPGMS, accessed 10 November 2022).

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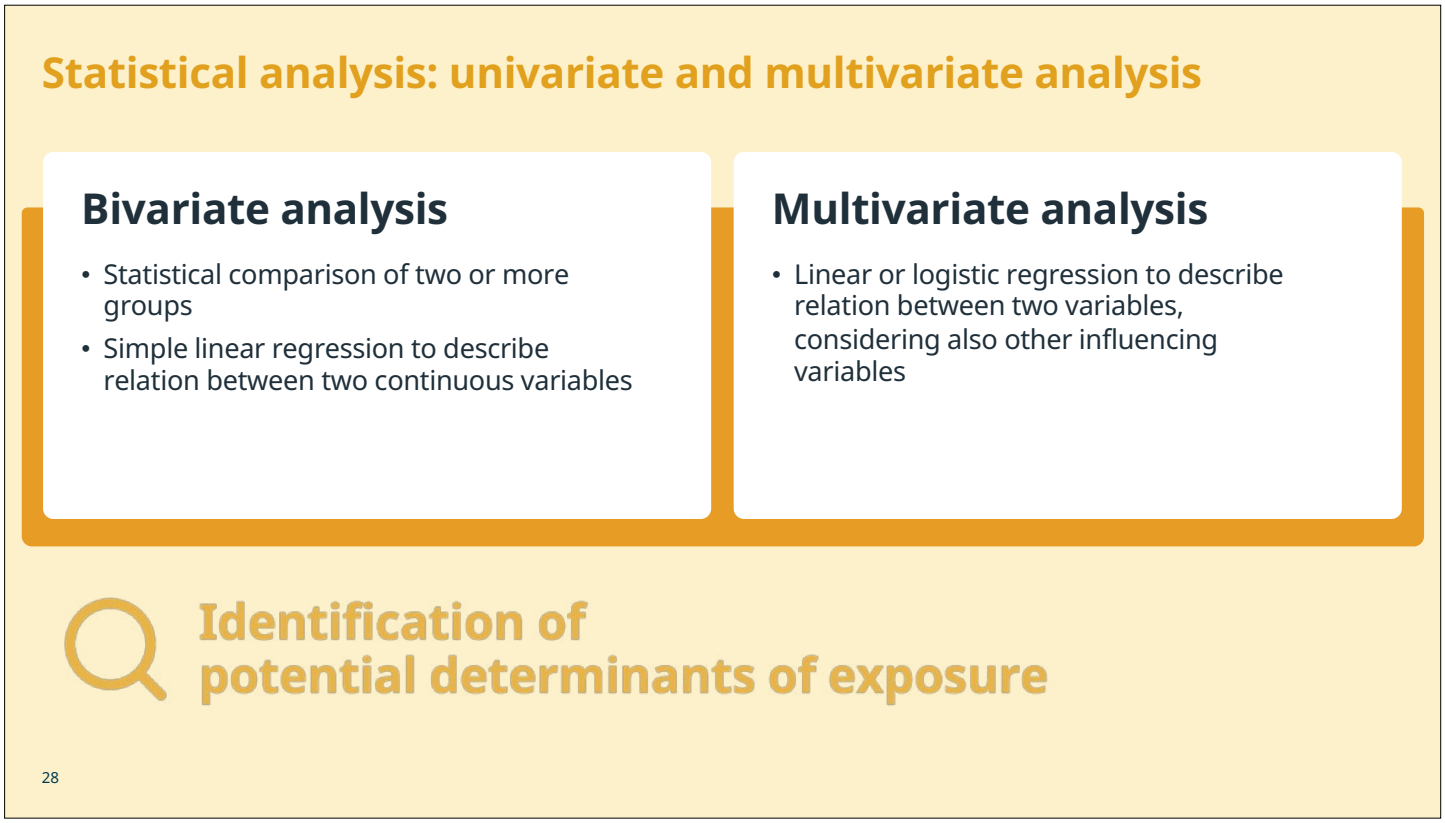

One of the objectives of statistical analysis is to identify potential determinants of exposure; this can be done through:

- statistical comparisons of the measured values between the selected groups (e.g. men vs women; smokers vs non-smokers); and
- linear regression (e.g. correlation between concentration of a substance in biomatrix and age of a subject in years).

Generally, a distinction is drawn between bivariate and multivariate analysis:

- bivariate analysis investigates relationship between two variables
- multiple linear regression considers multiple variables at the same time.

Sources

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Vrijheid M, Montazeri P, Rambaud L, Vogel N, Vlaanderen J, Remy S et al. HBM4EU deliverable D10.5: statistical analysis plan. Dessau-Roßlau: German Environment Agency; 2019 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5c2052c36&appId=PPGMS, accessed 10 November 2022).

Codebook and description of study population: example

No. Q	Name of variable	Explanation	Code	Type	Format
Q1	ID	ID number of participant		NUM	
Q2	Location	Location of residence	1 = urban, 2 = rural		
Q3	Date_of_interview	Date of the interview		Date	dd/mm/yy
Q4	Child_gender	Gender of child	1 = male, 2 = female	CAT	
Q5	Child_birthweight_g	Weight of the child	Kg	NUM	
Q6	Education_mother	Education level of mother	1 = no formal education; 2 = primary school; 3 = apprenticeship; 4 = secondary school; 5 = high school; 6 = university; 7 = master or PhD; 8 = don't know	CAT	
Q7	Source_water	Your main source of water drinking	1 = public water supply; 2 = commercial/bottled; 3 = private; 4 = don't know	CAT	

29

Mothers (N = 120)			
Parameter	**Statistics**	**Values**	
Age, years	Total N	120	
	Median	39	
	P25-P75	36	42
	Min-Max	30	46
Age distribution	Total N	120	
≤ 35 years	N, %	26	21.7%
35-40 years	N, %	48	40.0%
> 40 years	N, %	46	38.3%
Mercury containing thermometer broken in the house	Total N	118	
Yes	N, %	46	39.0%
No	N, %	72	61.0%
Energy saving lamp broken in the house	Total N	114	
Yes	N, %	15	13.2%
No	N, %	99	86.8%

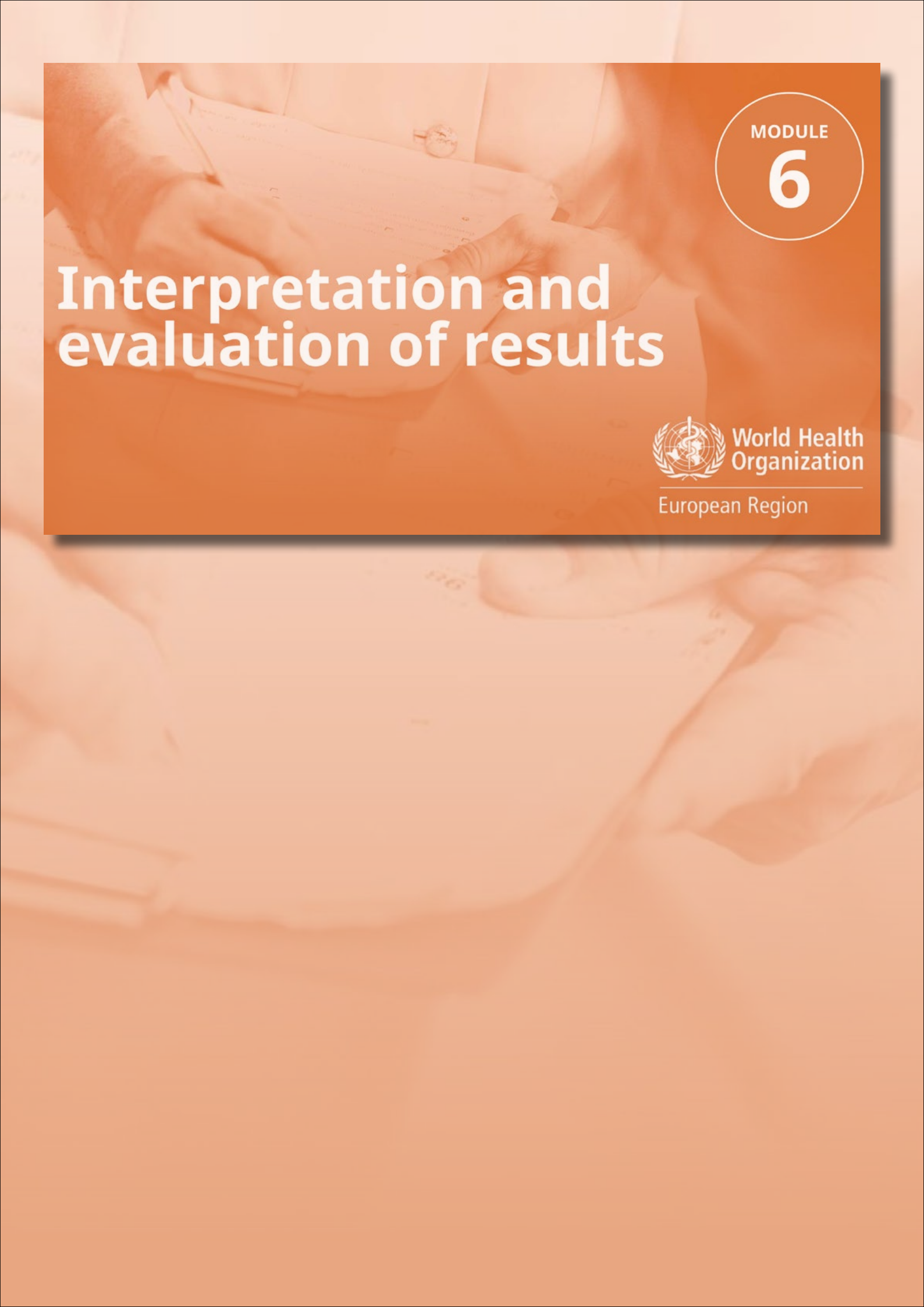
Typically, the biomarker data for toxic chemicals are right-skewed. Therefore, logarithmic transformation of data is usually performed to achieve normal distribution. It is required for proper interpretation of the output statistic of the statistical test applied.

Mostly, natural logarithms are used for log transformation. The figure on the slide illustrates that the arithmetic mean value should only be calculated if the raw data are normally distributed. With logarithmic transfomed data, the geometric mean is calculated. The geometric mean has an advantage over the arithmetic mean in that it is less affected by extreme values in a skewed distribution.

Notes: CAT: category; NUM: number; P25-P75: percentile 25-75; Q: question.

Sources

Vrijheid M, Montazeri P, Rambaud L, Vogel N, Vlaanderen J, Remy S et al. HBM4EU deliverable D10.5: statistical analysis plan. Dessau-Roßlau: German Environment Agency; 2019 (https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5c2052c36&appId=PPGMS, accessed 10 November 2022).



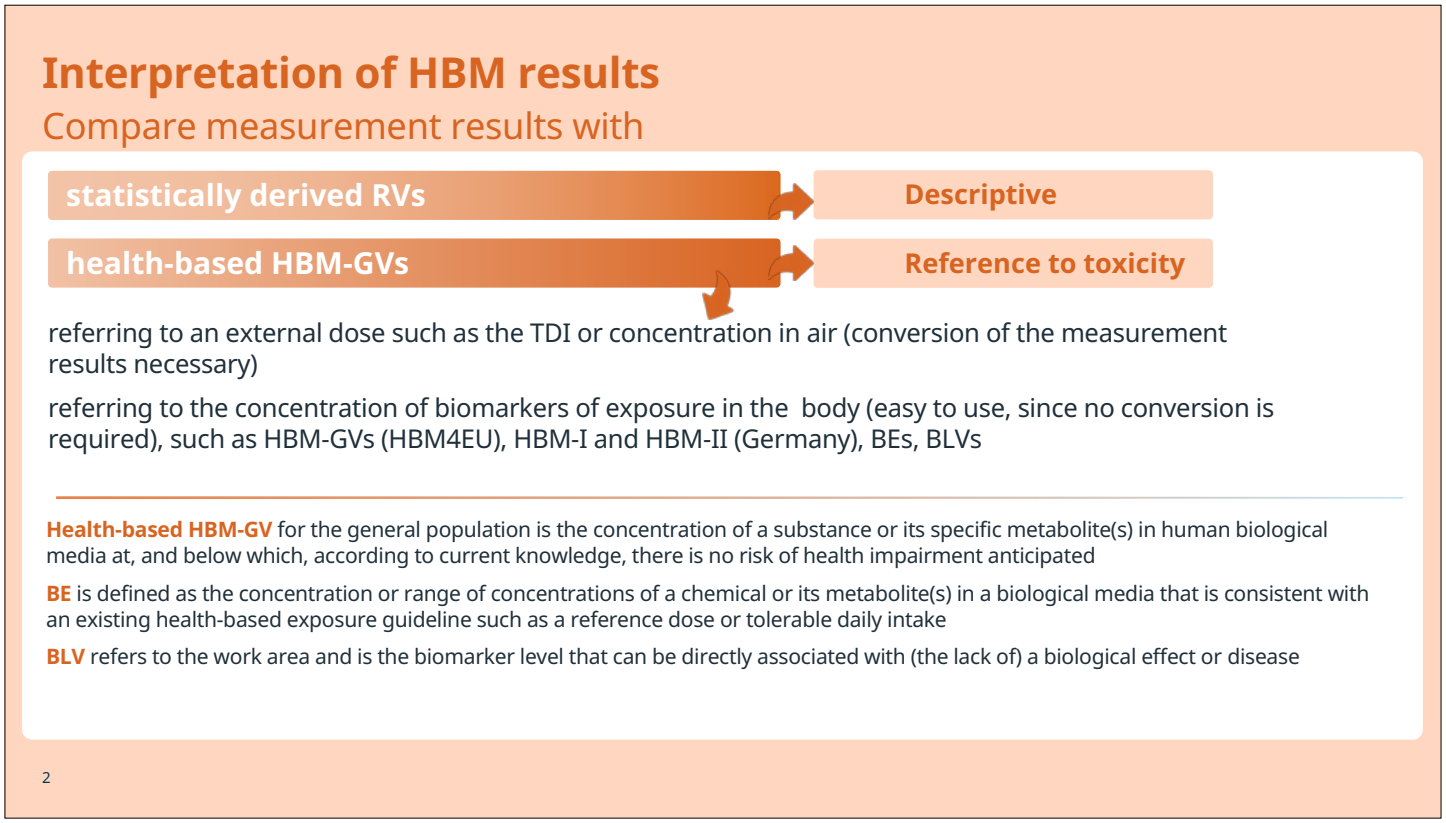
MODULE

6

Interpretation and evaluation of results

World Health Organization

European Region



The results of HBM can then be evaluated in comparison with the GVs.

Reference values (RVs) are statistically derived from empirical studies. RVs do not provide criteria for identifying health risks, which can be achieved with health-based HBM-GVs, BE, TDI or ADI.

Notes: ADI: acceptable daily intakes; BE: biomonitoring equivalent; BLV: biological limit value; GVs: guidance values; HBM-GVs: human biomonitoring guidance values; HBM4EU: European Human Biomonitoring Initiative; RVs: reference values; TDI: tolerable daily intake.

Sources

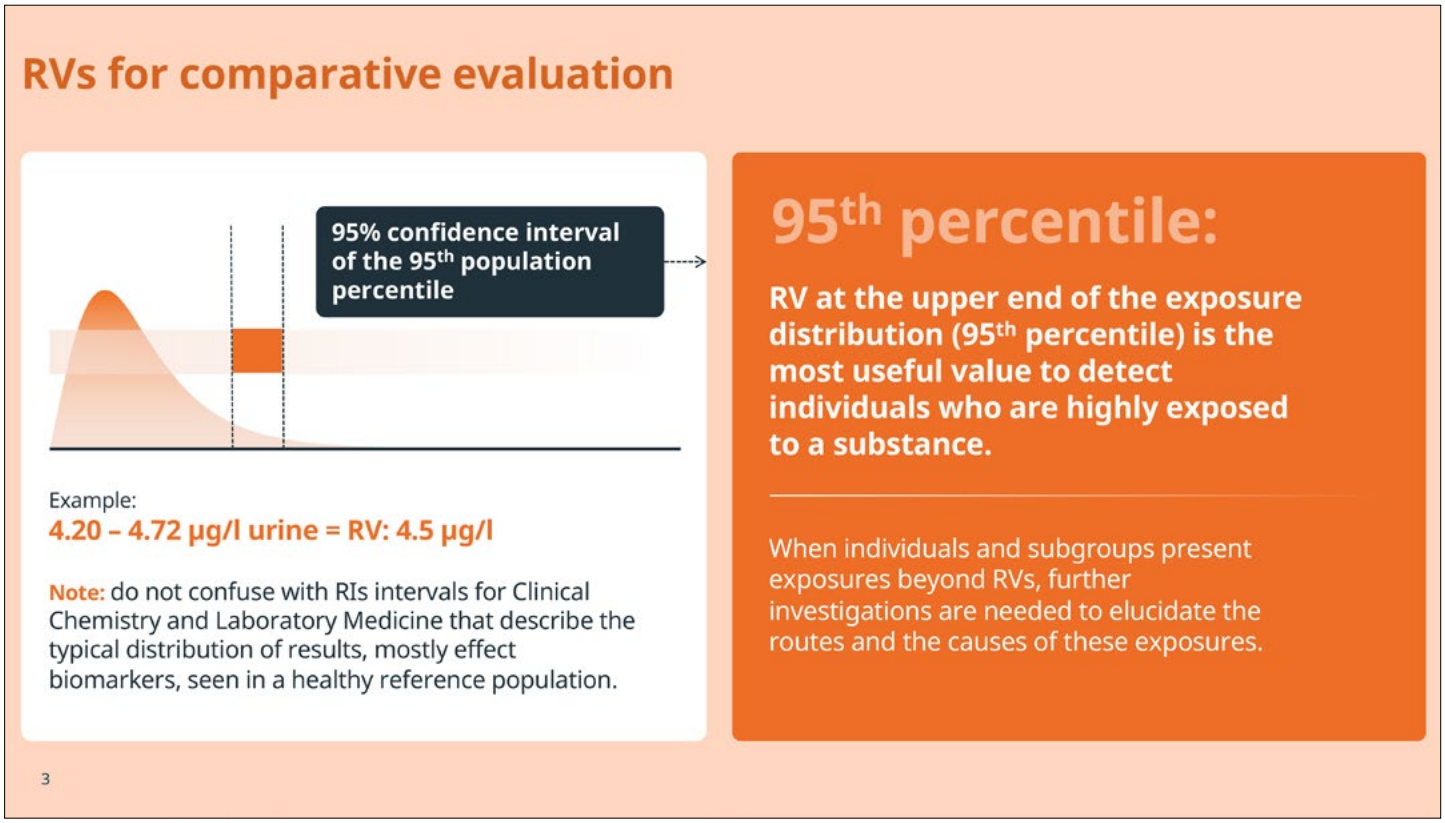
Canadian health measures survey (CHMS) human biomonitoring data for environmental chemicals [website]. Ottawa: Government of Canada; 2021 (https://open.canada.ca/data/en/dataset/8cc88229-8132-4ccd-a3dd-b456579158c6, accessed 10 November 2022).

Vogel N, Conrad A, Apel P, Rucic E, Kolossa-Gehring M. Human biomonitoring reference values: differences and similarities between approaches for identifying unusually high exposure of pollutants in humans. Int J Hyg Environ Health. 2019;222(1):30-33. doi: 10.1016/j.ijheh.2018.08.002.

Louro H, Heinälä M, Bessems J, Buekers J, Vermeire T, Woutersen M et al. Human biomonitoring in health risk assessment in Europe: current practices and recommendations for the future. Int J Hyg Environ Health. 2019;222(5):727-37. doi: 10.1016/j.ijheh.2019.05.009.

Apel P, Rousselle C, Lange R, Sissoko F, Kolossa-Gehring M, Ougier E. Human biomonitoring initiative (HBM4EU): strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. Int J Hyg Environ Health. 2020;230:113622. doi: 10.1016/j.ijheh.2020.113622.

Apel P, Angerer J, Wilhelm M, Kolossa-Gehring M. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int J Hyg Environ Health. 2017;220(2 Pt A):152-66. doi: 10.1016/j.ijheh.2016.09.007.



From an HBM and public health research perspective, RVs are needed to detect individuals who are highly exposed to a substance of interest and might need increased attention in RA. Identifying individuals or subgroups with exposure beyond the RVs suggests that further investigation is needed to elucidate routes and determinants of this exposure to find the likely key reasons for these enhanced levels compared with that in the overall population.

Notes: HBM: human biomonitoring; RA: risk assessment; RI: reference interval; RV: reference value.

Sources

Iavicoli I, Leso V, Fontana L. The reference values in the interpretation of toxicological data. Med Lav. 2019;110(4):251-70. doi: 10.23749/mdl.v110i4.8662.

Vogel N, Conrad A, Apel P, Rucic E, Kolossa-Gehring M. Human biomonitoring reference values: differences and similarities between approaches for identifying unusually high exposure of pollutants in humans. Int J Hyg Environ Health. 2019;222(1):30-33. doi: 10.1016/j.ijheh.2018.08.002.

Representativity in RVs

The sample size of the reference population should be sufficiently large to include the main sociodemographic variables:

- **Age**
- **Ethnicity**
- **Sex**
- **Other** (lifestyle, socioeconomic status, educational level, etc.)

RVs can also be derived for subgroups (if they are large enough)

4

RVs need to be derived from population-representative samples (or representative for a specific subpopulation of interest) with sufficient sample sizes.

Notes: RV: reference value.

Sources

Iavicoli I, Leso V, Fontana L. The reference values in the interpretation of toxicological data. Med Lav. 2019;110(4):251-70. doi: 10.23749/mdl.v110i4.8662.

Since some studies do not include subgroups with specific properties (e.g. high fish consumption), which might per se cause unusually high exposure to substances (or groups of substances), a uniform convention is needed as to whether, and how, extreme values and values of specific groups are handled. For example, tobacco smoke is a major source of benzene and influences the levels of biomarkers of benzene exposure in both active and passive smokers; consequently, smoking is an important exposure determinant for benzene exposure assessment by HBM. Determinants that cannot be ascribed to the characteristics of the general population should be classified as exclusion criteria.

Notes: HBM: human biomonitoring.

Sources

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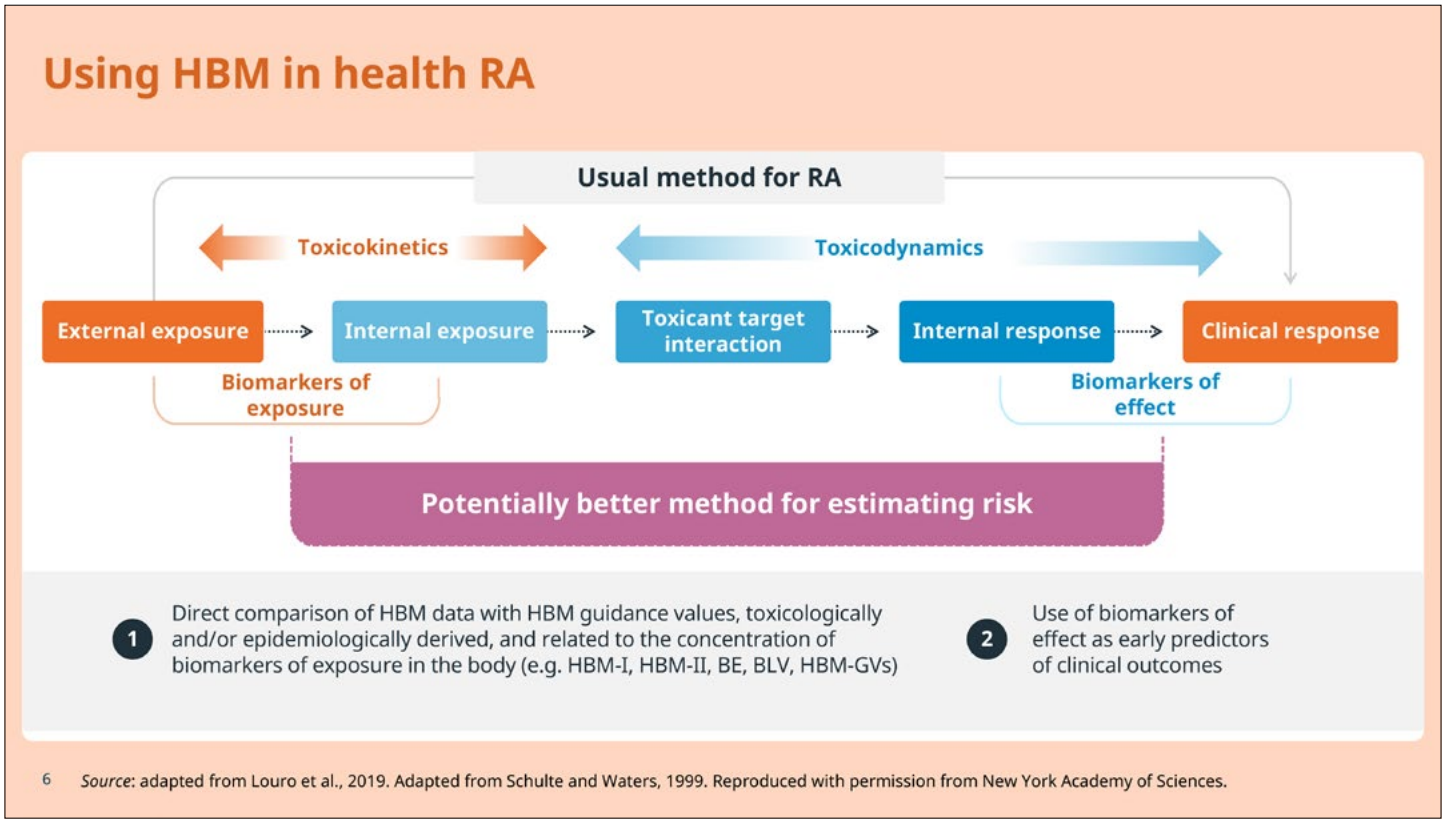

6 *Source*: adapted from Louro et al., 2019. Adapted from Schulte and Waters, 1999. Reproduced with permission from New York Academy of Sciences.

Most RA procedures focus on external doses to which humans are exposed via specific exposure routes. However, reference to exposure and/or effect biomarkers detectable in the body is considered a potentially better approach.

For the interpretation of measured concentrations of chemicals and/or their metabolites in biological matrices, health-based HBM GVs are available in some cases for easy direct comparison.

With regard to the general population, countries that have conducted national environmental and health studies over a long period have commissioned derivation of health-based HBM-GVs. For example, Germany uses the German HBM-I and HBM-II values derived by the German Human Biomonitoring Commission. A common strategy for deriving HBM health-based HBM GVs for the general population and for workers has recently been established and agreed as part of the HBM4EU.

Canada and the United States use biomonitoring equivalents introduced by the United States-based team from Summit Toxicology and also derived by Health Canada.

Notes: BE: biomonitoring equivalent; BLV: biological limit value; HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values; HBM4EU: European Human Biomonitoring Initiative; RA: risk assessment.

Sources

HBM Commission. Ableitung von Human-Biomonitoring (HBM)-Werten auf der Basis tolerabler Aufnahmemengen - Teil II: Grundlagen und Ableitungsweg [Derivation of human biomonitoring (HBM) values based on tolerable intake levels: part II: basis and derivation route]. Bundesgesundheitsbl. 2007;50(2):251-4. In German; doi: 10.1007/s00103-007-0146-5.

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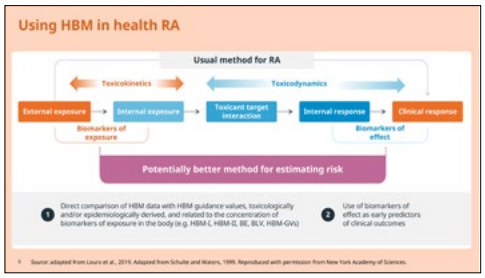

Louro H, Heinälä M, Bessems J, Buekers J, Vermeire T, Woutersen M et al. Human biomonitoring in health risk assessment in Europe: current practices and recommendations for the future. Int J Hygiene Environ Health. 2019;222(5):727–37. doi: 10.1016/j.ijheh.2019.05.009.

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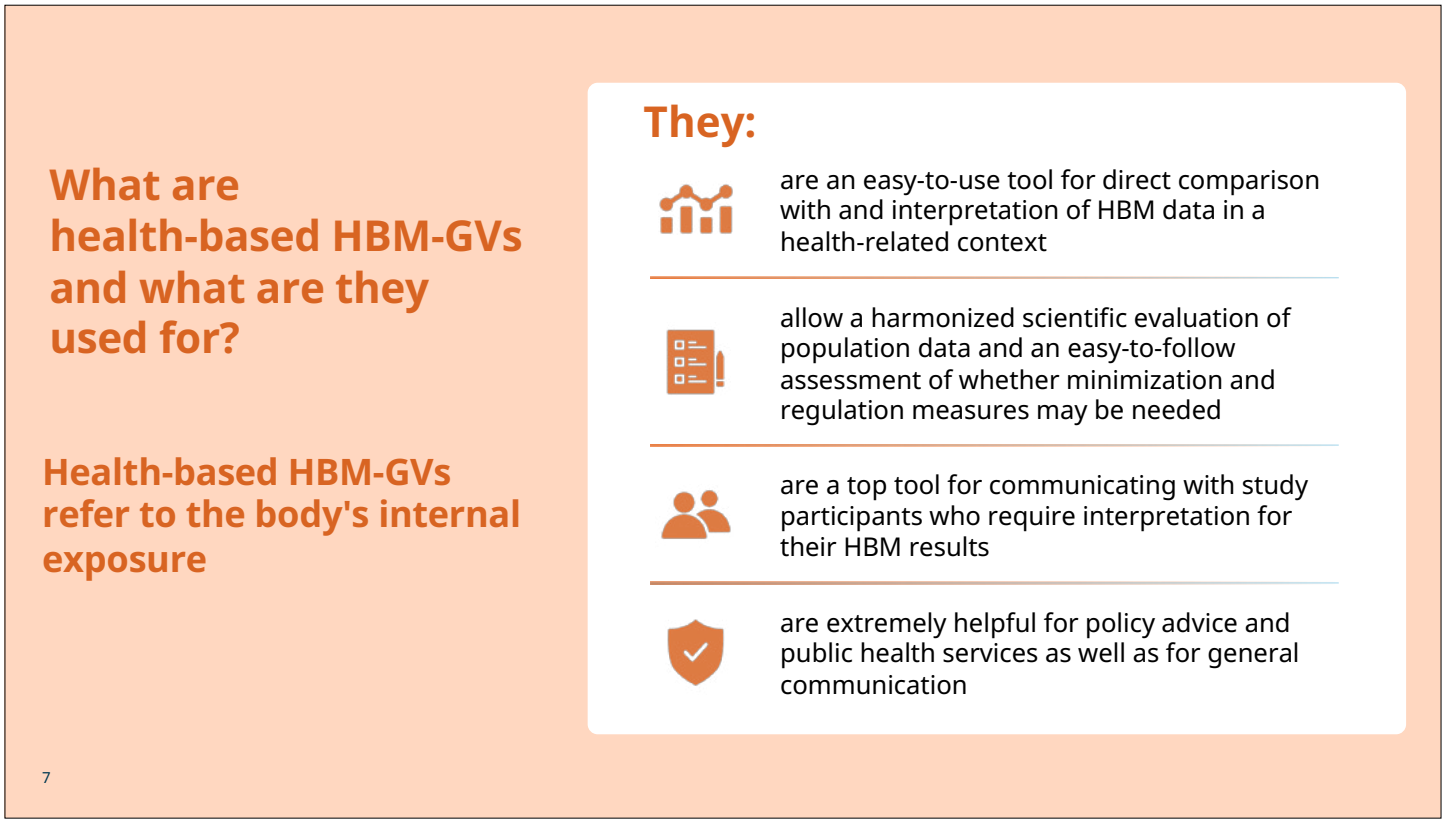

Notes: HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values.

Sources

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Definition of HBM-GV

$HBM\text{-}GV_{GenPop}$

For the general population:
concentration of a substance or its specific metabolite(s) in human biological media at and below which, according to current knowledge, there is no risk of health impairment anticipated

Equivalent to the HBM-I value of the German Human Biomonitoring Commission

If estimates of chemicals' concentrations in biological media are consistent with existing external exposure GVs (TRVs) that imply no effect for substances with an effect threshold, they correspond in these cases to certain BEs

8

Notes: BE: biomonitoring equivalent; GenPop: general population; GVs: guidance values; HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values.

Sources

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David M, Gerofke A, Lange R, Kolossa-Gehring M, Apel P. The European human biomonitoring initiative (HBM4EU): human biomonitoring guidance values (HBM-GVs) for the aprotic solvents *N*-methyl-2-pyrrolidone (NMP) and *N*-ethyl-2-pyrrolidone (NEP). Int J Hyg Environ Health. 2021;238:113856. doi: 10.1016/j.ijheh.2021.113856.

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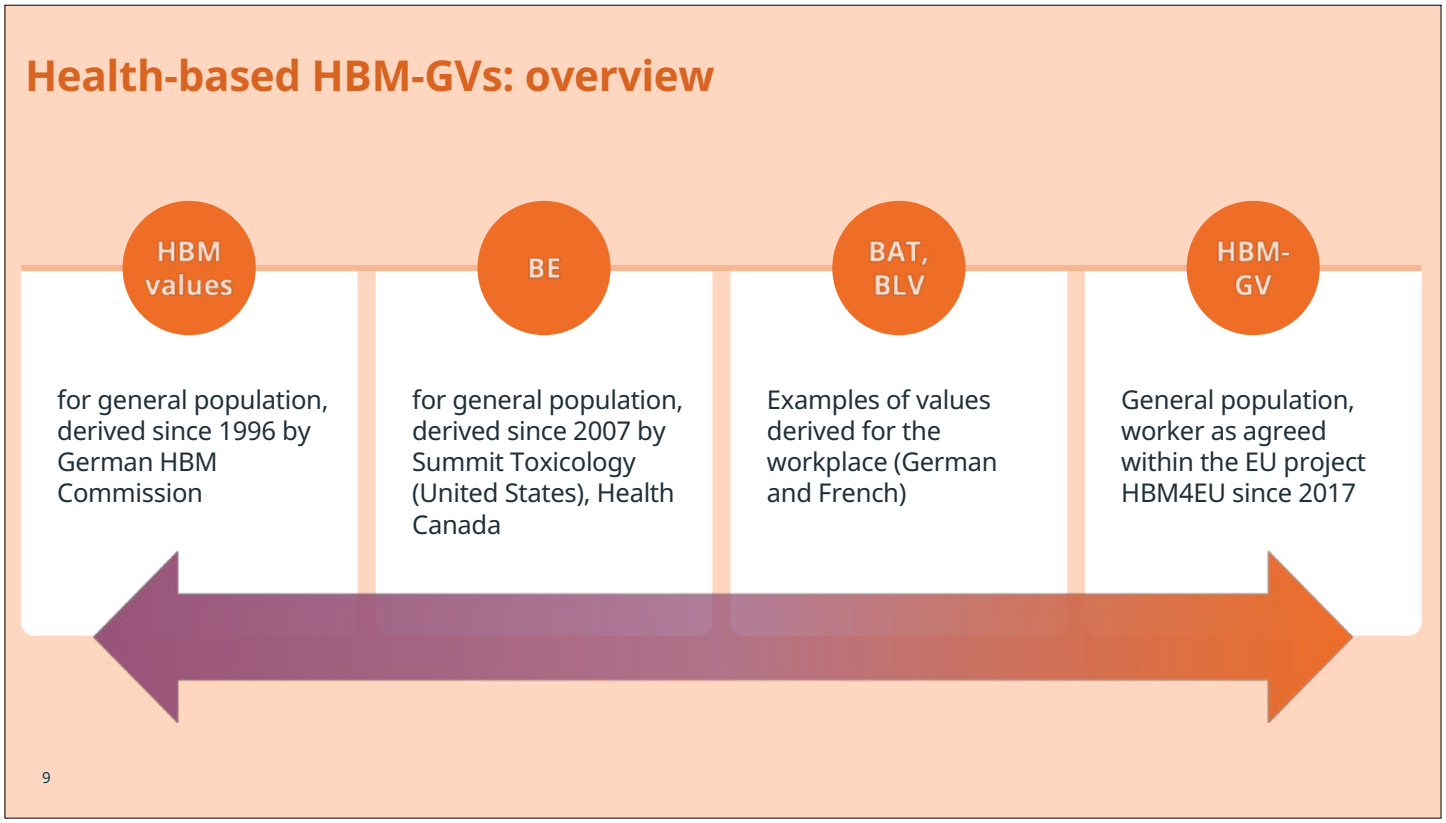
Meslin M, Beausoleil C, Zeman FA, Antignac J-P, Kolossa-Gehring M, Rousselle C et al. Human biomonitoring guidance values (HBM-GVs) for bisphenol S and assessment of the risk due to the exposure to bisphenols A and S in Europe. Toxics. 2022;10:228. doi: 10.3390/toxics10050228.



Currently, there are several types of health-based HBM-GVs accepted by different countries

- HBM-GVs: HBM-I and HBM-II of the German Human Biomonitoring Commission
- BE: introduced by the United States-based team from Summit Toxicology and also derived by Health Canada
- BAT: set by the German Research Foundation
- BLV: set by ANSES as well as by SCOEL
- HBM-GV: agreed within the EU project HBM4EU.

Notes: ANSES: French Agency for Food, Environmental and Occupational Health and Safety; BAT: biological tolerance value; BE: biomonitoring equivalent; BLV: biological limit value; EU: European Union; GenPop: general population; HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values; HBM4EU: European Human Biomonitoring Initiative; SCOEL: Scientific Committee on Occupational Exposure Limits.

Sources

Apel P, Angerer J, Wilhelm M, Kolossa-Gehring M. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int J Hyg Environ Health. 2017;220:152-66. doi: 10.1016/j.ijheh.2016.09.007.

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Health-based HBM-GVs: German example

Health impairment	Recommendation
Possible	• Provide environmental medical care • Reduce exposure immediately
HBM-II value	
Cannot be excluded with sufficient certainty	• Check the measurements (analytics, time course) • Identify specific sources of exposure • Reduce exposure with reasonable effort
HBM-I value	
Not to be expected according to current knowledge	• No need for action

10 *Source*: German Environment Agency. 2022. Reproduced with permission.

The German HBM assessment system is based on toxicological and/or epidemiological studies and distinguishes between two levels of risk of health impairment.

The HBM-I value represents the concentration of a substance in human biological material at and below which there is no risk for adverse health effects and no need for action.

The HBM-II value represents the concentration of a substance in human biological material at and above which there is an increased risk for adverse health effects and, consequently, an immediate need for exposure reduction measures and the provision of biomedical advice. The HBM-II-value is, therefore, be regarded as an intervention or action level.

For concentrations of a substance in human biological material above the HBM-I value but below the HBM-II value, the HBM result should be verified by further measurements. If these measurements confirm the original result, a search for potential sources of exposure should be conducted for minimizing or eliminating this exposure source. The HBM-I value, therefore, represents a test or control value.

Notes: HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values.

Sources

Apel P et al. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int J Hyg Environ Health. 2017;220:152-66. doi: 10.1016/j.ijheh.2016.09.007.

Human Biomonitoring Commission (HBM Commission): about [website]. Dessau-Roßlau: German Environment Agency; (https://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/human-biomonitoring-commission-hbm-commission (accessed 24 March 2023).

Example of German HBM-GVs (in extracts)

HBM values, derived by the Human Biomonitoring Commission of the German Environment Agency, date March 2020

Biomarker und biological material	Population group	HBM-I value	HBM-II value
Bisphenol A in urine [2012, updated 2015]	children; adults	0.1 mg/l; 0.2 mg/l	/
∑ PCB (138 + 153 + 180) in serum x 2 [2012]	infants, toddlers and women of child-bearing age	3.5 µg/l	7 µg/l
Glycolether which are metabolized to 2-methoxyacetic acid (MAA), urine [2014]	general population	0.4 mg MAA/g creatinine	1.6 mg MAA/g creatinine
Glycolether which are metabolized to 2-ethoxyacetic acid (EAA) , urine [2016]	adults	5 mg EAA/l	/
∑ DINCH®-metabolites OH-MINCH and cx-MINCH in urine [2014]	children; adults	3 mg/l; 4.5 mg/l	/
∑ DPHP-metabolites OH-MPHP and oxo-MPHP in urine [2015]	children; adults	1 mg/l; 1.5 mg/l	/
Hexabromocyclododecane (HBCD(D)) [2015]	general population	0.3 µg/g lipid (1.6 µg/l plasma)	/
Triclosan in urine [2015]	children; adults	2 mg/l; 3 mg/l	/
2-Mercaptobenzothiazole (2-MBT) in urine [2015]	children; adults	4.5 mg/l; 7 mg/l	/ possible sensitization not considered
∑ N-Methyl-2-pyrrolidone (NMP)-metabolites 5-Hydroxy-NMP and 2-Hydroxy-N-methylsuccinimide in urine [2015]	children; adults	10 mg/l; 15 mg/l	30 mg/l; 50 mg/l
∑ N-Ethyl-2-pyrrolidone (NEP)- metabolites 5-HNEP and 2-HESI in urine [2015]	children; adults	10 mg/l; 15 mg/l	25 mg/l; 40 mg/l
∑ 3-(4-Methylbenzylidene)-camphor (4-MBC)-metabolites 3-4CBHC and 3-4CBC in urine [2016]	children; adults	0.3 mg/l; 0.5 mg/l	/
PFOA in blood plasma [2016, 2020]	general population	2 µg/l	10µg/l
	women of child-bearing age		5 µg/l

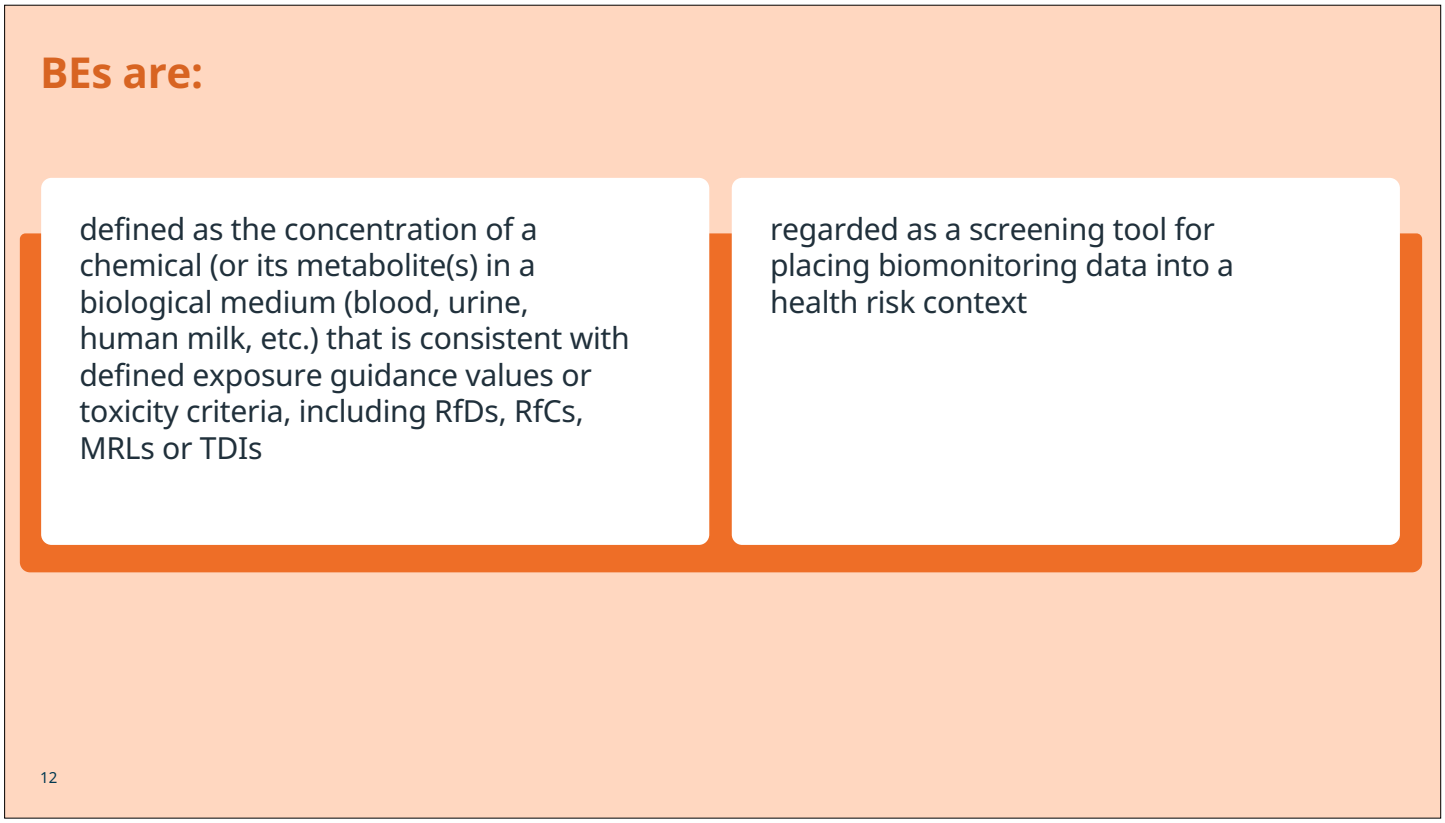
11 *Source*: German Environment Agency, 2022. Reproduced with permission.

All HBM values derived by the German HBM Commission can be found in a table on the homepage of UBA, which is updated as soon as new values are available.

Notes: HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values; UBA: German Environment Agency.

Sources

Human Biomonitoring Commission (HBM Commission): about [website]. Dessau-Roßlau: German Environment Agency; (https://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/human-biomonitoring-commission-hbm-commission (accessed 24 March 2023).



The potential significance of HBM data in the context of existing toxicology data and RA can be assessed if chemical-specific quantitative screening criteria are available. Such screening criteria would ideally be based on robust datasets relating potential adverse effects to biomarker concentrations in human populations. However, such assessments are data intensive and exist for only a few chemicals. As an interim approach, the concept of BE has been developed, which is defined as the concentration or range of concentrations of a chemical or its metabolites in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value such as a RfD or TDI or ADI.

Notes: ADI: acceptable daily intakes; BE: biomonitoring equivalent; HBM: human biomonitoring; MRL: minimal risk level; RA: risk assessment; RfC: reference concentrations; RfD: reference doses; TDI: tolerable daily intake.

Sources

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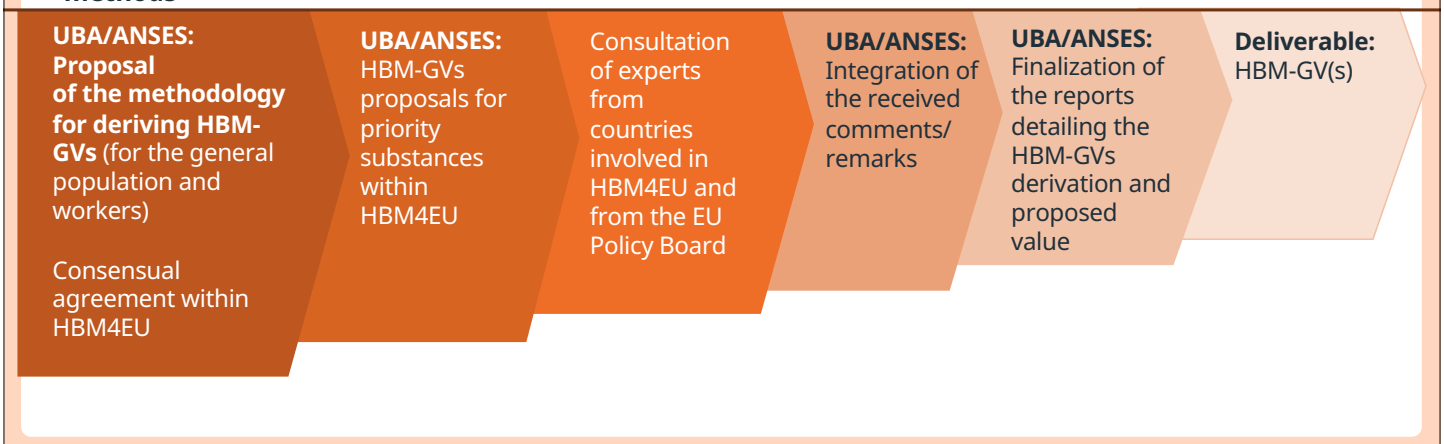
Health-based HBM-GVs: HBM4EU example

Enables consistent and comparable assessments of increasing HBM results obtained with standardized methods

A harmonized strategy for deriving HBM-GVs for internal concentrations has been set and subjected to a consultation procedure

HBM-GVs for 15 priority substances have been derived in the HBM4EU project



13 *Source*: adapted from Apel et al., 2020. Reproduced with permission from Elsevier.

Notes: ANSES: French Agency for Food, Environmental and Occupational; EU: European Union; HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values; HBM4EU: European Human Biomonitoring Initiative; UBA: German Environment Agency.

Sources

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David M, Gerofke A, Lange R, Kolossa-Gehring M, Apel P. The European human biomonitoring initiative (HBM4EU): human biomonitoring guidance values (HBM-GVs) for the aprotic solvents *N*-methyl-2-pyrrolidone (NMP) and *N*-ethyl-2-pyrrolidone (NEP). Int J Hyg Environ Health. 2021;238:113856. doi: 10.1016/j.ijheh.2021.113856.

Lamkarkach F, Ougier E, Garnier R, Viau C, Kolossa-Gehring M, Lange R et al. Human biomonitoring initiative (HBM4EU): human biomonitoring guidance values (HBM-GVs) derived for cadmium and its compounds. Environ Int. 2021;147:106337. doi: 10.1016/j.envint.2020.106337.

Lange R, Apel P, Rousselle C, Charles S, Sissoko F, Kolossa-Gehring M et al. The European Human Biomonitoring Initiative (HBM4EU): human biomonitoring guidance values for selected phthalates and a substitute plasticizer. Int J Hyg Environ Health. 2021;234:113722. doi: 10.1016/j.ijheh.2021.113722.

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Meslin M, Beausoleil C, Zeman FA, Antignac J-P, Kolossa-Gehring M, Rousselle C, Apel P et al. Human biomonitoring guidance values (HBM-GVs) for bisphenol S and assessment of the risk due to the exposure to bisphenols A and S in Europe. Toxics. 2022;10:228. doi: 10.3390/toxics10050228.

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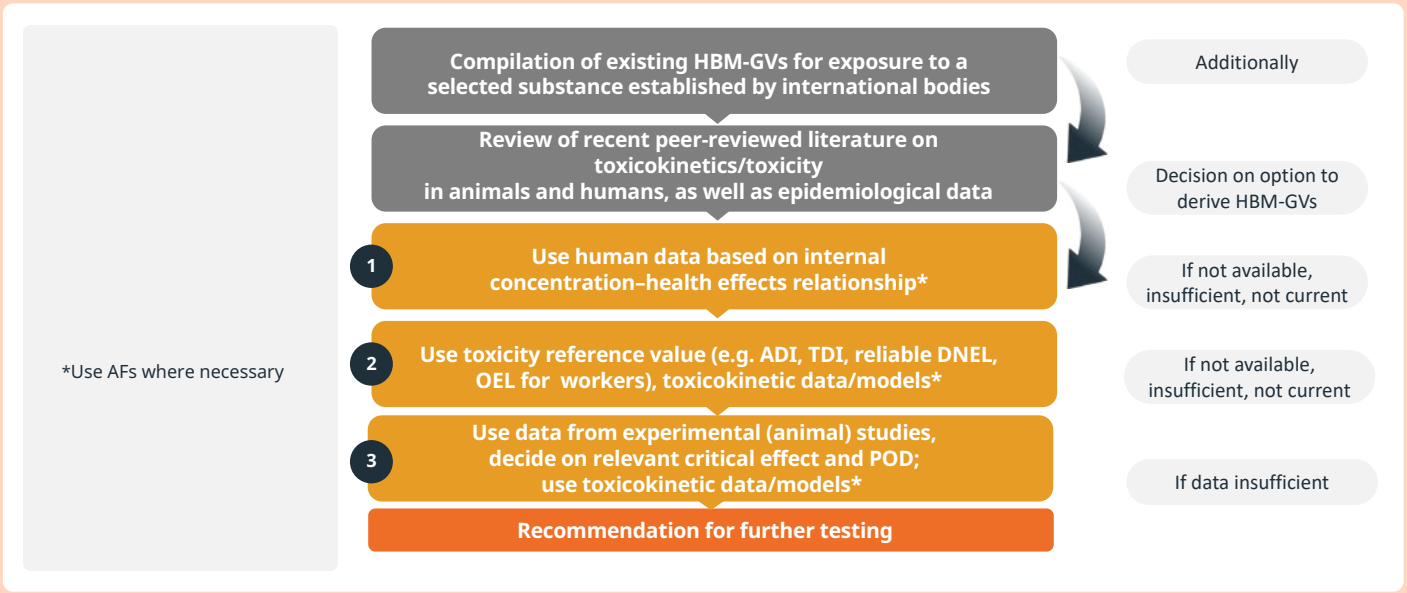
General procedure for deriving HBM-GVs



The preferred basis for deriving HBM-GVs are well-conducted human studies adequately reporting measured internal concentration levels of a substance, sampling times and analytical methods used, along with the relationships between concentrations of a substance or its metabolites in human biological media and the occurrence of adverse effects. In this way, assumptions and uncertainties underlying the extrapolation of toxicological animal data to humans are avoided. The POD* of the key study shall be chosen according to the critical effect, which is considered to be the most sensitive among all adverse effects that may arise from exposure to the substance (e.g. changes in morphology, physiology, growth, development, reproduction or life span resulting in an impairment of functional capacity, in an impairment of the capacity to offset additional stress, or in an increase in sensitivity).

*POD is the point on a toxicological dose–response curve generally corresponding to an estimated low effect level or no effect level. It can be set as one of several values: LOAEL, BMD or NOAEL, in a key study.

Notes: ADI: acceptable daily intake; AFs: assessment factors; BMD: benchmark dose; DNEL: derived no-effect level; HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values; LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level; OEL: occupational exposure limit; POD: point of departure; TDI: tolerable daily intake.

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Lamkarkach F, Ougier E, Garnier R, Viau C, Kolossa-Gehring M, Lange R et al. Human biomonitoring initiative (HBM4EU): human biomonitoring guidance values (HBM-GVs) derived for cadmium and its compounds. Environ Int. 2021;147:106337. doi: 10.1016/j.envint.2020.106337.

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Conversion of external dose into internal concentration of a biomarker of exposure

For the calculation of an HBM-GV based on a TRV (e.g. ADI) or a POD value from an animal test* the external dose must be converted into an internal concentration of a biomarker of exposure

One-compartment modelling

For compounds mainly eliminated through urine and for which suitable urinary biomarker(s) have been identified, biomarker(s)' concentrations consistent with TRV or TRV-like value may be calculated based on a urinary mass balance approach (steady state assumed)

Refinement by PBPK modelling

*Adjustment factors for inter- and intraspecies extrapolation to be applied to the POD to get a TRV-like value

Situation 1: the biomarker selected is the parent compound

$$\text{HBM} - \text{GV}_{\text{GenPop}} = \frac{\text{TRV} \cdot \text{Fue } (\textit{Substance})}{\textit{Daily urinary flow rate adjusted to the bw}}$$

Situation 2: the biomarker selected is relevant metabolite

$$\text{HBM} - \text{GV}_{\text{GenPop}} = \frac{\text{TRV} \; \frac{\text{MW(Metabolite)}}{\text{MW(Substance)}} \cdot \text{Fue (Metabolite)}}{\textit{Daily urinary flow rate adjusted to the bw}}$$

15

Notes: ADI: acceptable daily intakes; bw: body weight; Fue: fractional urinary excretion coefficient; GenPop: general population; HBM-GVs: human biomonitoring guidance values; MW: molecular weight; PBPK: physiologically based pharmacokinetic; POD: point of departure; TRV: toxicity reference values.

Sources

Apel P, Rousselle C, Lange R, Sissoko F, Kolossa-Gehring M, Ougier E. Human biomonitoring initiative (HBM4EU): strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. Int J Hyg Environ Health. 2020;230:113622. doi: 10.1016/j.ijheh.2020.113622.

Lange R, Apel P, Rousselle C, Charles S, Sissoko F, Kolossa-Gehring M et al. The European Human Biomonitoring Initiative (HBM4EU): human biomonitoring guidance values for selected phthalates and a substitute plasticizer. Int J Hyg Environ Health. 2021;234:113722. doi: 10.1016/j.ijheh.2021.113722.

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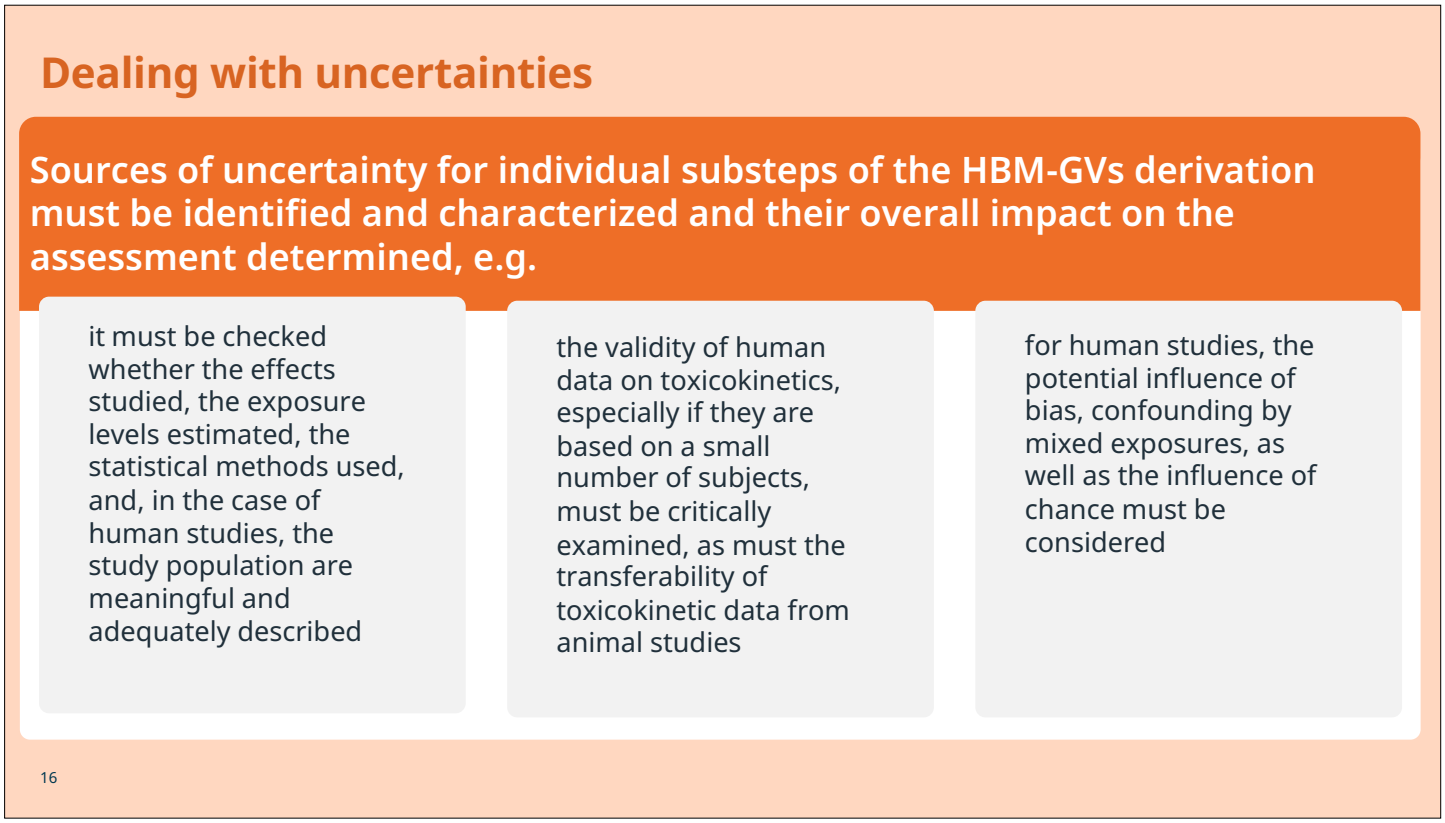
David M, Gerofke A, Lange R, Kolossa-Gehring M, Apel P. The European human biomonitoring initiative (HBM4EU): human biomonitoring guidance values (HBM-GVs) for the aprotic solvents *N*-methyl-2-pyrrolidone (NMP) and *N*-ethyl-2-pyrrolidone (NEP). Int J Hyg Environ Health. 2021;238:113856. doi: 10.1016/j.ijheh.2021.113856.



Notes: HBM-GVs: human biomonitoring guidance values.

Sources

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Indication of an overall confidence level

Obtained by equal consideration of the confidence levels (high, medium or low) of individual criteria

- Nature and quality of the data
- Choice of the critical effect and the mode of action
- Choice of the key study
- Choice of the POD
- Extrapolations across and within species

17

The overall confidence level is determined by a number of factors.

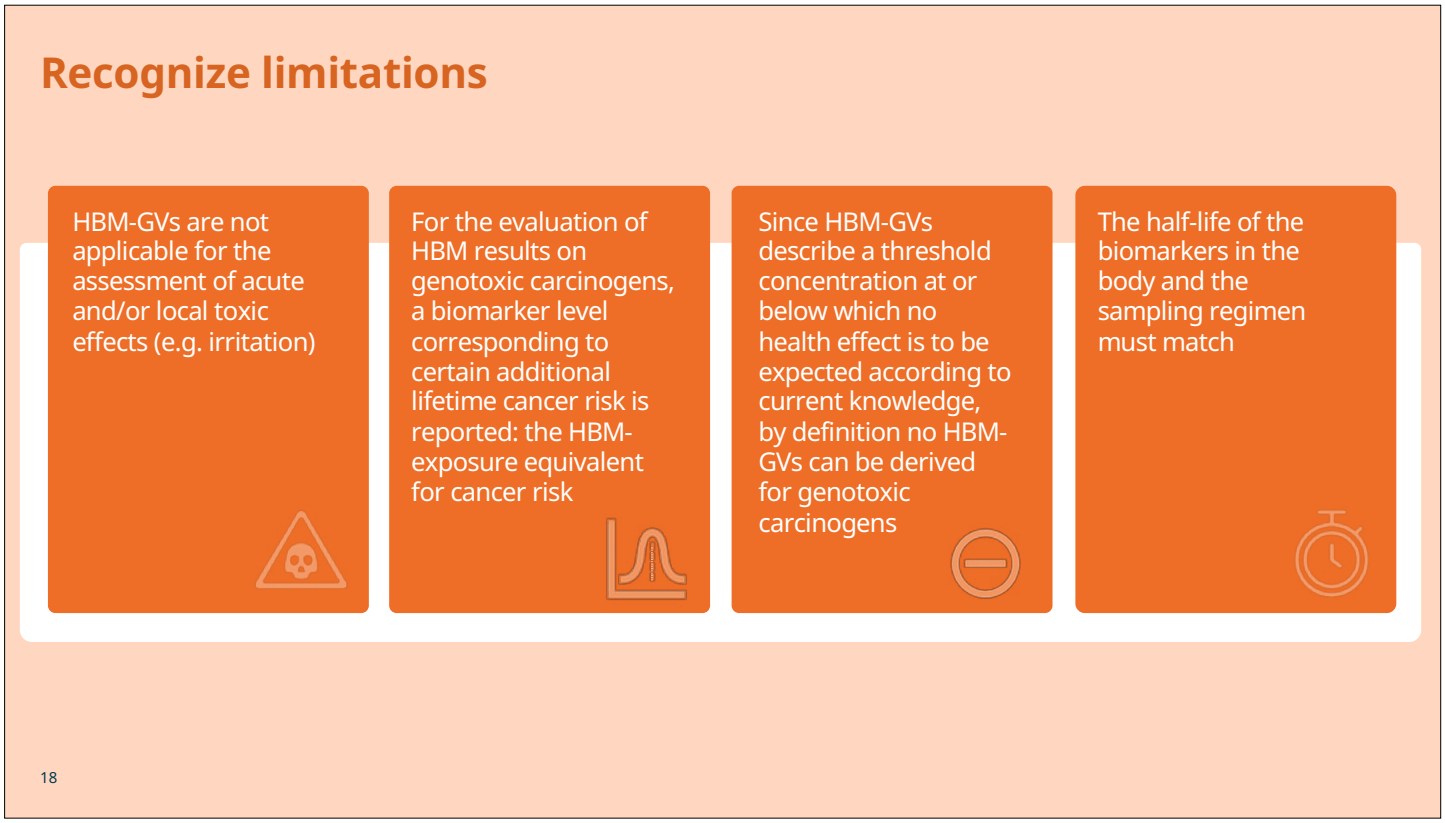
- The nature and quality of the data: epidemiological and/or toxicological studies should ideally cover different effects, exposure times and exposure windows; studies conducted in humans are preferred over animal studies.
- The critical effect and mode of action: the likelihood of transferability of the critical effect (as well as the mode of action) from animal species to humans should be mirrored by a confidence level.
- The key study: for a selected key animal study following an OECD guideline, at best a medium/high confidence level can be assigned to take into account uncertainties regarding the transferability of study results between species.

The confidence level for a critical dose (POD) is highest using a BMD, followed by NOAEL–LOAEL pair, which itself has a higher confidence level than the use of a single LOAEL or NOAEL. The quality of the dose–response relationship (possibly depending on the number of doses tested in the study and the difference in concentration between the doses tested) also determines the level of confidence in the choice of the critical dose. Extrapolation across and within species also depends on the suitability of available pharmacokinetic models and data.

Notes: BMD: benchmark dose; LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level; OECD: Organization for Economic Co-operation and Development; POD: point of departure.

Sources

Apel P, Rousselle C, Lange R, Sissoko F, Kolossa-Gehring M, Ougier E. Human biomonitoring initiative (HBM4EU): strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. Int J Hyg Environ Health. 2020;230:113622. doi: 10.1016/j.ijheh.2020.113622.



Notes: HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values.

Sources

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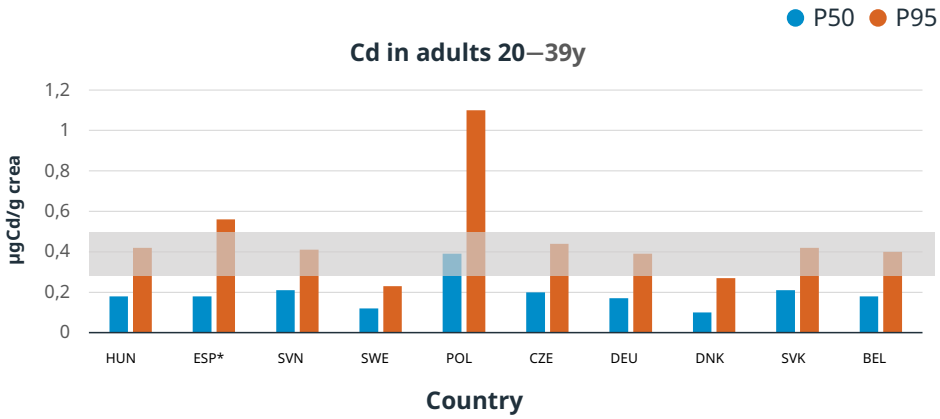
Application of health-based HBM-GVs for (impact) indicators within HBM4EU

What is the level of exposure in a population? What are the groups at risk?

Cd in adults aged 20—39 years



BEL: Belgium
CZE: Czechia
DEU: Germany
DNK: Denmark
ESP : Spain
HUN: Hungary
POL: Poland
SVK: Slovakia
SVN: Slovenia
SWE: Sweden

The grey band represents the alert values of urinary Cd for adults (21—40 years) considering accumulation and the HBM-GV_{GenPop} of Cd of 1 µg/g creatinine at the age of 55—60 years

19 *Source*: Lobo Vicente et al., 2021. Reproduced with permission from German Environment Agency.

Notes: Cd: cadmium; GenPop: general population; HBM-GVs: human biomonitoring guidance values; HBM4EU: European Human Biomonitoring Initiative; P50 and P95: percentile 50 and 95.

Sources

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Risk assessment

HBM in chemical RA: approaches

In public health care, as well as in the context of the marketing authorization of chemicals or products, the health risks for the people/consumers must be assessed and environmental exposure, chemical concentrations in the products or areas of product application must be regulated accordingly

HBM can be included in RA even when relatively few data are available, and its inclusion generally benefits the assessment

Various bodies provide for tiered approaches, e.g.

German HBM-Commission

HBM-I and HBM-II values

Health Canada

Qualitative approach 1
Applied when biomonitoring data indicate that general population exposure is limited or unlikely

Quantitative approach 2
Used when available biomonitoring data can be assessed against HBM-GVs

HBM4EU

the lower the margin of safety the higher should be the level of confidence of the applied approach

1st tier
One-compartment modelling-based derivation of HBM-GVs or reverse calculation of external exposure based on biomarker levels

2nd tier
Refinement by reliable PBPK modelling is used where, for example, the risk characterization ratio is close to 1

3rd tier
The most robust; requires measured data on correlations between external exposure and internal doses from well-controlled studies

21

Notes: HBM: human biomonitoring; HBM-GVs: human biomonitoring guidance values; HBM4EU: European Human Biomonitoring Initiative; PBPK: physiologically based pharmacokinetic; RA: risk assessment.

Sources

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Progress around application of HBM in RA

International examples of chemicals where the RA has benefited from HBM data include bisphenol A, phthalates, MOCA, chromium, cobalt, decabromodiphenyl ether and hexabromocyclododecane (brominated flame retardants), lead, perfluorinated chemicals (PFOS and PFOA), selenium, triclosan

The number of assessments that use HBM data continue to grow, e.g. in Canada recent assessment of aluminium, thallium, zinc

Canadian case studies:

- application HBM data in regulatory RA (triclosan case study)
- use of reverse (triclosan and phthalate case studies) and forward (selenium case study) dosimetry
- illustration of how HBM data can be critical in identifying risk (selenium case study, phthalates)
- combination of modelled exposure estimation with HBM data (phthalates, selenium)
- use of HBM for multiple metabolites (phthalates)

22

Notes: HBM: human biomonitoring; MOCA: 2-chloroaniline; PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulfonate; RA: risk assessment.

Sources

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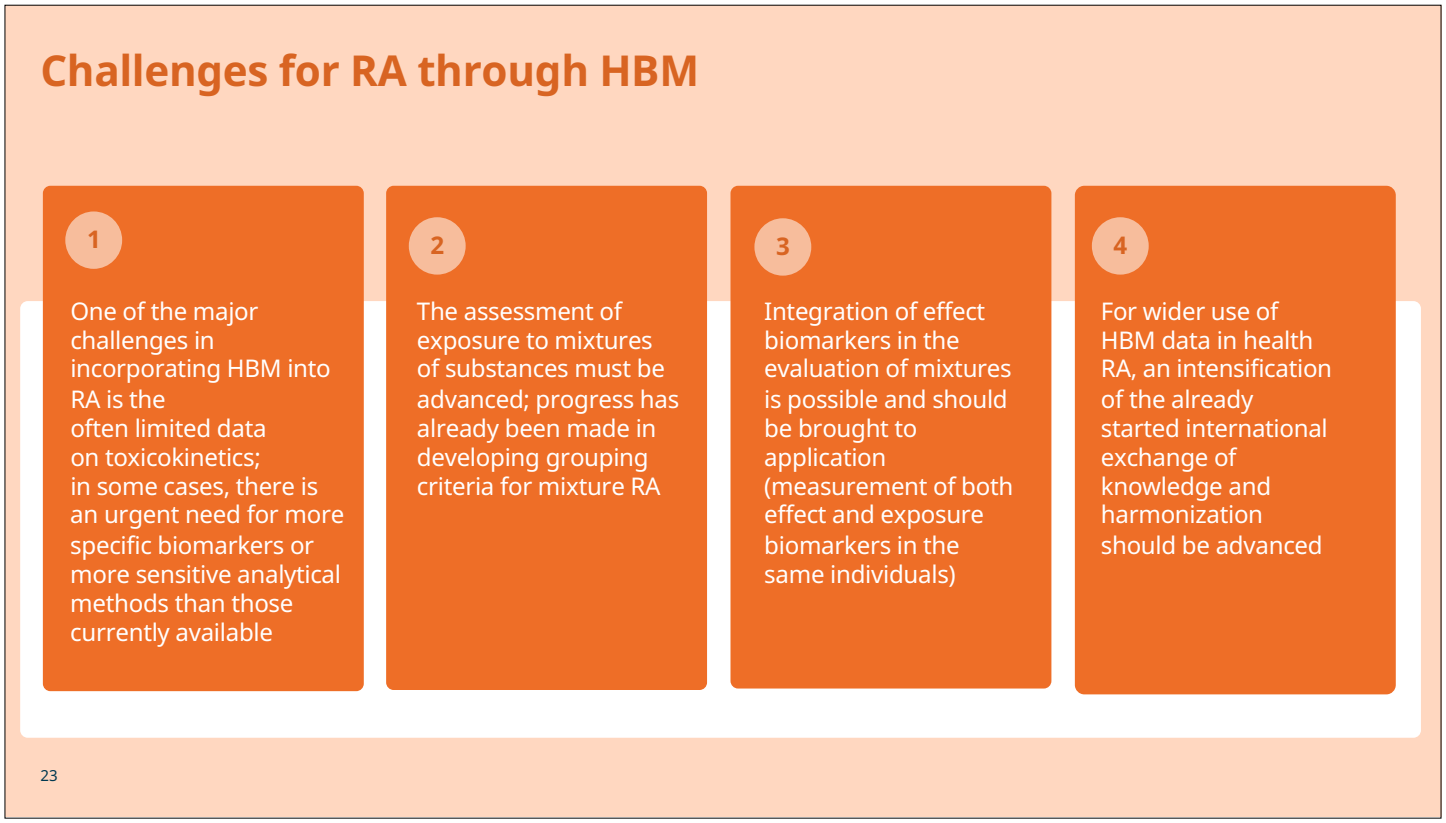

Notes: HBM: human biomonitoring; RA: risk assessment.

Sources

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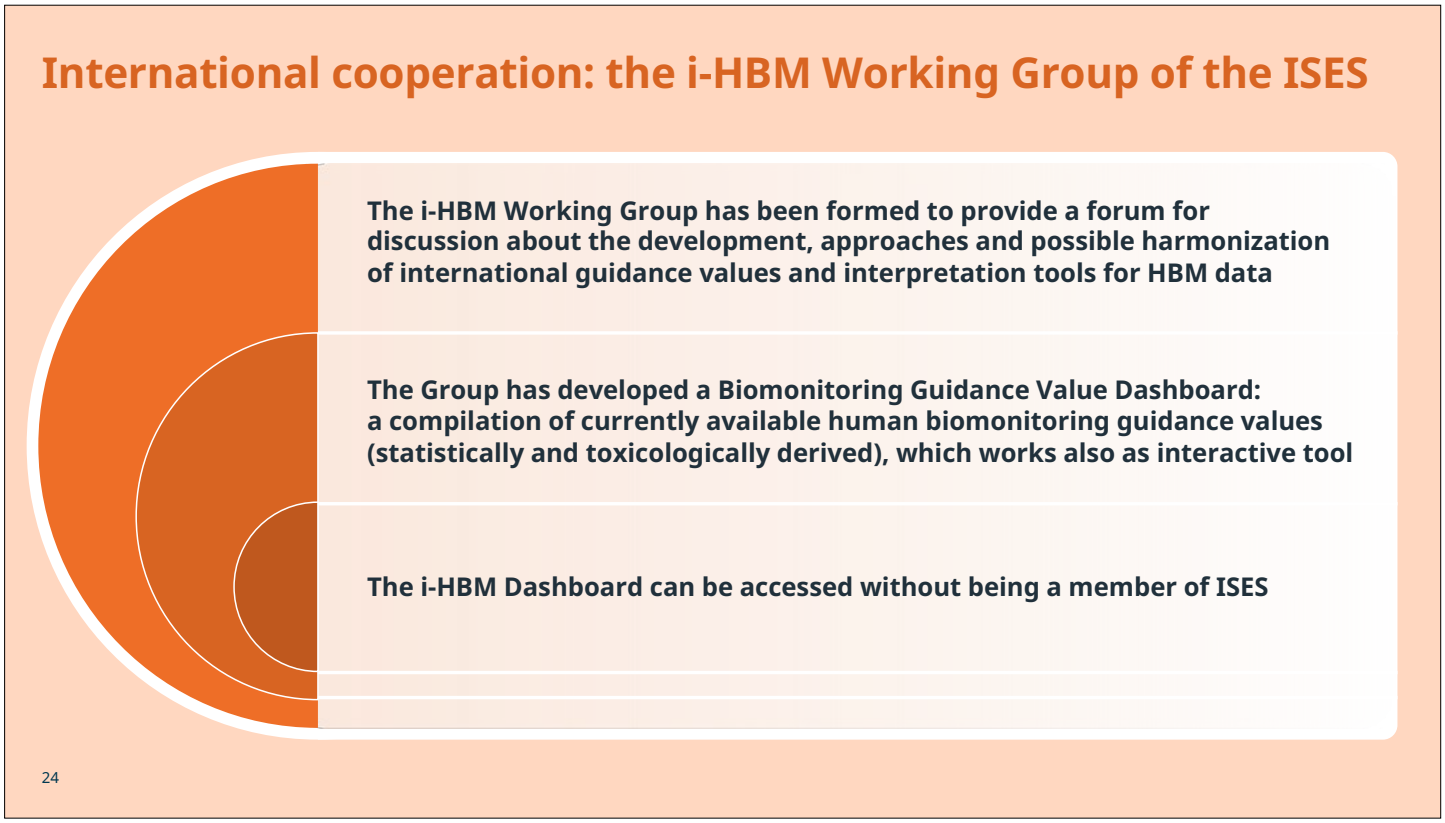

Notes: HBM: human biomonitoring; ISES: the International Society of Exposure Science.

Sources

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Nakayama SF, St-Amand A, Pollock T, Apel P, Bamai YA, Barr DB et al. Interpreting biomonitoring data: Introducing the international human biomonitoring (i-HBM) working group's health-based guidance value (HB2GV) dashboard. Int. J. Hyg. Environ. Health. 2023;247:114046. doi: 10.1016/j.ijheh.2022.114046.

C

Communication of HBM results/risk communication

Notes: HBM: human biomonitoring.

26 *Source*: adapted from National Research Council, 2006. Reproduced with permission from National Academies Press.

Three periods of extensive communication campaigns are identified:

- prior to and at the onset of the sampling period
- during the survey
- at the dissemination of results stage.

Communication steps (particularly prior to the survey conduct) are closely linked with community involvement in the recruitment phase.

Notes: HBM: human biomonitoring.

Sources

Committee on Human Biomonitoring for Environmental Toxicants, National Research Council. Human biomonitoring for environmental chemicals. Washington (DC): National Academies Press; 2006 (https://www.nap.edu/catalog/11700/human-biomonitoring-for-environmental-chemicals, accessed 10 November 2022).

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Communication of HBM results

Communication of individual and population risks

The fundamental goal of risk communication is:

- to provide meaningful, relevant and accurate information in clear and understandable terms, targeted to a specific audience
- to facilitate understanding of complex technical issues – such as exposure to the chemical, the associated health risks and risk-reduction measures – to bridge the gap between lay people and experts and to help people make more informed and healthier choices

The stakeholders categories for communication are:

policy-makers

health-care professionals

the general public

local communities

individuals involved in the study

industry

non-governmental organizations

scientists

27

Before communicating the result of an HBM study, careful consideration needs to be given to the assessment of individual and population risks, based on the measured concentrations of chemicals and the questionnaire data, as well as on the main goals of risk communication, uncertainties, taking into account different target groups and their needs. For example, if the HBM survey reveals low exposure levels and low or negligible health risks, the main purpose would be to inform participants of the results and to use this as an opportunity to raise awareness and educate. Whereas, if the survey showed a high level of exposure to a pollutant, communication of results would include more information about health risks and risk-reduction measures, including on preventing exposure and promoting safer behaviours.

It is crucial to identify the most effective channels to communicate the message and to get support from central and local authorities and the medical community.

Notes: HBM: human biomonitoring.

Sources

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/334181, accessed 10 November 2022).

End-users of HBM results: HBM4EU example

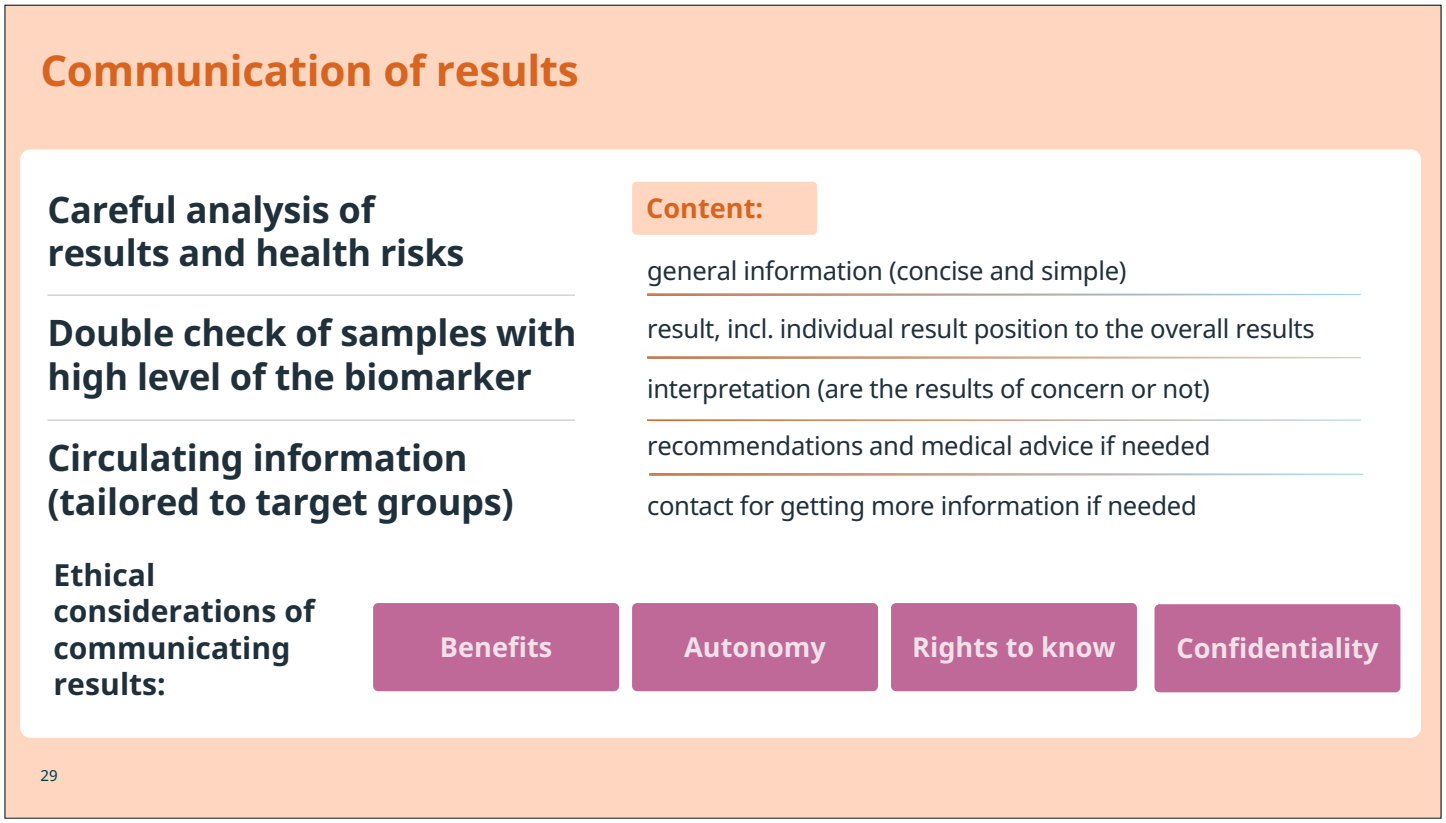
To ensure that the results are exploited and generate impact there is a need to actively engage with a broad range of end-users at national and international level:

28

Notes: HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative; IGO – intergovernmental organization.

Sources

2020 Strategy for the communication and dissemination of HBM4EU results. Dessau-Roßlau: German Environment Agency; 2017 (Deliverable Report D2.10; https://www.hbm4eu.eu/wp-content/uploads/2017/03/Deliverable-2.10-2020-Strategy-for-the-communication-and-dissemination-of-HBM4EU-results.pdf, accessed 10 November 2022).



Communication of study results to individuals who contributed samples is one of the ethical challenges facing researchers conducting biomonitoring studies. In the absence of documented health risks, health-based guidelines or established reference ranges for many environmental chemicals, investigators must evaluate the potential risks of psychological and financial harm (e.g. loss of insurance) of sharing biomonitoring data (beneficence) with the individual's right to know.

Generally, the appropriate disclosure of individual results will be determined on a case-by-case basis, considering the level of evidence associating tissue levels with direct effects on the health of the individual and balancing the right to know with the potential for harm.

Sources

Exley K, Cano N, Aerts D, Biot P, Casteleyn L, Kolossa-Gehring M et al. Communication in a human biomonitoring study: focus group work, public engagement and lessons learnt in 17 European countries. Environ Res. 2015;141:31-41. doi: 10.1016/j.envres.2014.12.003.

Haines DA, Arbuckle TE, Lye E, Legrand M, Fisher M, Langlois R et al. Reporting results of human biomonitoring of environmental chemicals to study participants: a comparison of approaches followed in two Canadian studies. J Epidemiol Community Health. 2011;65(3):191–8. doi: 10.1136/jech.2008.085597.

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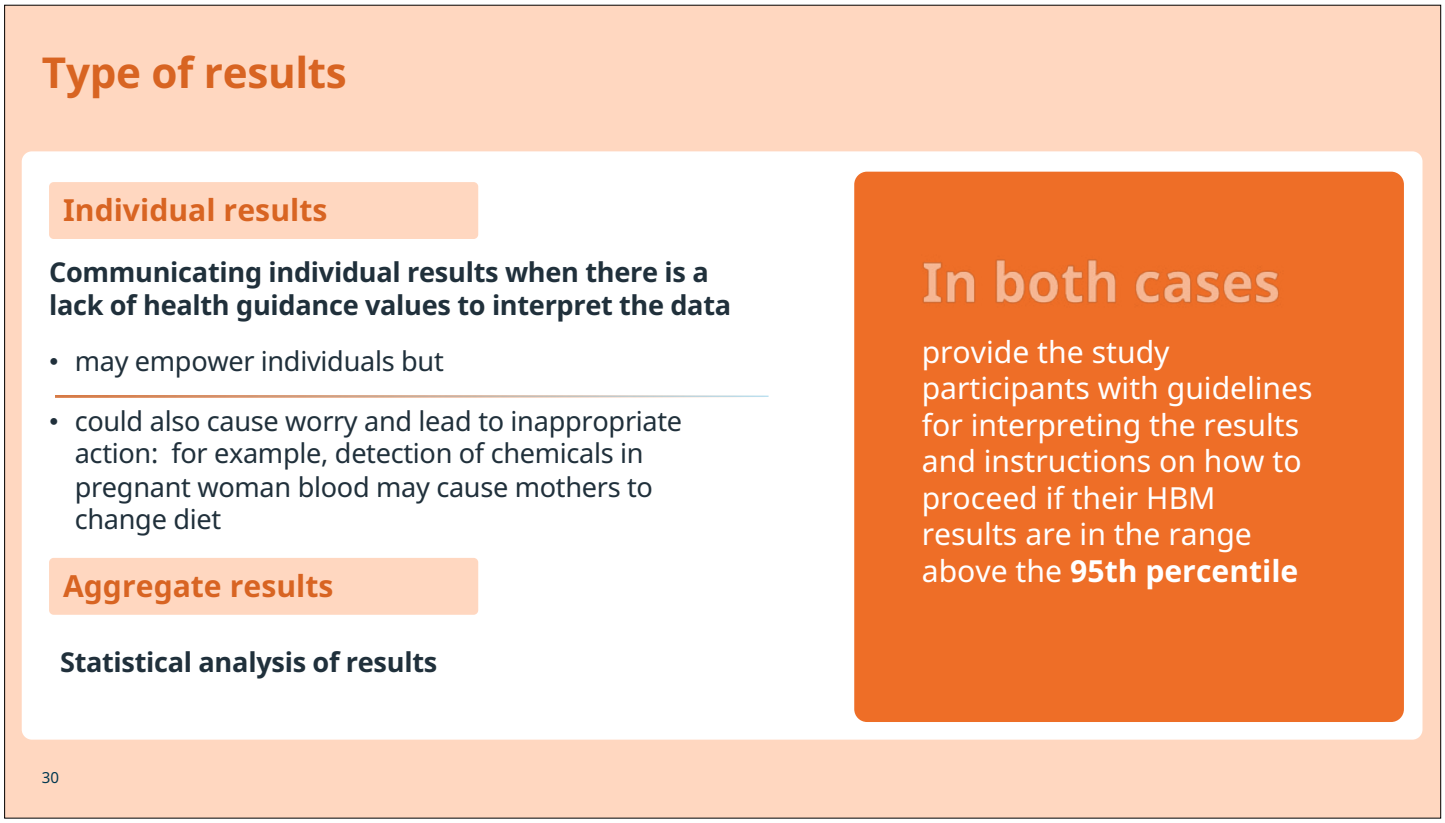
Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/334181, accessed 10 November 2022).



Notes: HBM: human biomonitoring.

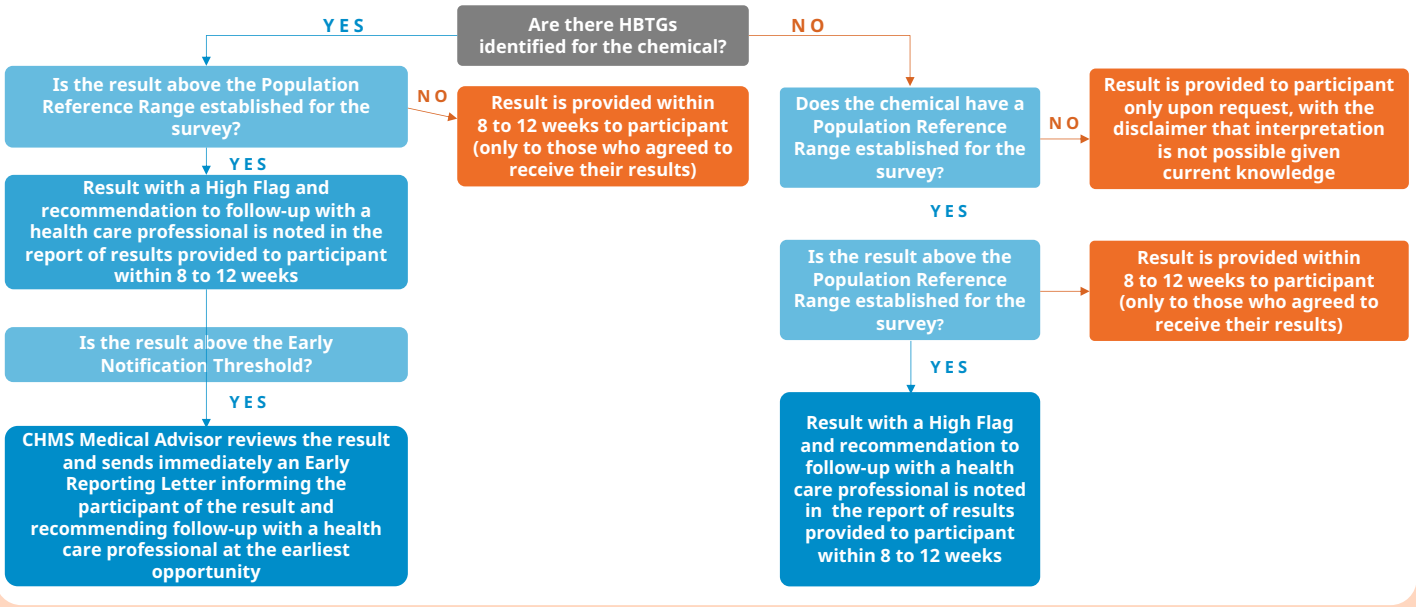
Sources

Exley K, Cano N, Aerts D, Biot P, Casteleyn L, Kolossa-Gehring M et al. Communication in a human biomonitoring study: focus group work, public engagement and lessons learnt in 17 European countries. Environ Res. 2015;141:31-41. doi: 10.1016/j.envres.2014.12.003.

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/334181, accessed 10 November 2022).

Haines DA, Arbuckle TE, Lye E, Legrand M, Fisher M, Langlois R et al. Reporting results of human biomonitoring of environmental chemicals to study participants: a comparison of approaches followed in two Canadian studies. J Epidemiol Community Health. 2011;65(3):191–8. doi: 10.1136/jech.2008.085597.

CHMS approach to reporting HBM results to participants



31 *Source*: Haines et al., 2011. Reproduced with permission from BMJ Publishing Group Ltd.

The strategy to communicate results to participants in the CHMS was developed with the advice and expert opinion of the Laboratory Advisory Committee, the Physician Advisory Committee and the reference laboratory performing the environmental chemical analyses. One of the main reasons motivating people to participate in the survey was the opportunity to receive their individual test results. Following the REB decision and national legislation, individuals have rights of access to personal information about themselves held by a Federal Government Institution.

In CHMS, all chemicals for which there was a HBTG had an established population reference range. When reporting individual results to study participants, three scenarios and associated actions were proposed:

- if an individual level is above an HBTG, then the individual result should be provided, and the participant notified as soon as the result is obtained;
- if an individual level is below a HBTG, then the individual result is provided at the end of the study, if requested;
- for chemicals that do not have HBTGs, the individual and study group results (range) should be provided at the end of the study, if requested.

Notes: CHMS: Canadian Health Measures Survey; HBM: human biomonitoring; HBTGs: health-based tissue guideline; REB: the Health Canada's Research Ethics Board.

Sources

Haines DA, Arbuckle TE, Lye E, Legrand M, Fisher M, Langlois R et al. Reporting results of human biomonitoring of environmental chemicals to study participants: a comparison of approaches followed in two Canadian studies. J Epidemiol Community Health. 2011;65(3):191–8. doi: 10.1136/jech.2008.085597.

Communication of results: tailoring messages for the audience (I)

To policy-makers, including government health-care and environmental protection authorities

Summary of the HBM study findings and proposal for further steps in risk reduction measures

To health-care professionals

- general information on the chemical(s)
- health effects
- main sources of exposure and exposure routes
- revealed risk of exposure
- diagnostic and treatment (practical recommendations in terms of HBM results)
- risk reduction measures
- vulnerable groups

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The summary for policy-makers should include information about the levels and distribution of exposure to the chemical(s) in a population, existing and projected health risk at population level, the main sources of exposure, as well as available and feasible actions and measures to reduce exposure and health risk. Ideally, a preventive action plan should be developed, with a proposed timeline and economic analysis of its implementation as well as information on good practice.

Notes: HBM: human biomonitoring.

Sources

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).

Communication of results: tailoring messages for the audience (II)

To general public and communities

misunderstanding should be avoided

populations at higher risk should be identified

recommendation on reducing exposure in the risk group should be included and explained

local conditions should be considered

risk perception by population should not be ignored

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Risk communication messages for the public and communities should be formulated in a way that avoids misunderstandings and undue concerns. It is recommended to include the following information:

- the meaning of the HBM survey results; and
- recommendations on reducing exposure to the chemical (e.g. Hg) and/or preventing health risks (e.g. fish consumption advice in exposure to methylmercury); it is essential to ensure that the risk communication process takes into consideration public perceptions;

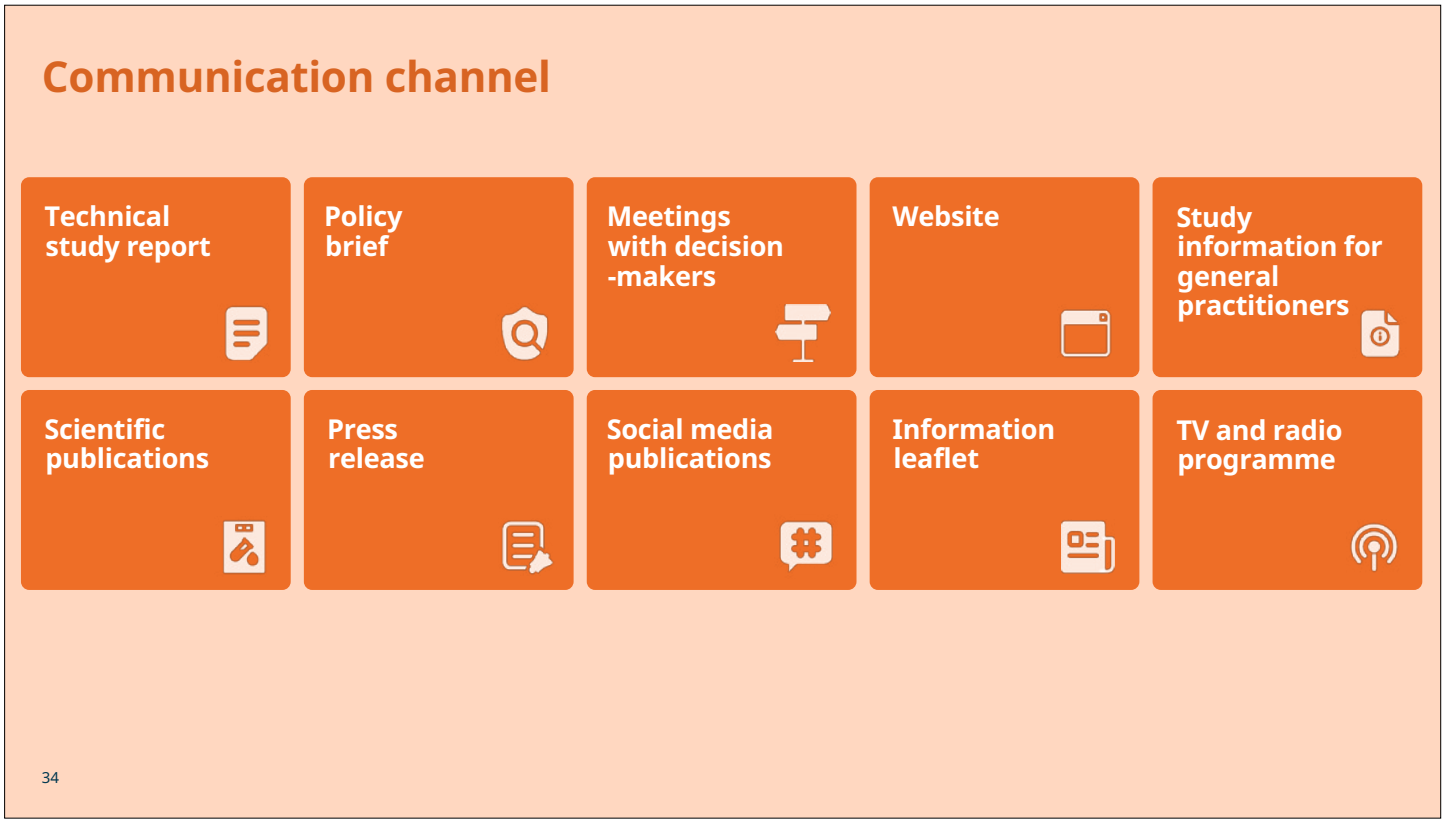
A community can be segmented, and different segments can receive different messages according to their specific needs.

Notes: HBM: human biomonitoring; Hg: mercury.

Sources

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/334181, accessed 10 November 2022).

WHO strategic communications framework for effective communications. Geneva: World Health Organization; 2017 (https://www.who.int/docs/default-source/documents/communicating-for-health/communication-framework.pdf, accessed 10 November 2022).



Sources

WHO strategic communications framework for effective communications. Geneva: World Health Organization; 2017 (https://www.who.int/docs/default-source/documents/communicating-for-health/communication-framework.pdf, accessed 10 November 2022).

Reporting of individual result (*example*): Total Hg in hair sample

	Name:
Level of total Hg measured in hair	0.8 µg/g hair
Health based reference value(s)	1.9 µg/g (European Food safety authority) 1 µg/g (United States EPA for pregnant women)
What does your result mean?	Your result is below the reference value
Do I need to do anything?	**a)** There is no need for action. **b)** We would recommend reducing exposure as much as possible. Since mercury in hair mainly reflects exposure through fish consumption you should avoid eating mercury-containing fish species like tuna fish or shark.

35 *Source*: EFSA, 2012. US EPA, 1997.

Notes: Hg: mercury; EPA: Environmental Protection Agency.

Sources

Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).

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Assessment of prenatal exposure to mercury: standard operating procedures. Copenhagen: WHO Regional Office for Europe; 2018 (https://apps.who.int/iris/handle/10665/332161, accessed 19 January 2023).

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MODULE 7

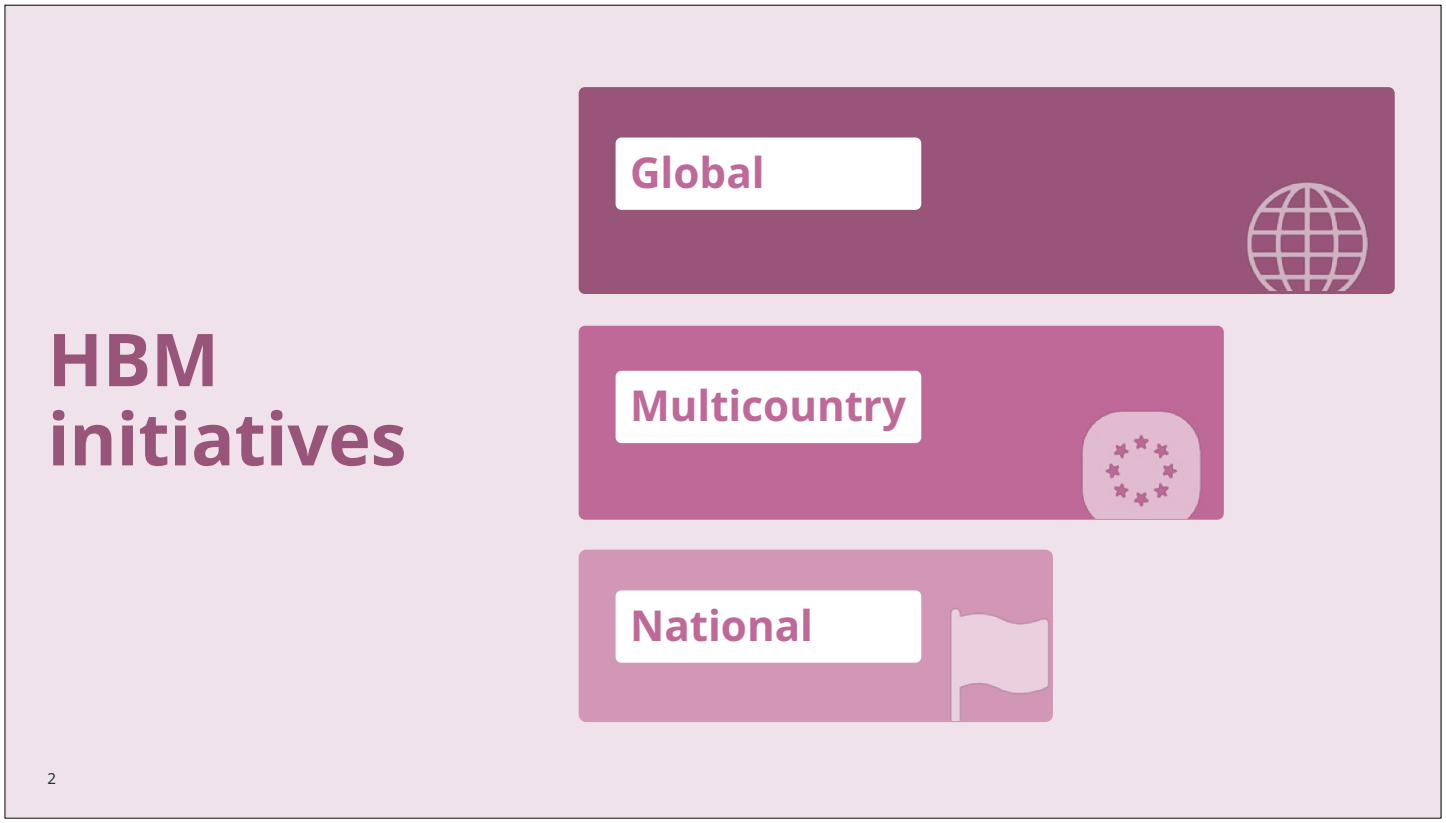
Existing HBM experience and initiatives

Global: Stockholm Convention on Persistent Organic Pollutants, Minamata Convention on Mercury

Multicountry: European Human Biomonioring Initiative, Artic Monitoring Assesmment Programme

National (examples from Belgium, Canada, Czechia, Germany, Japan, Republic of Korea, Slovenia and the United States)

World Health Organization
European Region



There are many HBM studies, surveys and projects in many countries around the world and their number increasing. Just in Europe, a total of 192 HBM studies were reported from 29 European countries in 2017.

At global level, there are two initiatives to date (the Stockholm Convention for persistent organic pollutants and the Minamata Convention for Mercury. There are multicountry projects and activities in Europe and other regions (HBM4EU, AMAP, etc.).

Notes: AMAP: Arctic Monitoring and Assessment Programme; HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative.

Sources

Human biomonitoring: facts and figures. Copenhagen: WHO Regional Office for Europe; 2015 (https://apps.who.int/iris/handle/10665/164588, accessed 10 November 2022).

Choi J, Mørck TA, Joas A, Knudsen LE. Major national human biomonitoring programs in chemical exposure assessment. Environ Sci. 2015;3:782-802. doi: 10.3934/environsci.2015.3.782.

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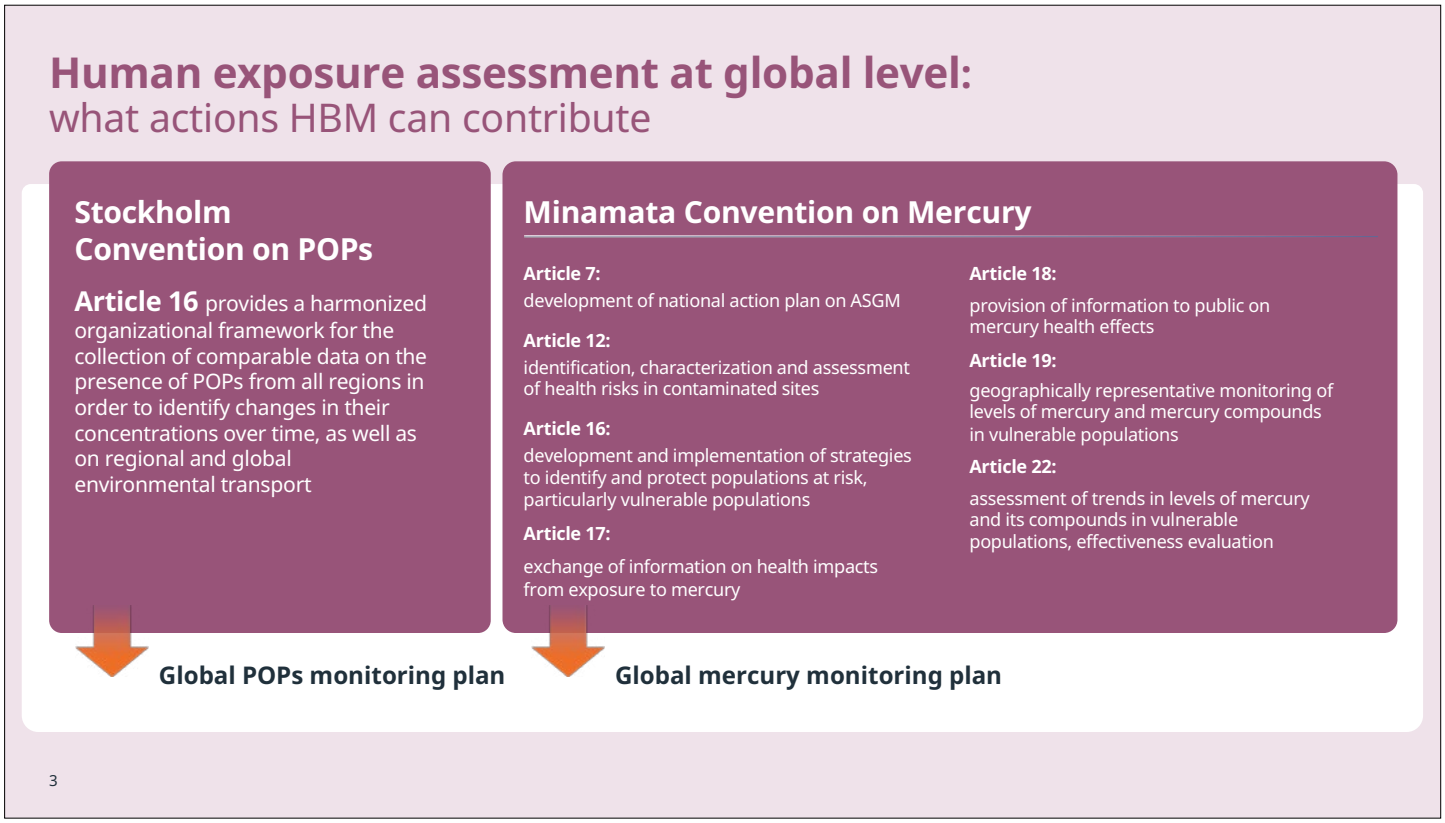
Minamata convention on mercury [website]. Geneva: United Nations Environment Programme, Secretariat of the Minamata Convention; 2022 (http://chm.pops.int/, accessed 10 November 2022).

European Human Biomonitoring Initiative [website]. Brussels: European Commission; 2023 (https://cordis.europa.eu/project/id/733032/, accessed 15 May 2023).

Human health in the Arctic 2021: summary for policy-makers. Tromsø: Arctic Monitoring and Assessment Programme; 2021 (https://www.amap.no/documents/download/6756/inline, accessed 10 November 2022).



The Stockholm Convention and the Minamata Convention encourage countries to assessment exposure and monitor trends, including through using HBM. The human health component warrants use of indicators that would prove that the exposure of humans to toxic chemicals is decreasing.

POPs global HBM surveys occurred from 1987 to 1992 and since 2007 have been carried out in a uniform manner globally. The mercury HBM is still being finalized but build on existing HBM activities carried out nationally and regionally.

Notes: ASGM: artisanal and small-scale gold mining; HBM: human biomonitoring; POPs: persistent organic pollutants.

Sources

Global POPs monitoring plan: Stockholm convention on persistent organic pollutants [website]. Geneva: Secretariat of the Stockholm Convention; 2022 (https://www.unep.org/explore-topics/chemicals-waste/what-we-do/persistent-organic-pollutants/global-monitoring, accessed 10 November 2022).

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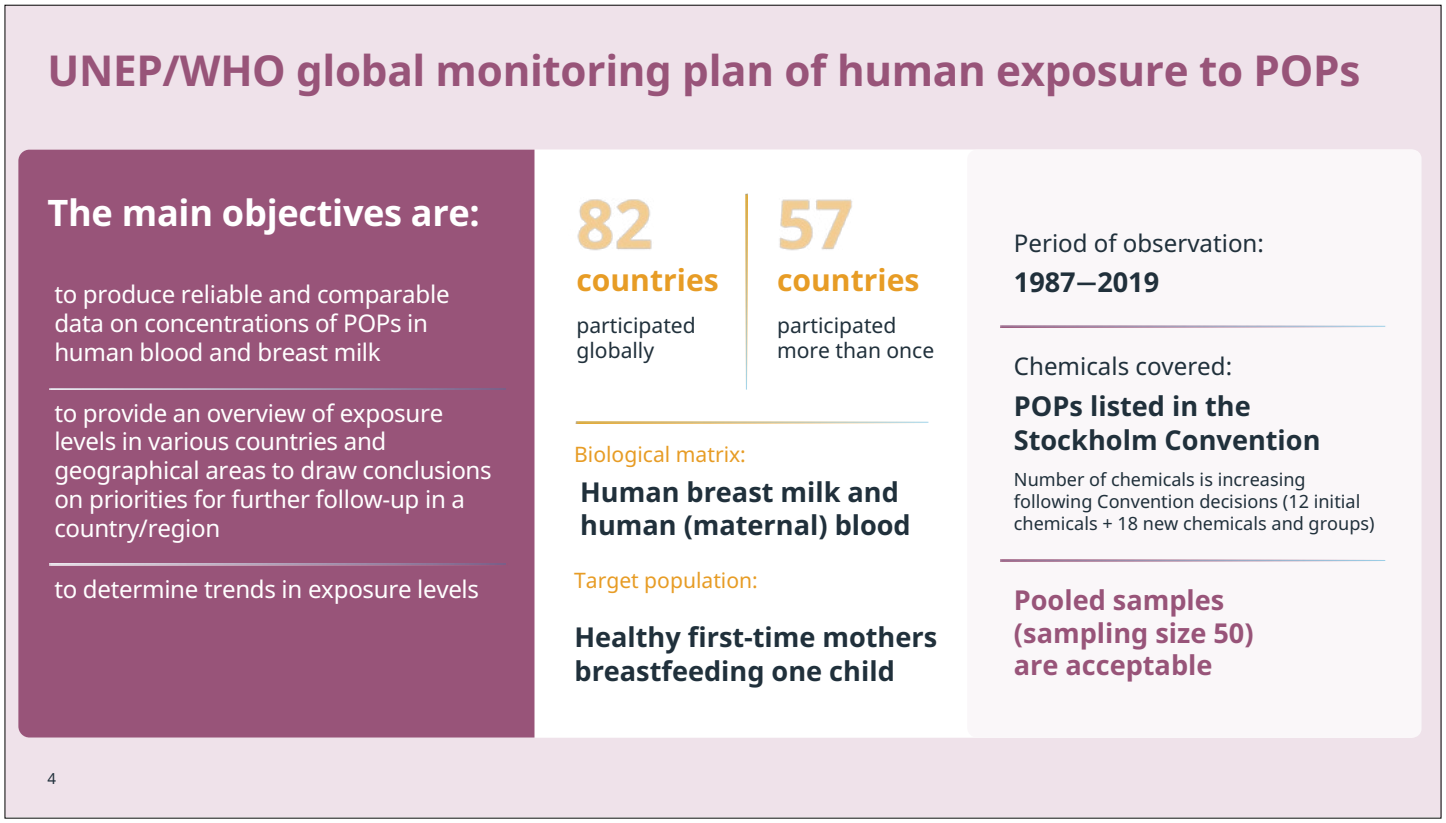

WHO surveys performed mainly in Europe and North America in 1987—1989 and 1992—1993 exclusively focused on three POPs groups (polychlorinated biphenyls, polychlorinated dibenzo-*p*-dioxins and dibenzofurans). In 2001–2003, a larger global survey was implemented, covering the 12 POPs initially listed in the Stockholm Convention. Following the ratification of the Stockholm Convention, WHO and the UNEP organized surveys on a regular basis. These studies significantly enlarged the geographical scope, providing representative results for all regions of the globe. Currently, the survey covers the 30 POPs listed in the Stockholm Convention. The programme assists national and regional capacity-building by supporting technical/analytical capability to detect POPs in humans.

Notes: POPs: persistent organic pollutants; UNEP: United Nations Environment Programme.

Sources

Guidance on the global monitoring plan for persistent organic pollutants. Nairobi: United Nations Environment Programme; 2013 (https://www.unep.org/explore-topics/chemicals-waste/what-we-do/persistent-organic-pollutants/global-monitoring, accessed 10 November 2022).

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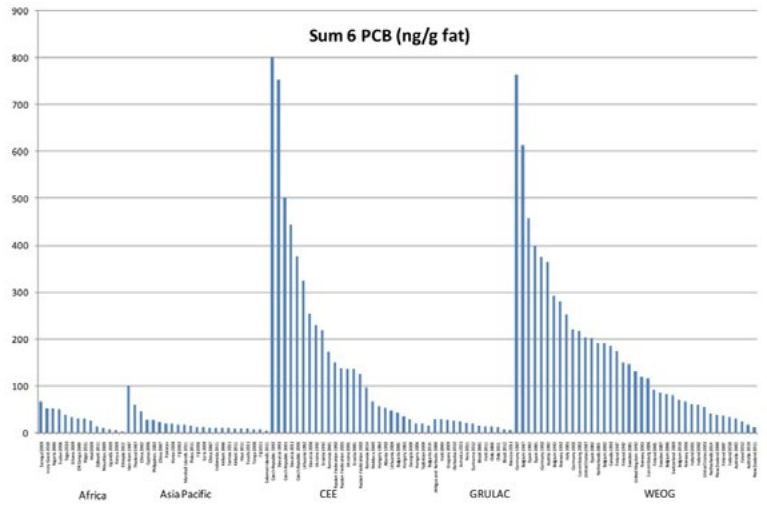
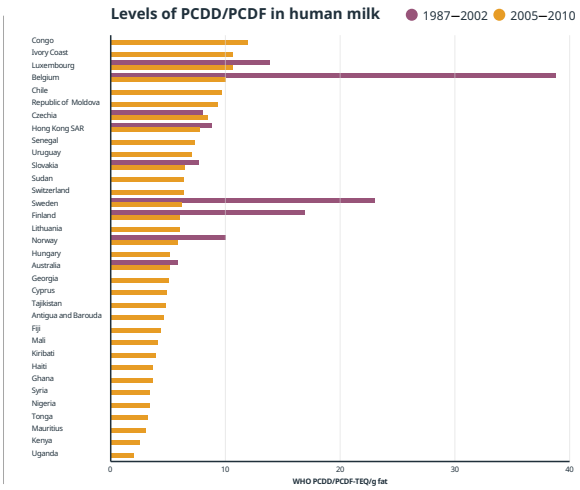
Stockholm convention global monitoring plan data warehouse. Geneva: Secretariat of the Stockholm Convention; 2022 (http://www.pops-gmp.org/, accessed 10 November 2022).

Monitoring reports [online database]. Geneva: Secretariat of the Stockholm Convention; 2022 (http://chm.pops.int/Implementation/GlobalMonitoringPlan/MonitoringReports/tabid/525/Default.aspx, accessed 10 November 2022).

van den Berg M, Kypke K, Kotz A, Tritscher A, Lee SY, Magulova K et al. WHO/UNEP global surveys of PCDDs, PCDFs, PCBs and DDTs in human milk and benefit-risk evaluation of breastfeeding. Arch Toxicol. 2017;91(1):83-96. doi: 10.1007/s00204-016-1802-z.

POPs global monitoring: spatial difference





Indicator PCB in human milk (Sum 6 PCB; ng/g fat)

Levels of PCDD/PCDF (Sum 17 PCDD/PCDF) and indicator PCB (Sum 6 PCB) in human breast milk: survey results in 2005–2010 and comparison with 1980s levels

5 *Source :* UNEP, 2017. Reproduced with permission from United Nations Environment Programme, Secretariat of the Stockholm Convention.

Notes: PCB; polychlorinated biphenyl; PCDD: dibenzo-p-dioxin; PCDF: dibenzofuran; PCDF-TEQ: toxic equivalent of PCDF; POPs: persistent organic pollutants.

Sources

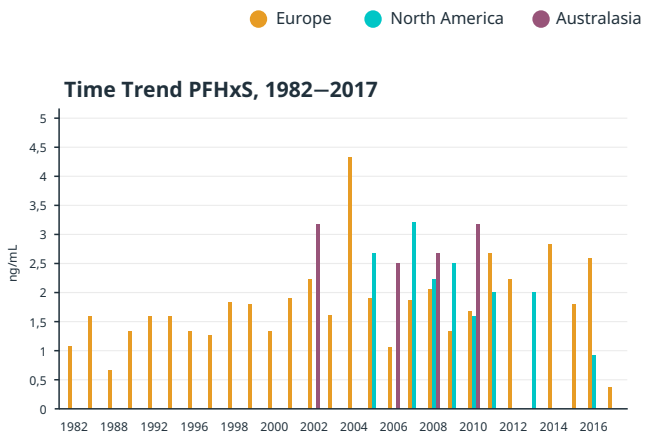
Monitoring reports [online database]. Geneva: Secretariat of the Stockholm Convention; 2022 (http://chm.pops.int/Implementation/GlobalMonitoringPlan/MonitoringReports/tabid/525/Default.aspx, accessed 10 November 2022).

Stockholm convention global monitoring plan data warehouse. Geneva: Secretariat of the Stockholm Convention; 2022 (http://www.pops-gmp.org/, accessed 10 November 2022).

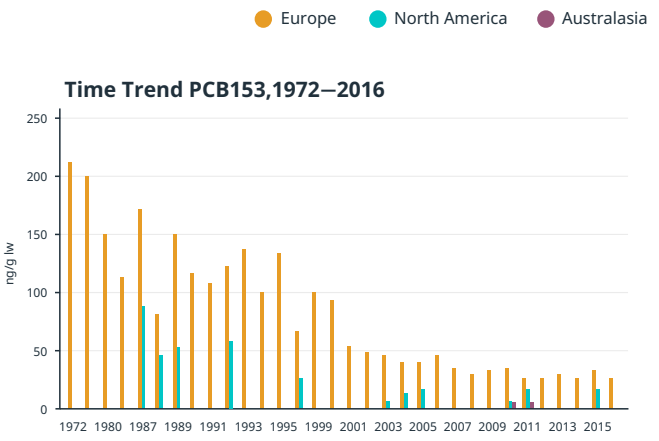
Fourth WHO-coordinated survey of human milk for persistent organic pollutants in cooperation with UNEP: guidelines for developing a national protocol. Geneva: World Health Organization; 2008.

Second global monitoring report. Geneva: United Nations Environment Programme, Secretariat of the Stockholm Convention; 23 January 2017 (UNEP/POPS/COP.8/INF/38; http://chm.pops.int/TheConvention/ConferenceoftheParties/Meetings/COP8/tabid/5309/Default.aspx, accessed 10 November 2022).

POPs global monitoring: time trends



Time trend for concentrations of PFHxS in human blood for Australasia, Europe and North America



Time trend for concentrations of PCB153 in breast milk for Australasia, Europe and North America

6 *Source*: UNEP, 2021. Reproduced with permission from United Nations Environment Programme, Secretariat of the Stockholm Convention.

The levels of majority of POPs* are decreasing over time in human milk and/or blood. Some of the newer POPs show an increase over time followed by a decrease. This is the case of brominated flame retardants PBDEs and HBCD. Data for PFOS and PFOA also indicate a similar increasing tendency followed by a decrease. This shows that restrictions and banning of production and use of these chemicals are successful in achieving their objectives in reducing contamination and human exposure.

*DDT, toxaphene, chlordane, dieldrin, HCB, HCH, toxaphene, chlordane and PCB, PCDF, PCDD, PCP.

Notes: DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; HBM: human biomonitoring; PBDE: polybrominated diphenyl ethers; PCB: polychlorinated biphenyls; PCDD: dibenzo-p-dioxin; PCDF: dibenzofuran; PFOS: perfluorooctanoic acid; POPs: persistent organic pollutants; UNEP: United Nations Environment Programme.

Sources

Guidance on the global monitoring plan for persistent organic pollutants. In: Tenth Meeting of the Conference of the Parties to the Stockholm Convention. Geneva: Secretariat of the Stockholm Convention; 2022 (UNEP/POPS/COP.10/INF/42; http://chm.pops.int/TheConvention/ConferenceoftheParties/Meetings/COP10/tabid/8397/Default.aspx, accessed 10 November 2022).

Global monitoring plan for persistent organic pollutants under the Stockholm Convention Article 16 on effectiveness evaluation: third regional monitoring report Western Europe and Others Group (WEOG) Region 2021. Geneva: United Nations Environment Programme, Secretariat of the Stockholm Convention; 29 March 2021 (http://chm.pops.int/implementation/globalmonitoringplan/monitoringreports/tabid/525/default.aspx, accessed 10 November 2022).

UNEP/WHO global HBM survey: benefits

The UNEP/WHO breast milk survey:

- use the harmonized methodology for sampling and data analysis
- is cost effective and provides data needed for decision-making
- provides new and extended scientific data
- generates comparable data allowing evaluation of temporal and spatial trends
- covers PCB, PCDD/PCDF, DDT/DDE, PBDEs and PFOS, with less information about the levels of the newly included compounds and generally not detectable compounds in blood and milk, such as aldrin and endrin
- confirms that the levels of legacy POPs in human milk and blood, such as PCDD/PCDF, PCB, and DDT/DDE, have been and continue to be on the decline
- assists regional capacity-building in developing countries by supporting technical/analytical capability to detect regional trends of POPs in humans

7

Notes: DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; HBM: human biomonitoring; PBDE: polybrominated diphenyl ethers; PCB: polychlorinated biphenyls; PCDD: dibenzo-p-dioxin; PCDF: dibenzofuran; PFOS: perfluorooctanoic acid; POPs: persistent organic pollutants; UNEP: United Nations Environment Programme.

Sources

Second global monitoring report. In: Eighth Meeting of the Conference of the Parties to the Stockholm Convention, Geneva, Switzerland, 24 April — 5 May 2017. Geneva: Secretariat of the Stockholm Convention; 2017 (UNEP/POPS/COP.8/INF/38; http://chm.pops.int/theconvention/conferenceoftheparties/meetings/cop8/tabid/5309/default.aspx, accessed 10 November 2022).

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May 2023).

UNEP/WHO global HBM survey: challenges

- Growing list of POPs is contributing to increasing analysis and reporting requirements for monitoring programmes
- National programmes evaluating time trends of chemicals in breast milk and/or blood are important, but levels are often not directly comparable with those in other regions because of differences in study design and populations
- Highly specialized analytical equipment and methods are required for some POPs, especially for detection at trace levels
- Rising costs associated with additional POPs in the list and analytical needs are increasing pressure on long-term programmes and diminishing feasibility of establishing new programme recommendations for human milk surveys
- No consistency in countries participation in the surveys
- Financial support is needed for countries with limited capacities

8

Notes: HBM: human biomonitoring; POPs: persistent organic pollutants; UNEP: United Nations Environment Programme.

Sources

Second global monitoring report. In: Eighth Meeting of the Conference of the Parties to the Stockholm Convention, Geneva, Switzerland, 24 April — 5 May 2017. Geneva: Secretariat of the Stockholm Convention; 2017 (UNEP/POPS/COP.8/INF/38; http://chm.pops.int/theconvention/conferenceoftheparties/meetings/cop8/tabid/5309/default.aspx, accessed 10 November 2022).

Global monitoring programme of exposure to Hg

Proposed framework for using HBM for effectiveness evaluation:

Government-led national biomonitoring programmes, regional initiatives and/or academic-led studies

A harmonized approach so that programmes are purposefully designed to fill data gaps, build capacities and support the effectiveness evaluation

Target population: general population as well as vulnerable groups

Biomarkers: urine, blood, hair
(depending on the form of Hg and other factors)

Survey protocol

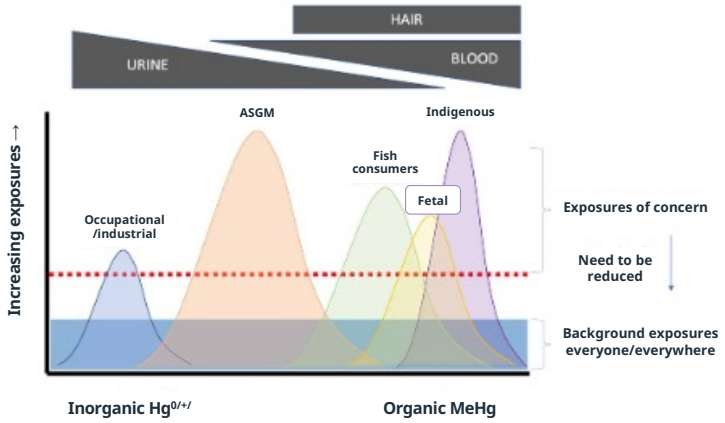


Diagram of accepted Hg biomarkers (at top) in relation to the different chemical forms of Hg that these biomarkers represent exposure to (at bottom)

Key population groups identified to be of concern from the Global Mercury Assessment 2018 are outlined in the middle of the figure, along with a horizontal band along the bottom that represents the general population

9 *Source*: UNEP, 2021. Reproduced with permission from United Nations Environment Programme, Secretariat of the Minamata Convention.

The recent Global Mercury Assessment 2018 showcased biomonitoring efforts worldwide ranging from engagement of vulnerable communities located in remote and resource-limited settings to national surveys implemented by government agencies involving thousands of participants.

The selection of a specific target population is commonly guided by the interests of the parties or relevant organizations carrying out the monitoring activities. For example, pregnant women, workers and community members living around artisanal small-scale gold mining sites, Indigenous people and local communities in certain areas.

Notes: ASGM: artisanal and small-scale gold mining; HBM: human biomonitoring; Hg: mercury; MeHg: methylmercury.

Sources

Guidance for identifying populations at risks from mercury exposure. Geneva: World Health Organization; 2008 (https://www.who.int/publications/m/item/guidance-for-identifying-populations-at-risk-from-mercury-exposure, accessed 10 November 2022).

Basu N, Horvat M, Evers DC, Zastenskaya I, Weihe P, Tempowski J. A state-of-the-science review of mercury biomarkers in human populations worldwide between 2000 and 2018. Env Health Perspect. 2018;126(10):106001. doi: 10.1289/EHP3904.

Guidance on monitoring of mercury and mercury compounds to support evaluation of the effectiveness of the Minamata Convention: giving effect to article 22: effectiveness evaluation, Geneva: United Nations Environment Programme, Secretariat of Minamata Convention; 23 September 2021 (UNEP/MC/COP.4/INF/12; https://mercuryconvention.org/en/documents/guidance-monitoring-mercury-and-mercury-compounds-support-effectiveness-evaluation-0, accessed 10 November 2022).

Hg HBM: WHO approach

Focus on prenatal exposure because of vulnerability to neurotoxicity

Target population:
Mothers who have just delivered a child

Recruitment:
During antenatal visits or at maternity wards

Biological matrix:
Cord blood, hair, urine

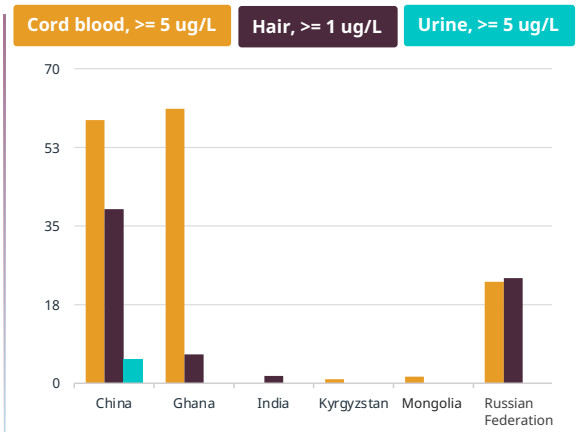
Sampling size:
250

Applicability:
Both general population and subgroups (e.g. hot spots)

Epidemiological questionnaire:
To identify sources of exposure

Analytical methods:
CV-AAS/AFS

Percentage individuals above reference level



Source: WHO pilot survey (2016–2018) (unpublished)

10

Notes: CV-AAS/AFS: cold vapour atomic absorption spectrometry/atomic fluorescence spectroscopy; HBM: human biomonitoring; Hg: mercury.

Sources

Assessment of prenatal exposure to mercury: human biomonitoring survey. The first survey protocol: a tool for developing national protocols. Copenhagen: WHO Regional Office for Europe; 2018 (https://www.who.int/publications/i/item/WHO-EURO-2020-1069-40815-55163, accessed 15 May2023).

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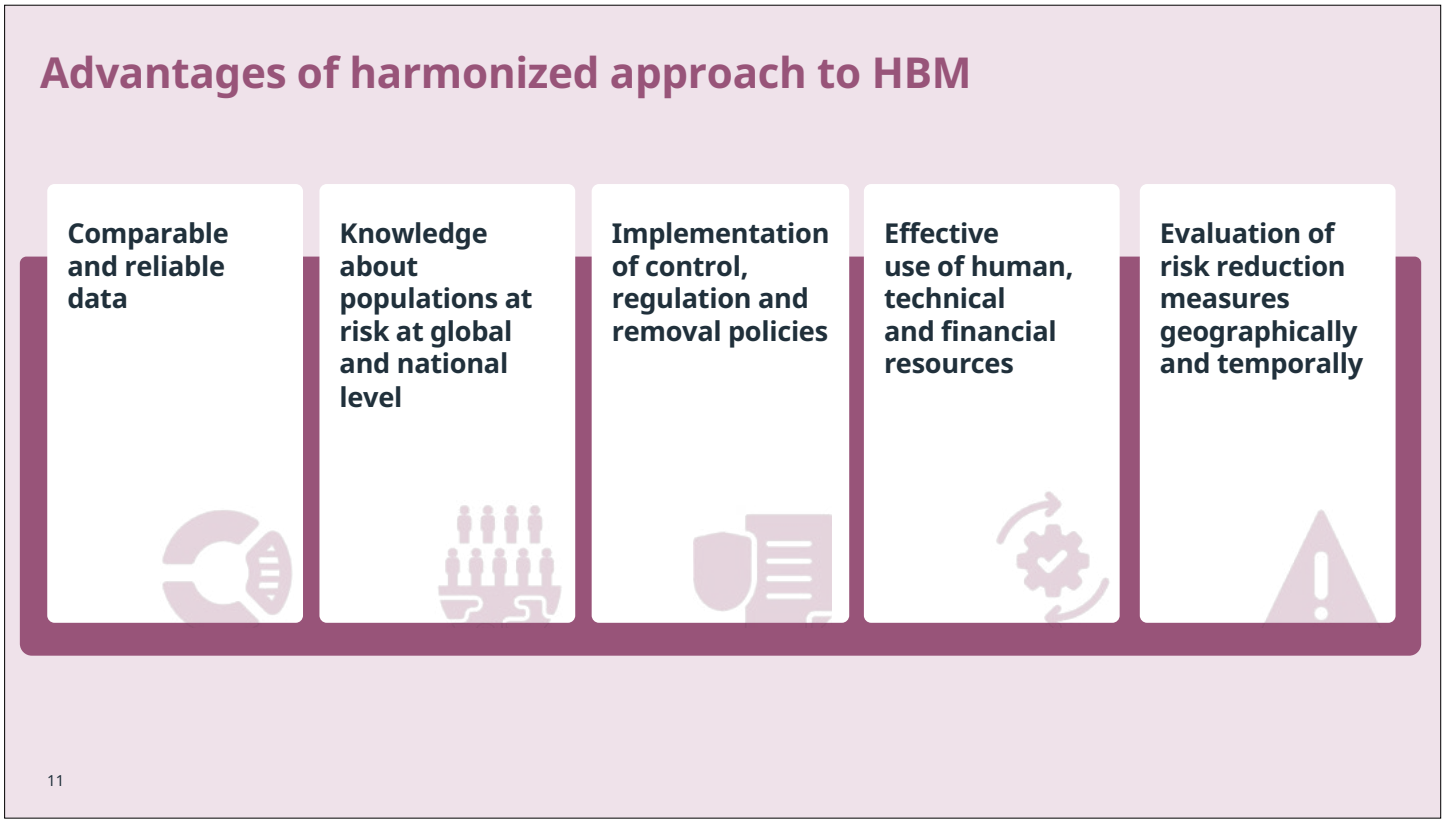

Notes: HBM: human biomonitoring.

Sources

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Mercury global monitoring plan. In: Minamata Convention on Mercury [website]. New York: UN Environment Programme; 2022 (mercuryconvention.org, accessed 10 November 2022).

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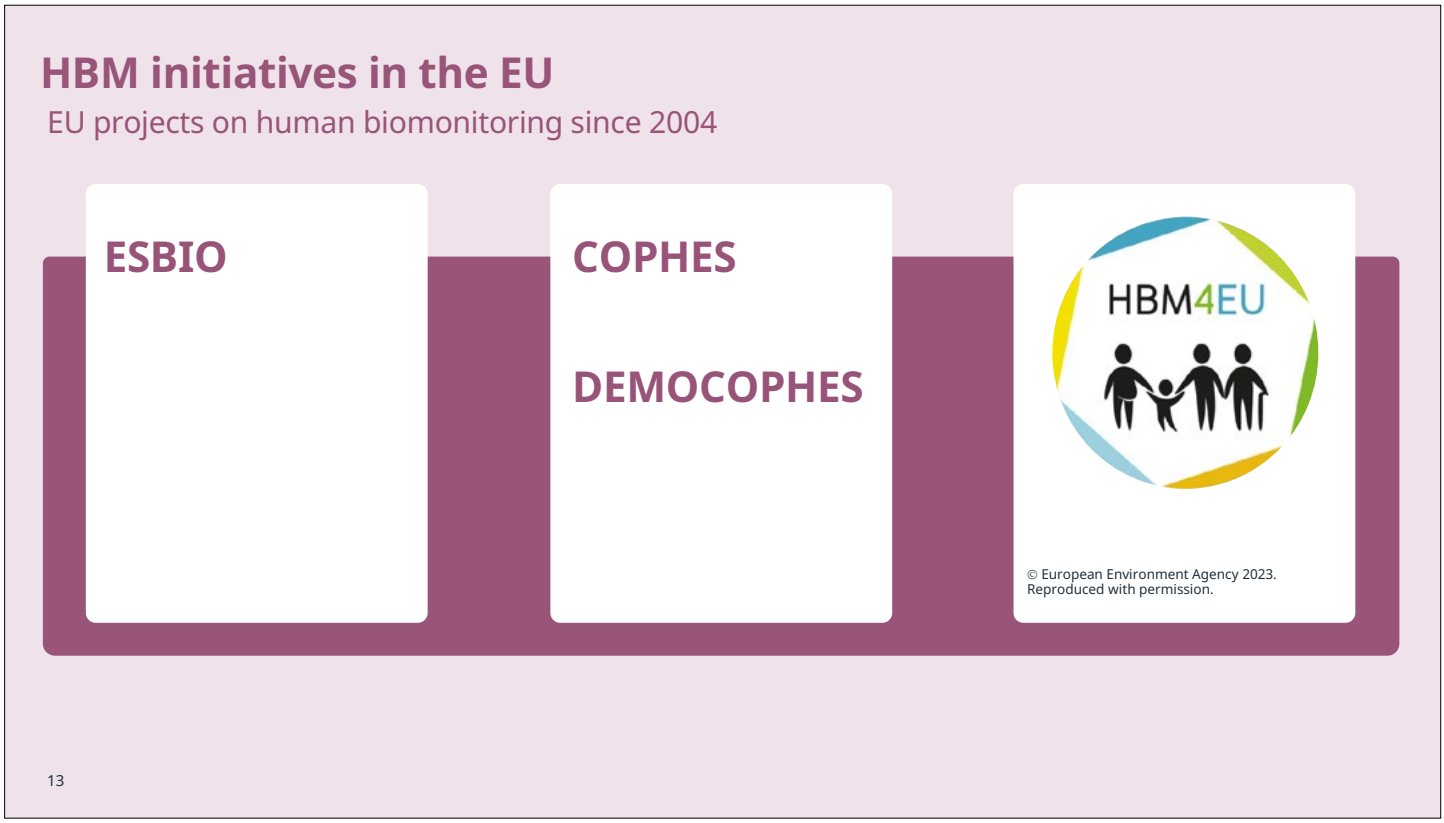
Multicountry initiatives



The EU has initiated a number of projects using HBM or being HBM in nature. Projects that examined the feasibility of HBM in the EU started in 2004 and were followed by COPHES/DEMOCOPHES in 2009–2012. More recently, the HBM4EU in 2016–2021 has aimed at harmonizing collected experience.

Notes: COPHES: Consortium to Perform Human Biomonitoring on a European Scale; DEMOCOPHES Demonstration of a Study to Coordinate and Perform Human Biomonitoring on a European Scale; ESBIO: Expert Team to Support BIO monitoring in Europe; EU: European Union; HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative.

Sources

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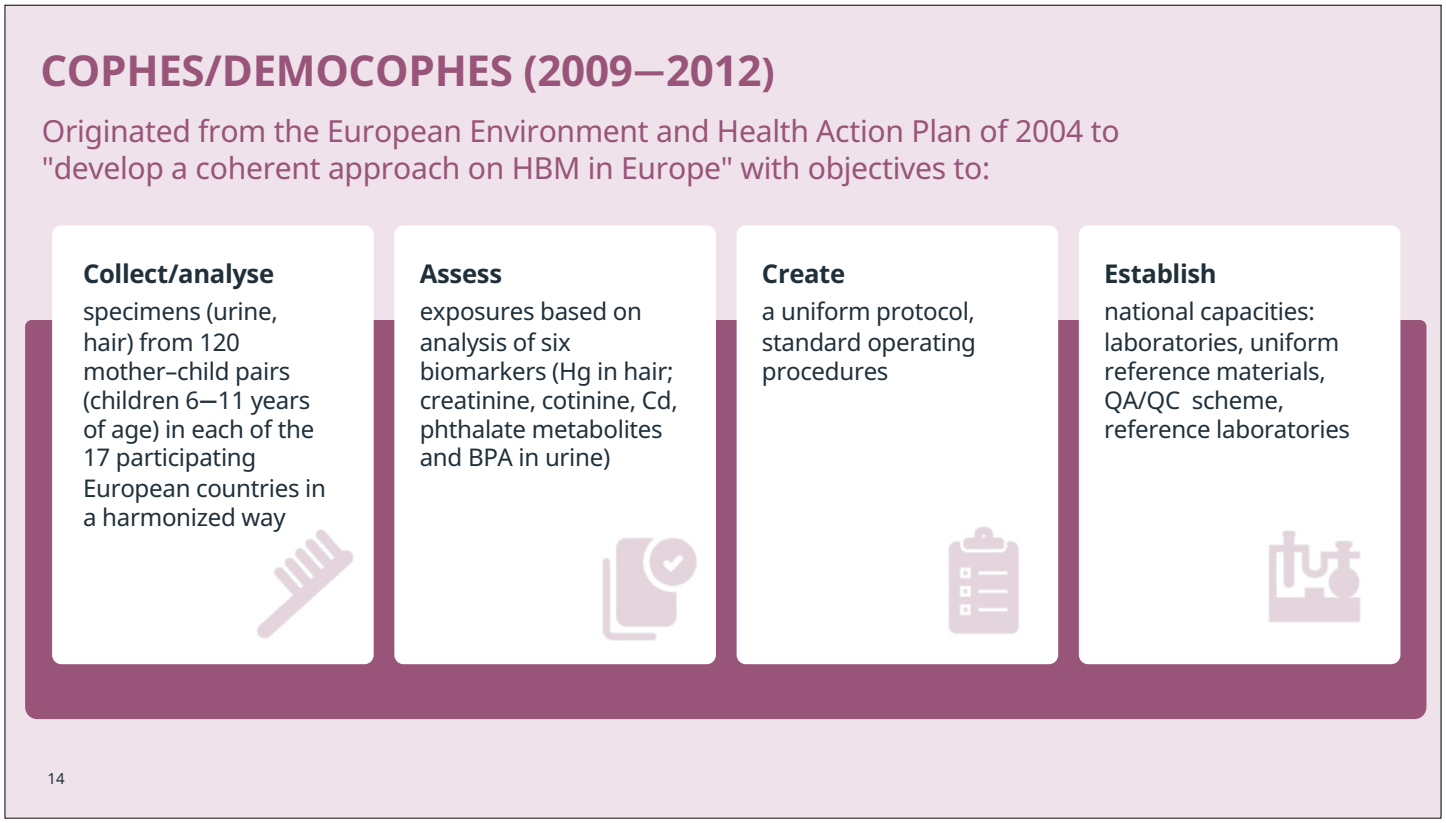

Notes: BPA: bisphenol A; Cd: cadmium; COPHES: Consortium to Perform Human Biomonitoring on a European Scale; DEMOCOPHES: Demonstration of a Study to Coordinate and Perform Human Biomonitoring on a European Scale; HBM: human biomonitoring; Hg: mercury; QA/QC: quality assurance/quality control.

Sources

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Project DEMOCOPHES. Dessau-Roßlau: German Environment Agency; 2019 (https://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/human-biomonitoring-in-europe/project-democophes, accessed 10 November 2022).

Schindler BK, Esteban M, Koch HM, Castano A, Koslitz S, Cañas A et al. The European COPHES/DEMOCOPHES project: towards transnational comparability and reliability of human biomonitoring results. Int J Hyg Environ Health. 2014;217(6):653-61. doi: 10.1016/j.ijheh.2013.12.002.

HBM4EU (2017–2022): objectives

- Coordinate and advance HBM in Europe through joint actions of
  - **30 countries and 117 partner institutions**
  - **the European Environment Agency**
  - **the European Commission (funded the activity)**
- Generate evidence of the actual exposure in the European population to chemicals and the possible health effects to support policy-making
- Build bridges between research and policy in order to deliver benefits to society in terms of enhanced chemical safety
- Represents a novel collaboration between scientists, chemical risk assessors and risk managers, including several Commission institutions, EU agencies and policy representatives at the national level

HBM4EU work will continue within the European PARC project

15

Notes: HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative; PARC: Partnership for the Assessment of Risks from Chemicals.

Sources

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Kolossa-Gehring M, Pack LK, Hulck K, Gehring T (2023) HBM4EU from the Coordinator's perspective: lessons learnt from managing a large-scale EU project. Int J Hyg Environ Health. 2023;247:114072. doi: 10.1016/j.ijheh.2022.114072.

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HBM4EU: priority chemicals

Acrylamide	Cd	Hg
Aniline family	Chemical mixtures	Mycotoxins
Aprotic solvents	Cr VI	Per/polyfluorinated compounds
As	Emerging chemicals	Pesticides
Benzophenones	Flame retardants	Phthalates and Hexamoll® DINCH
Bisphenols	Pb	PAHs

16

Notes: As: arsenic; Cd: cadmium; Cr: chromium; Hg: mercury; HBM4EU: European Human Biomonitoring Initiative; DINCH: 1,2-cyclohexane dicarboxylic acid ester; PAHs: polycyclic aromatic hydrocarbons; Hexamoll© DINCH: non-phralate plasticizer (BASF); Pb: lead.

Sources

Ougier E, Ganzleben C, Lecoq P, Bessems J, David M, Schoeters G et al. Chemical prioritisation strategy in the European Human Biomonitoring Initiative (HBM4EU) - Development and results. Int J Hyg Environ Health. 2021;236:113778. doi: 10.1016/j.ijheh.2021.113778.

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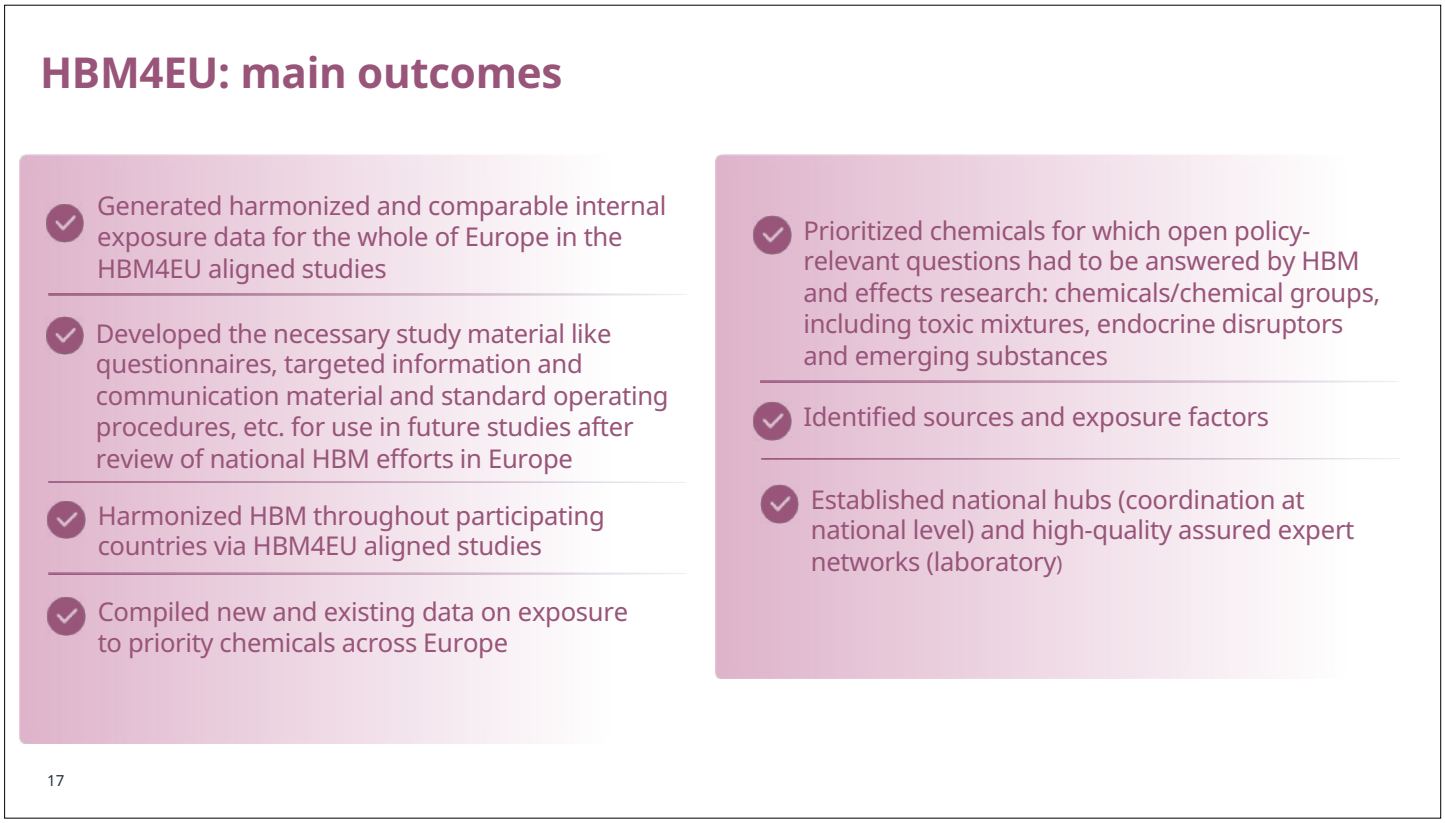

Notes: HBM: human biomonitoring; HBM4EU: European Human Biomonitoring Initiative.

Sources

Govarts E, Gilles L, Rodriguez ML, Santonen T, Apel P, Alvito P et al. Harmonized human biomonitoring in European children, teenagers and adults: EU-wide exposure data of 11 chemical substance groups from the HBM4EU Aligned Studies (2014–2021). Int J Hyg Environ Health. 2023;249:114119. doi: 10.1016/j.ijheh.2023.114119.

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Lobo Vicente J, Ganzleben C, Gasol R, Marnane I, Gilles L, Buekers J et al. HBM4EU results support the Chemicals' Strategy for Sustainability and the Zero-Pollution Action Plan. Int J Hyg Environ Health. 2023;248:114111. doi: 10.1016/j.ijheh.2023.114111.

The AMAP

The programme began in 1991

to advise the governments of the eight Arctic countries (Canada, Denmark/Greenland, Finland, Iceland, Norway, the Russian Federation, Sweden and the United States) on matters relating to threats to the Arctic region from pollution

to produce sound science-based, policy-relevant assessments and public outreach products to inform policy and decision-making

HBM covers:

- POPs and CEC
- heavy metals, with a particular focus on Hg

Location of recent and ongoing blood monitoring, temporal trend and human health cohort studies around the Arctic

Disclaimer: the designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

18 *Source*: AMAP, 2015.

The network of the AMAP was established to assess the implications and impacts of pollution on the health of Arctic residents. The biomonitoring programme monitors concentrations of contaminants in in maternal blood and breastmilk in the eight circumpolar nations and assesses spatial and temporal patterns/trends and potential health effects at present and future levels.

A broad range of health effects research is carried out within the framework of the Programme: neurodevelopment, cardiovascular diseases, metabolic and immune dysfunction, obesity, diabetes, etc.

The measured contaminants include:

POPs: oxychlordane, *trans*-nonachlor; *p*,*p*′-DDT; *p*,*p*′-DDE; toxaphene; PCBs (99, 118, 138, 153, 180); Aroclor 1260, Σ14 PCBs; hexachlorobenzene; mirex; heavy metals (total and organic Hg); Pb; Cd; selenium; emerging contaminants, pharmaceutics, personal care products (e.g. PBDEs (47, 99, 100, 153, 183, 209); PFOS; PFOA); TBBPA; PCP; hydroxylated PCBs (107, 146, 187).

Notes: AMAP: Arctic Monitoring and Assessment; DDE: dichloroethylene; DDT: dichlorodiphenyltrichloroethane; HBM: human biomonitoring; Hg: mercury: Pb: lead; PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulfonate; PBDE: polybrominated diphenyl ethers; PCB: polychlorinated biphenyls; PCP: pentachlorophenol; POPs: persistent organic pollutants; TBBPA: tetrabromobisphenol A.

Sources

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National initiatives

Examples from Belgium, Canada, Germany, Czechia, Japan, Republic of Korea, Slovenia and the United States

FLEHS 2002–2020

More than 20 years of follow up of general population (three age groups) and hot spots

More than 8000 participants

Combination of cross-sectional and cohort studies and samples stored in biobank

Reference values for more than 80 biomarkers of exposure and of effect:

Classical pollutants:

heavy metals, dioxins, PCBs, PAHs, DDT, etc.

"New" pollutants:

phthalates, musks, parabens, organophosphate pesticides, etc.

Biomarkers of effect:

genotoxicity markers, hormone levels, non-invasive markers in breath condensate, fertility markers, questionnaires (e.g. asthma and allergy), etc.

Chemicals of emerging concern

20

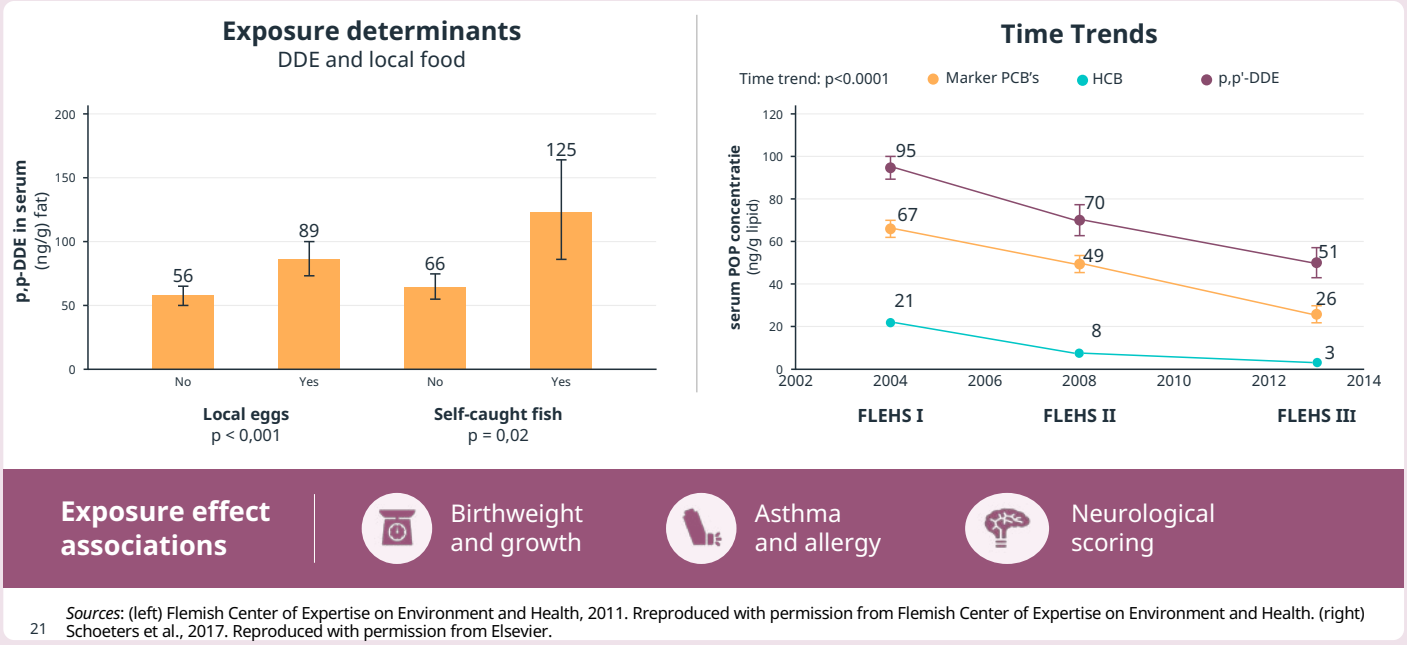
Four rounds of national HBM were conducted in Belgium over 2002–2020. FLEHS I–III were financed by the Flemish Department of Science and Innovation, Nature and Energy and the Agency for Care and Health; FLEHS IV was financed by the Department of Environment. The FLEHS is coordinated by VITO, and carried out by an interdisciplinary consortium with involvement of Flemish universities.

Notes: DDT: dichlorodiphenyltrichloroethane; HBM: human biomonitoring; FLEHS: The Flemish Human Biomonitoring Program; PAHs: polycyclic aromatic hydrocarbons; PCBs: polychlorinated biphenyls; VITO: the Flemish Institute for Technological Research.

Sources

Schoeters G, Den Hond E, Colles A, Loots I, Morrens B, Keune H et al. Concept of the Flemish human biomonitoring programme. Int J Hyg Environ Health. 2012;215(2):102–8. doi: 10.1016/j.ijheh.2011.11.006.

Objective: identification of highly exposed population subgroups



21 *Sources*: (left) Flemish Center of Expertise on Environment and Health, 2011. Rreproduced with permission from Flemish Center of Expertise on Environment and Health. (right) Schoeters et al., 2017. Reproduced with permission from Elsevier.

Notes: DDE: dichloroethylene; HCB: hexachlorobenzene; FLEHS: The Flemish Human Biomonitoring Program; PCB: polychlorinated biphenyls; POPs: persistent organic pollutants.

Sources

Schoeters G, Verheyen VJ, Colles A, Remy S, Martin LR, Govarts E et al. Internal exposure of Flemish teenagers to environmental pollutants: results of the Flemish Environment and Health Study 2016–2020 (FLEHS IV). Int J Hyg Environ Health. 2022;242:113972. doi: 10.1016/j.ijheh.2022.113972.

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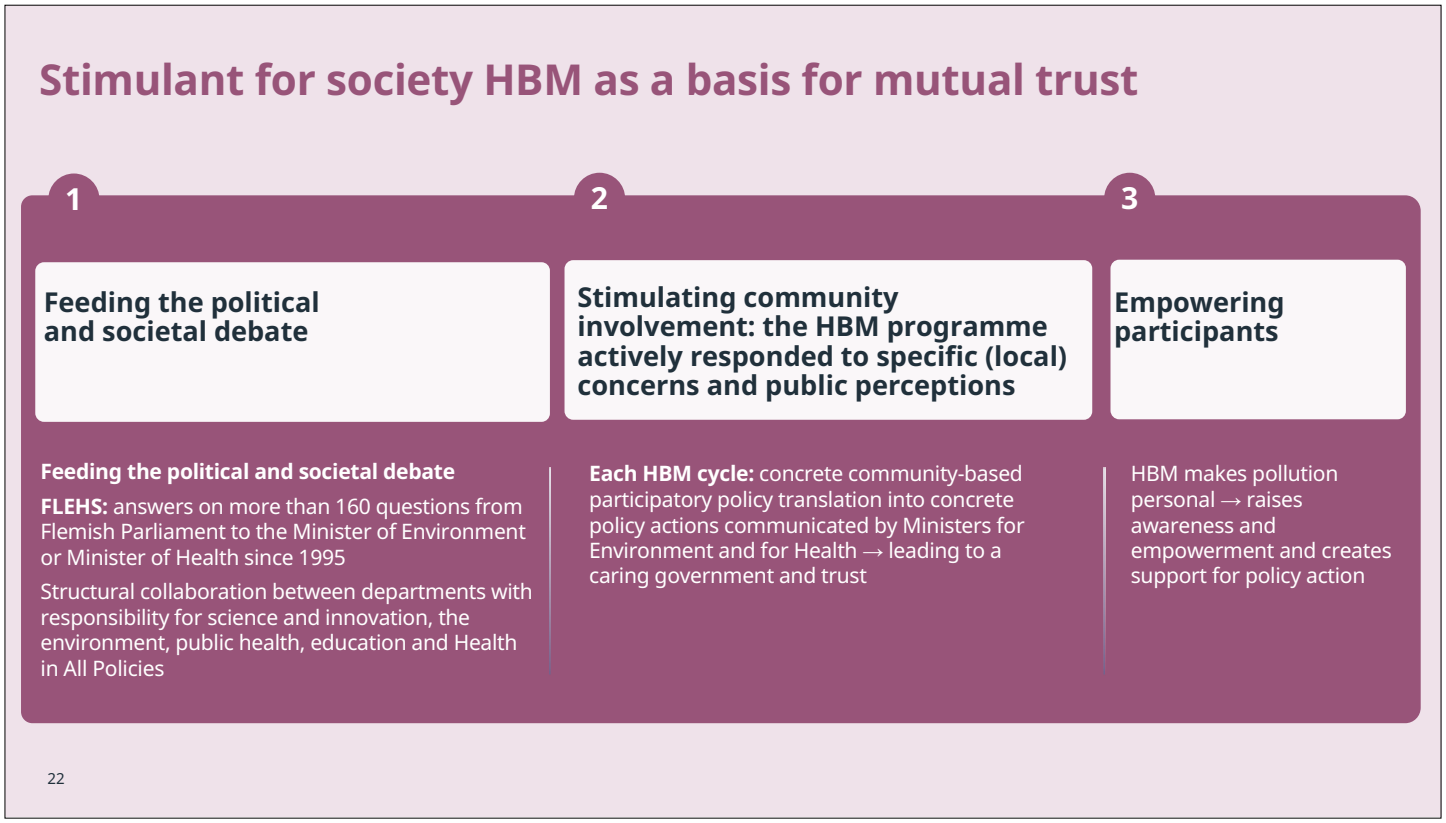
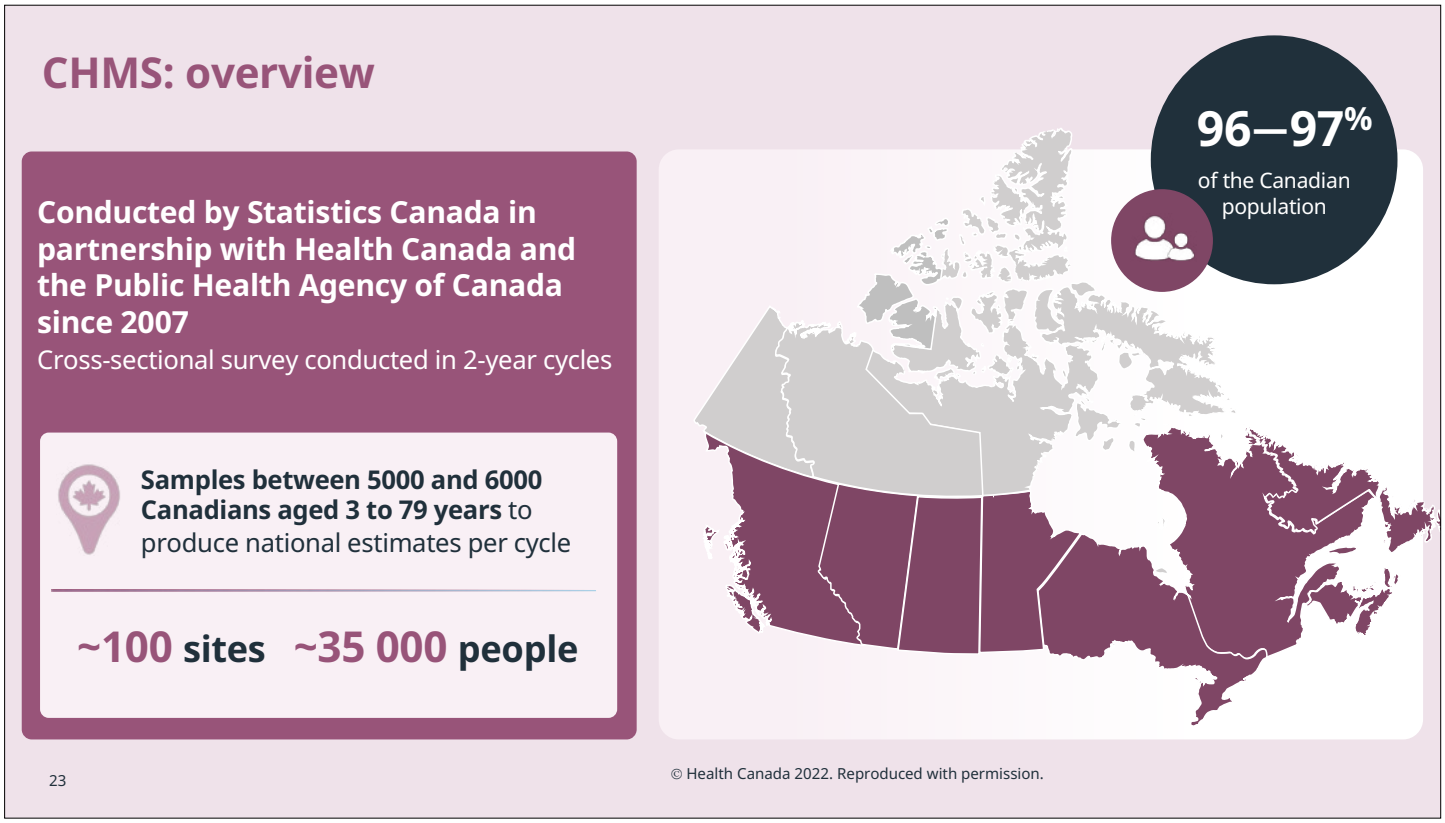


Notes: HBM: human biomonitoring; FLEHS: The Flemish Human Biomonitoring Program.

Sources

Reynders H, Colles A, Morrens B, Mampaey M, Coertjens D, Koppen G et al. The added value of a surveillance human biomonitoring program: the case of FLEHS in Flanders (Belgium). Int J Hyg Environ Health. 2017;220(2 Pt A):46-54. doi: 10.1016/j.ijheh.2016.09.013.



Data from the CHMS biomonitoring component have been used to inform and support the Government of Canada in its ongoing monitoring, surveillance, risk management and regulatory activities, which are required by multiple legislative acts such as the CEPA. Biomonitoring data are used:

- as evidence in RA;
- to track effectiveness of risk management actions (such as working in close collaboration with the Risk Management Bureau on the Performance Measurement Evaluation Report, for which many indicators have also been developed using CHMS biomonitoring data); and
- for chemical prioritization.

There are other national surveys in Canada, such as the FNBI, the MIREC and the Northern Contaminants Programs.

Notes: CHMS: the Canadian Health Measures Survey; FNBI: the First Nations Biomonitoring Initiative; MIREC: the Maternal-Infant Research on Environmental Chemicals; RA: risk assessment.

Sources

Biomonitoring content summary for the Canadian Health Measures Survey: cycles 1–6 (2007–2019). Ottowa: Government of Canada; 2019 (https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/biomonitoring-content-summary-canadian-health-measures-survey.htm, accessed 10 November 2022).

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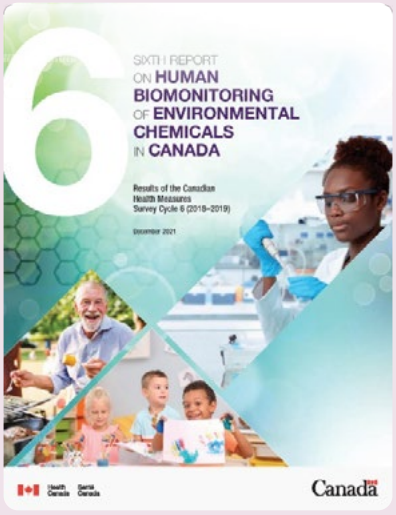
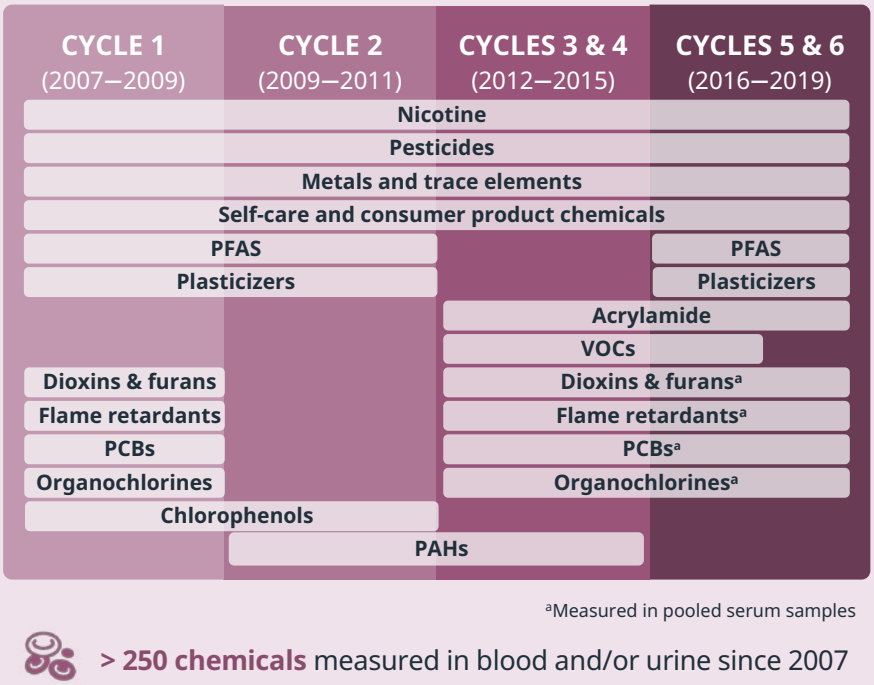
CHMS: environmental chemicals





24 *Source*: (left) Health Canada, 2021. Reproduced with permission from Health Canada.

In total, over 250 chemicals have been measured in at least one cycle, with the latest cycle data released December 2021. Some chemical groups have been measured in each cycle while others have been cycled in and out of the survey.

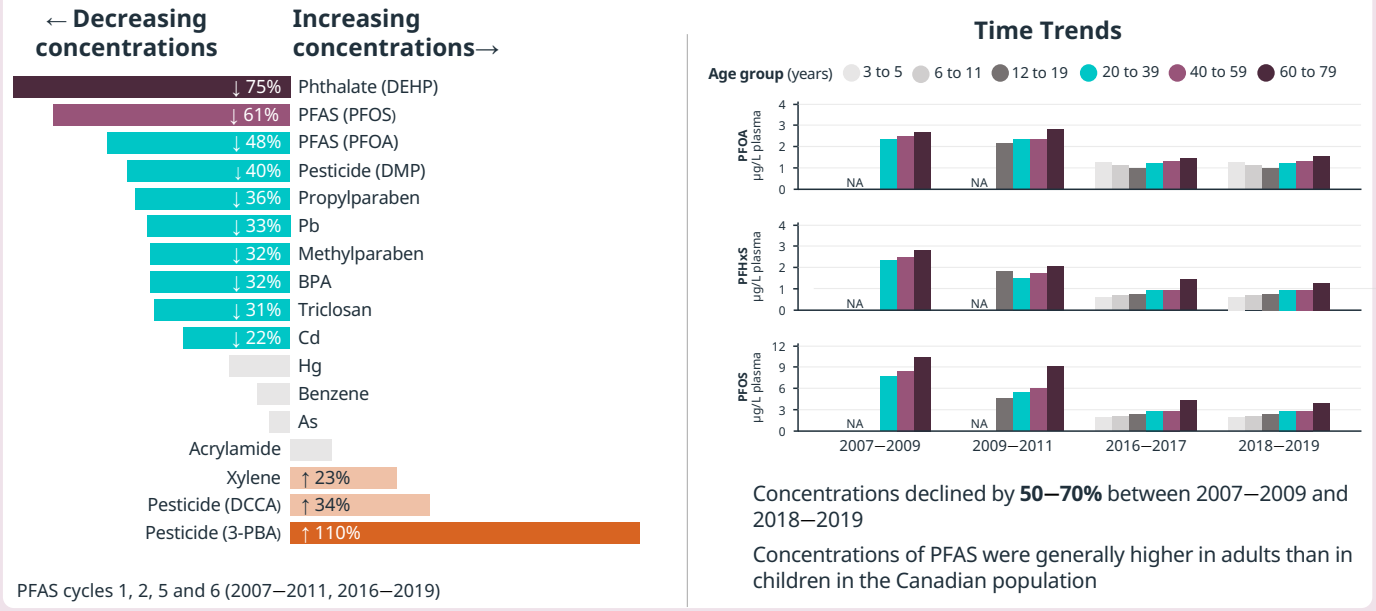
Notes: CHMS: the Canadian Health Measures Survey; PAHs: polycyclic aromatic hydrocarbons; PFAS: per- and polyfluoroalkyl substances; PCBS: polychlorinated biphenyls; VOCs: volatile organic compounds.

Sources

Human biomonitoring resources [online database]. Ottowa: Government of Canada; 2021 (https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/environmental-contaminants/human-biomonitoring-resources.html, accessed 10 November 2022).

Biomonitoring content summary for the Canadian Health Measures Survey: cycles 1–6 (2007–2019). Ottowa: Government of Canada; 2019 (https://www.canada.ca/en/health-canada/services/environmental-workplace-health/environmental-contaminants/human-biomonitoring-environmental-chemicals/canadian-health-measures-survey.html, accessed 10 November 2022).

CHMS: outcomes from the HBM component



25 *Source*: Health Canada, 2022. Reproduced with permission from Health Canada.

HBM data from the CHMS are reported primarily through national reports, the latest being the Sixth Report of Human Biomonitoring of Environmental Chemicals.

Biomonitoring factsheets were added to the CHMS in 2021 to provide visualizations of the latest data on Canadians exposure to environmental chemical. They highlight changes in chemical exposures over time, distributions across age groups, differences between males and females and comparisons with data from other biomonitoring initiatives in Canada or the National Health and Nutrition Examination Survey in the United States.

With more than 10 years of data published, Canada's national biomonitoring programme has multiple cycles of data on several chemicals, allowing the programme to begin looking at trends. Most of the chemicals presented are decreasing over time. It also shows that establishing and maintaining a biomonitoring programme is a long-term commitment. It can take up to 10 years to accumulate enough data to establish trends and see changes in exposure patterns.

Notes: As: arsenic; BPA: bisphenol A; Cd: cadmium; CHMS: the Canadian Health Measures Survey; Hg: mercury; DEHP: Di(2-ethylhexyl)phthalate; DCCA: trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid; DMP: dimethylphosphate; HBM human biomonitoring; Pb: lead; 3-PBA: 3-phenoxybenzoic acid; PFAS: per- and polyfluoroalkyl substances; PFHxS: perfluorohexanesulfonic; PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulfonate.

Sources

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GerES

Survey	Period	Size
GerES I	1985—1986	**2731** adults
GerES II	1990—1992	**4287** adults **812** children
GerES III	1997—1999	**4822** adults
Ger IV	2003—2006	**1790** children
GerES V	2014—2017	**2294** children & adolescents
GerES VI	*2023—2024*	***1500*** *adults*

Cross-sectional population representative study

- 167 sampling locations (GerES V)
- Human biomonitoring (first-morning void urine, blood)
- Ambient monitoring at home
- Interviews on exposure-relevant behaviours and other exposure factors
- Investigation of associated health outcomes
- Toxicological interpretation using health-based guidance values of the German Human Biomonitoring Commission

GerES

Cooperation: Health + Environment

26 *Sources:* (top) Mauz et al., 2017. Reproduced with permission from Robert Koch Institute. (bottom) © German Environment Agency 2023. Reproduced with permission.

There are two main German HBM initiatives: the GerES and the ESB.

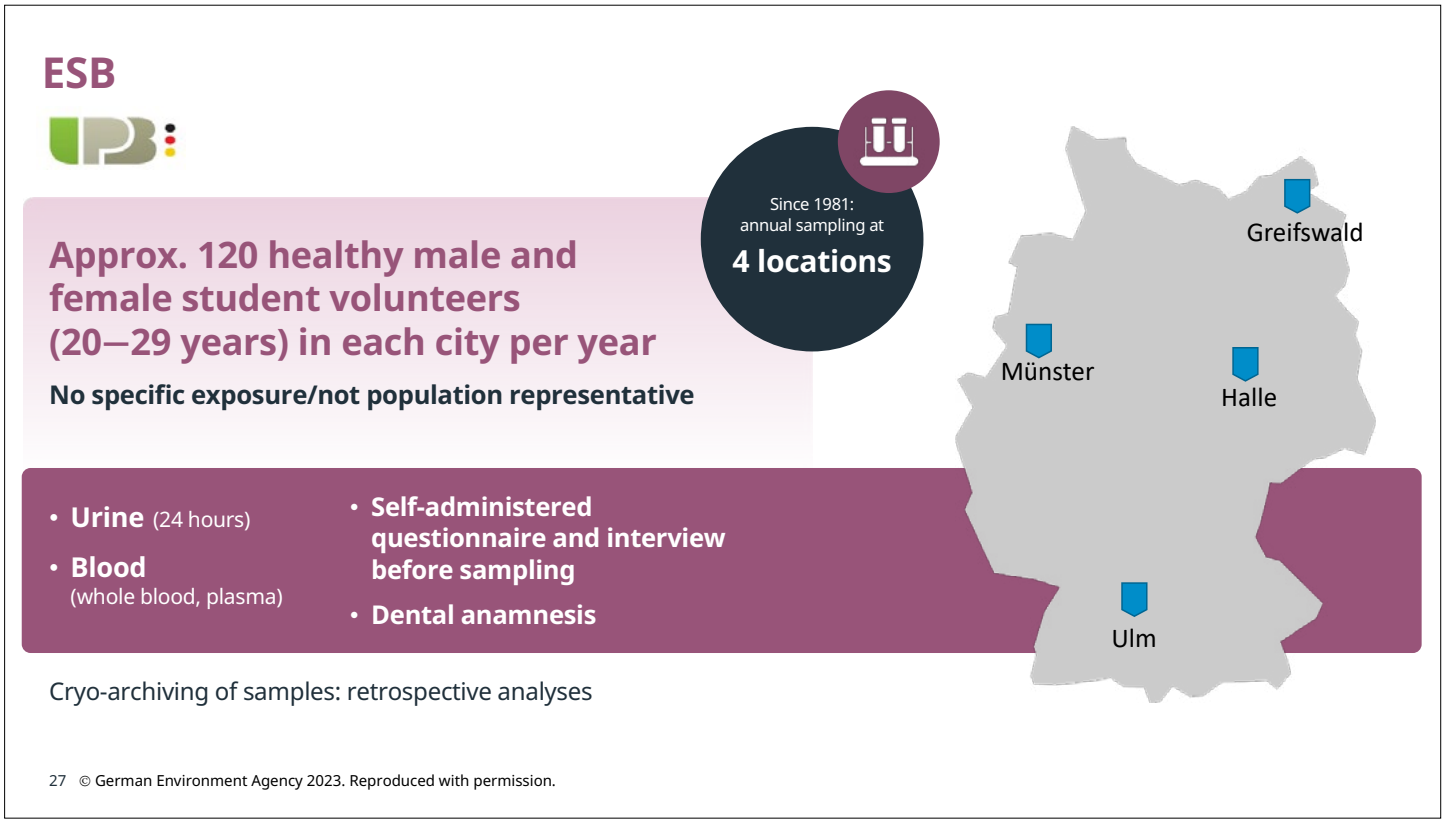
Notes: ESB: the German Environmental Specimen Bank ; GerES: German Environmental Survey.

Sources

The German Environmental Specimen Bank [website]. Dessau-Roßlau: German Environment Agency; 2022 (https://www.umweltprobenbank.de/en/documents, accessed 10 November 2022).

Kolossa-Gehring M, Becker K, Conrad A, Schröter-Kermani C, Schulz C, Seiwert M Environmental surveys, specimen bank and health related environmental monitoring in Germany. Int J Hyg Environ Health. 2012;215(2):120-126. doi: 10.1016/j.ijheh.2011.10.013.

Mauz E, Gößwald A, Kamtsiuris P et al. New data for action. Data collection for KiGGS Wave 2 has been completed: concepts and methods. J Health Monit 2017; 2 (S3): 2–27; doi: 10.17886/RKI-GBE-2017-105.



The ESB is an archive for samples that can be used to document and assess the quality of the environment in which we live. These samples are representative of a particular area and are collected regularly in order to monitor changes of pollution over the course of time.

Notes: ESB: German Environmental Specimen Bank.

Sources

German environmental survey, GerES 2014—2017 [website]. Dessau-Roßlau: German Environment Agency; 2022 (https://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/german-environmental-surveys/german-environmental-survey-2014-2017-geres-v, accessed 10 November 2022).

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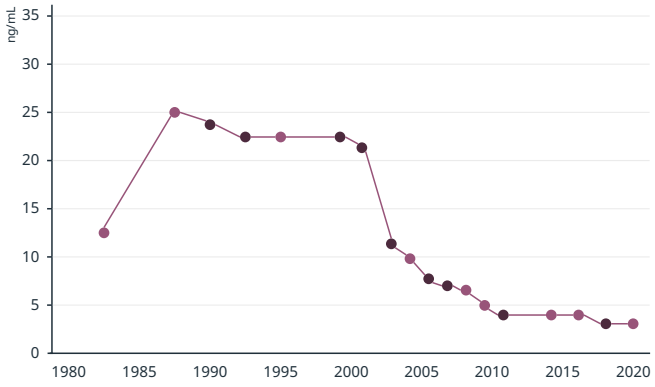
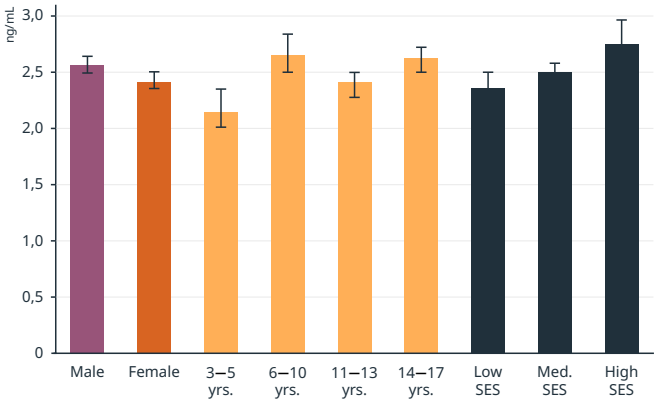
ESB and GerES: PFOS example

ESB data show time trend of exposure
GerES data show representative exposure, evaluating the potential issue for highly exposed subgroups





Time trend of exposure ESB
Adults aged 20–29 years

Representative data GerES V (2014–2017)
sex, age groups, SES

28

Notes: ESB: German Environmental Specimen Bank; GerES: German Environmental Survey; PFOS: perfluorooctane sulfonate; SES: socioeconomic status.

Sources

The German Environmental Specimen Bank [website]. Dessau-Roßlau: German Environment Agency; 2022 (https://www.umweltprobenbank.de/en/documents, accessed 10 November 2022).

German environmental survey, GerES 2014–2017 [website]. Dessau-Roßlau: German Environment Agency; 2022 (https://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/german-environmental-surveys/german-environmental-survey-2014-2017-geres-v, accessed 10 November 2022).

Duffek A, Conrad A, Kolossa-Gehring M, Lange R, Rucic E, Schulte C et al. Per- and polyfluoroalkyl substances in blood plasma – Results of the German Environmental Survey for children and adolescents 2014–2017 (GerES V). Int J Hyg Environ Health. 2020;228: 113549. doi: 10.1016/j.ijheh.2020.113549.

Göckener B, Weber T, Rüdel H, Bücking M, Kolossa-Gehring M. Human biomonitoring of per- and polyfluoroalkyl substances in German blood plasma samples from 1982 to 2019. Environment International. 2020;145:106123; doi: 10.1016/j.envint.2020.106123.

Health-based assessment of internal exposures

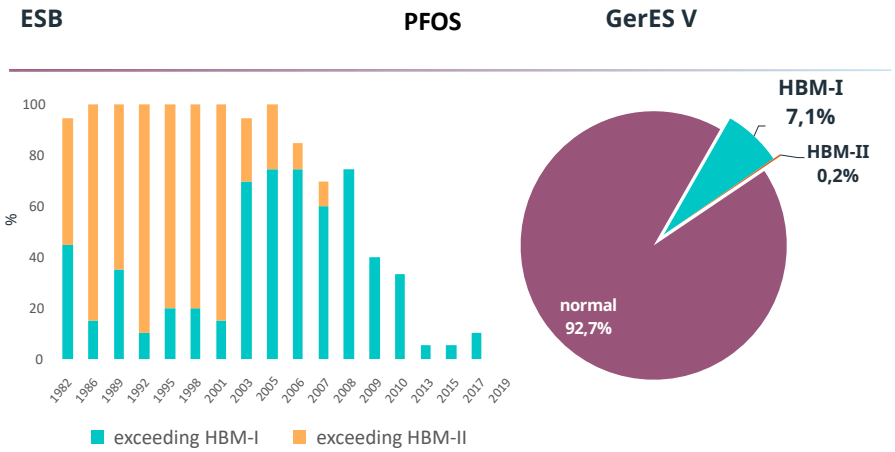
HBM Commission of the German Environment Agency
develops toxicologically derived health-based guidance values

At or above HBM-I value:

adverse health effects, according to current knowledge, cannot be ruled out with sufficient certainty

At or above HBM-II value:

adverse health effects are possible; need for exposure reduction and medical advice



29

Notes: ESB: German Environmental Specimen Bank; HBM: human biomonitoring; GerES: German Environmental Survey; PFOS: perfluorooctane sulfonate.

Sources

Reference and HBM values. Dessau-Roßlau: German Environment Agency; 2022 (https://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/human-biomonitoring-commission/reference-hbm-values, accessed 10 November 2022).

Apel P, Angerer J, Wilhelm M, Kolossa-Gehring M. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int J Hyg Environ Health. 2017;220(2, Part A):152-66. doi: 10.1016/j.ijheh.2016.09.007.

HBM initiatives and experience in Czechia

National HBM programme launched in 1994

as an integral part of the nationwide EHMS, overseen by the Czech Ministry of Health and National Institute of Public Health

Populations including in the HMB:

Adults aged 18—58 years (total 4472 participants, last sampling 2018), about 350—500 participants/year

Children aged 8—10 years (total 1916 participants, last sampling in 2016)

Breastfeeding first-time mother (total 5667 participants, last sampling in 2017)

Sampling

Organized on a yearly basis between 1994 and 2018

Biomarkers

Pb, Cd, Hg, Cu, Se, Zn in blood and urine of adults and children (+ hair)

Indicator PCBs, DDT, DDE, HCB and HCHs in human milk and blood serum of adults

cytogenetic changes in peripheral lymphocytes in blood of adults and children

30

Notes: Cd: cadmium; Cu: copper; DDE: dichloroethylene; DDT: dichlorodiphenyltrichloroethane; EHMS: Environmental Health Monitoring System; HCB: hexachlorobenzene; HCHs: hexachlorocyclohexanes; HBM: human biomonitoring; HG: mercury; PCBS: polychlorinated biphenyls; Pb: lead; Se: selenium; Zn: zink.

Sources

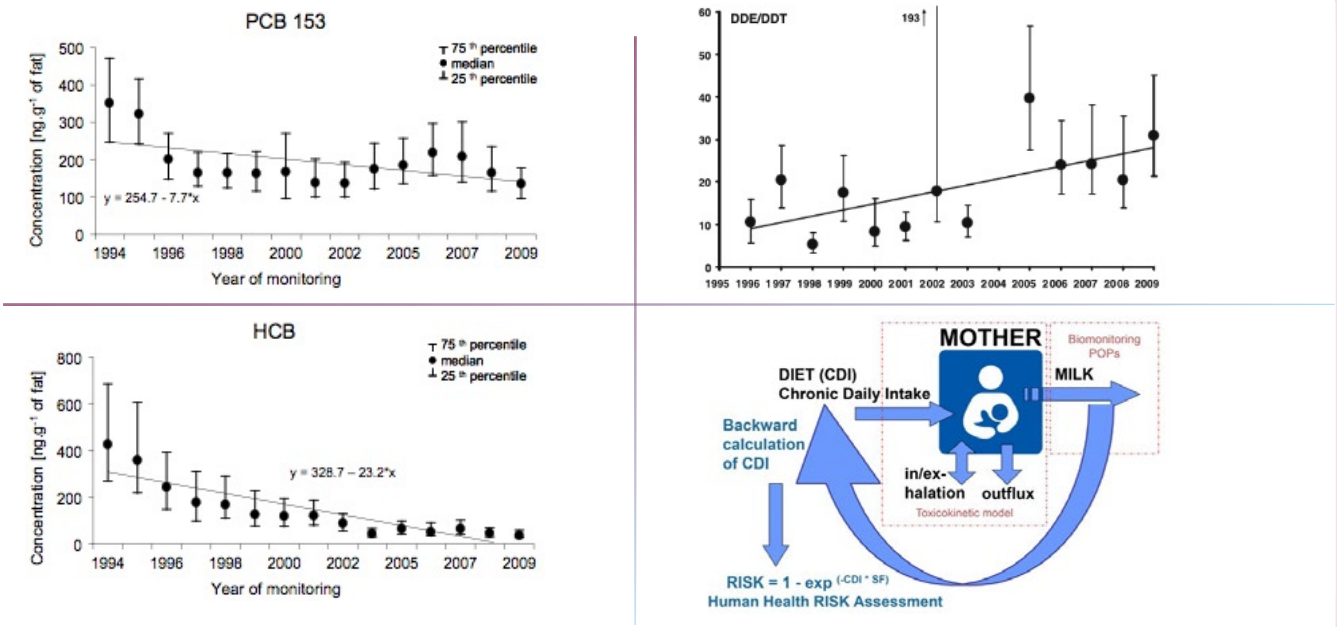
Yearbooks/summary reports on environmental health monitoring system in the Czech Republic [online database]. Prague: State Institute of Health; 2022 (in Czech; http://www.szu.cz/tema/zivotni-prostredi/odborne-zpravy-1, accessed 10 November 2022).

Choi J, Mørck TA, Joas A, Knudsen LE. Major national human biomonitoring programs in chemical exposure assessment. Environ Sci. 2015;3:782-802. doi: 10.3934/environsci.2015.3.782.

Černá M, Krsková A, Cejchanová M, Spěváčková V. Human biomonitoring in the Czech Republic: an overview. Int J Hyg Environ Health. 2011;215(2):109-19. doi: 10.1016/j.ijheh.2011.09.007.

Černá M, Puklová V, Hanzlíková L, Sochorová L, Kubínová R. 25 years of HBM in the Czech Republic. Int. J. Hyg. Environ. 2017;220:3-5. doi: 10.1016/j.ijheh.2016.08.004.

Long-term monitoring of human milk in Czechia



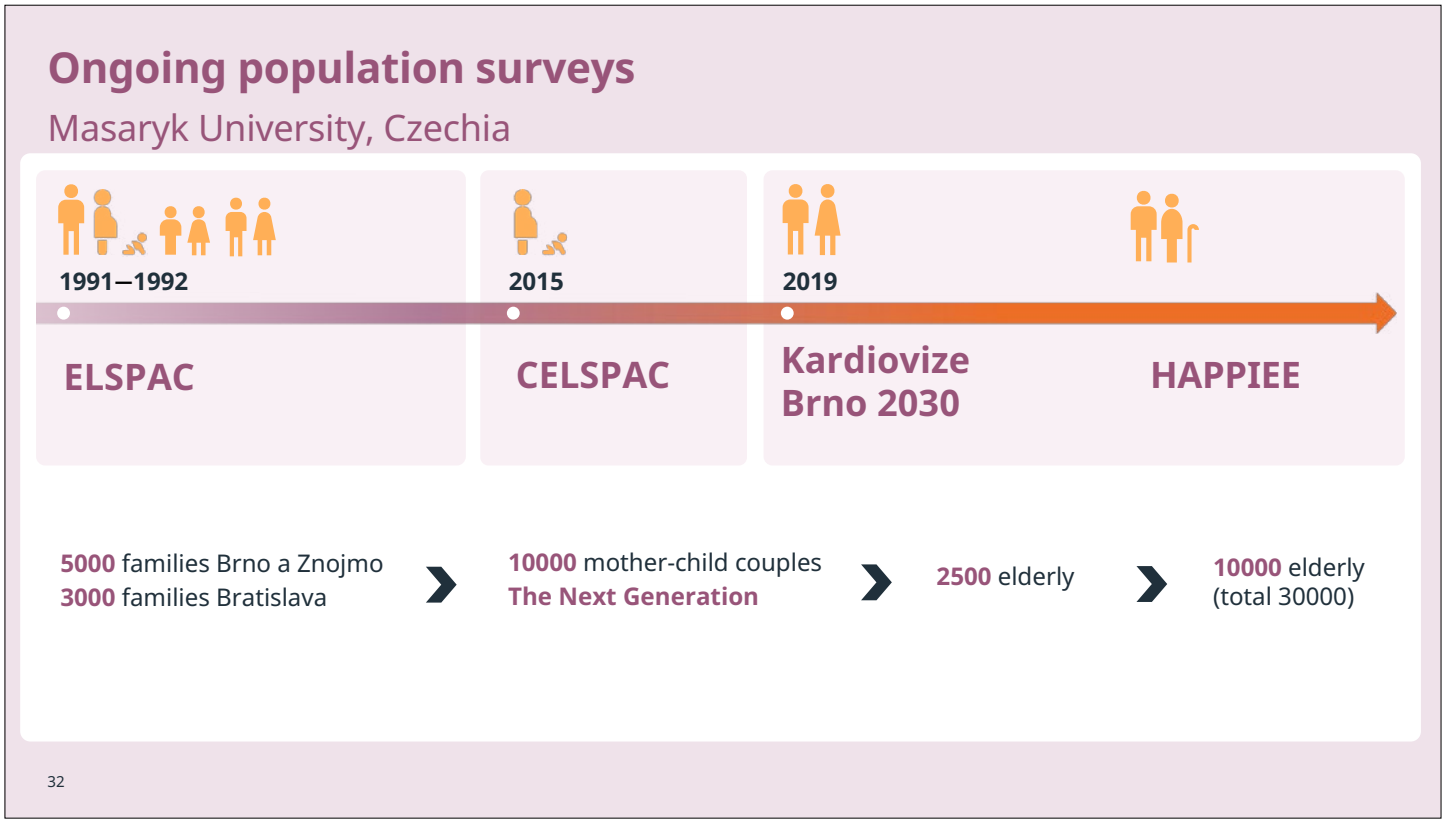
31 *Sources*: (left) adapted from Mikeš et al., 2012. Reproduced with permission from Springer Nature. (right) © Pavel Čupr. Reproduced with permission.

Notes: CDI: chronic daily intake; DDE: dichloroethylene; DDT: dichlorodiphenyltrichloroethane; HCB: hexachlorobenzene; PCB: polychlorinated biphenyls; POPs: persistent organic pollutants; RA: risk assessment.

Sources

Bányiová K, Černá M, Mikeš O, Komprdová K, Sharma A, Gyalpo T et al. Long-term time trends in human intake of POPs in the Czech Republic indicate a need for continuous monitoring. Environ Int. 2017;108:1–10. doi: 10.1016/j.envint.2017.07.008.

Mikeš O, Čupr P, Kohút L, Krsková A, Černá M. Fifteen years of monitoring of POPs in the breast milk, Czech Republic, 1994-2009: trends and factors. Environ Sci Pollut Res Int. 2012;19(6):1936-43. doi: 10.1007/s11356-012-0798-z.



The ELSPAC was initiated in Czechia 1991—1992, with follow-up in 2012 and ongoing. Originally 7000 families enrolled (South Moravia) and it continues with the next generation and young adults.

Notes: CELSPAC: The European Longitudinal Study for Pregnancy and Childhood in Czechia; HAPPIEE: Health, Alcohol and Psychosocial Factors in Eastern Europe.

Sources

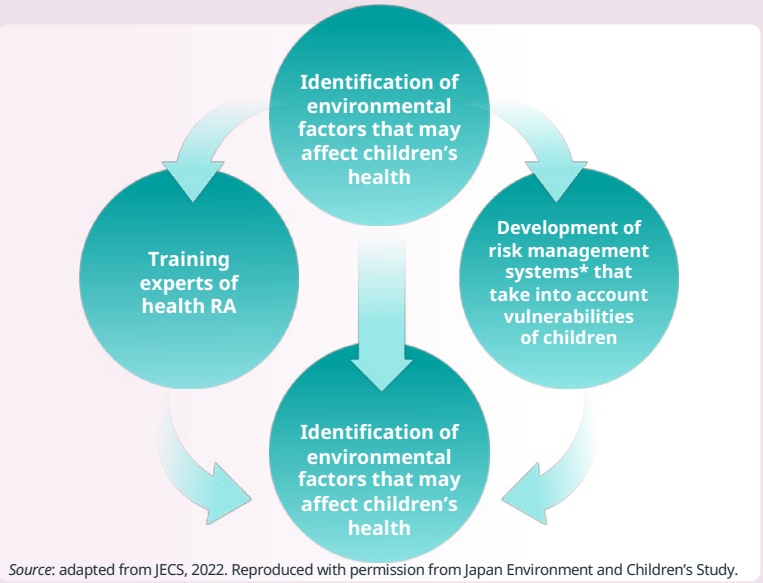
Celspac [website]. Brno: Masaryk University; 2022 (in Czech; www.celspac.cz, accessed 10 November 2022).

JECS (I)

Aims of JECS

JECS aims to create a healthy environment for raising future generations of children by identifying environmental factors that affect children's health and development and establishing risk management systems that take into account vulnerabilities of children.

Programme supported by the Ministry of the Environment and implemented by the National Institute for Environmental Studies with the Medical Support Centre of the National Centre for Child Health and Development



Source: adapted from JECS, 2022. Reproduced with permission from Japan Environment and Children's Study.

*Examples of risk management systems: Development of improved screening criteria for chemical substance regulation; improvement of environmental standards, e.g. air, water and soil quality standards; and encouragement of environment-related policies initiated by the Ministry for the Environment and other ministries, e.g. setting up new household commodity regulations and standards.

33

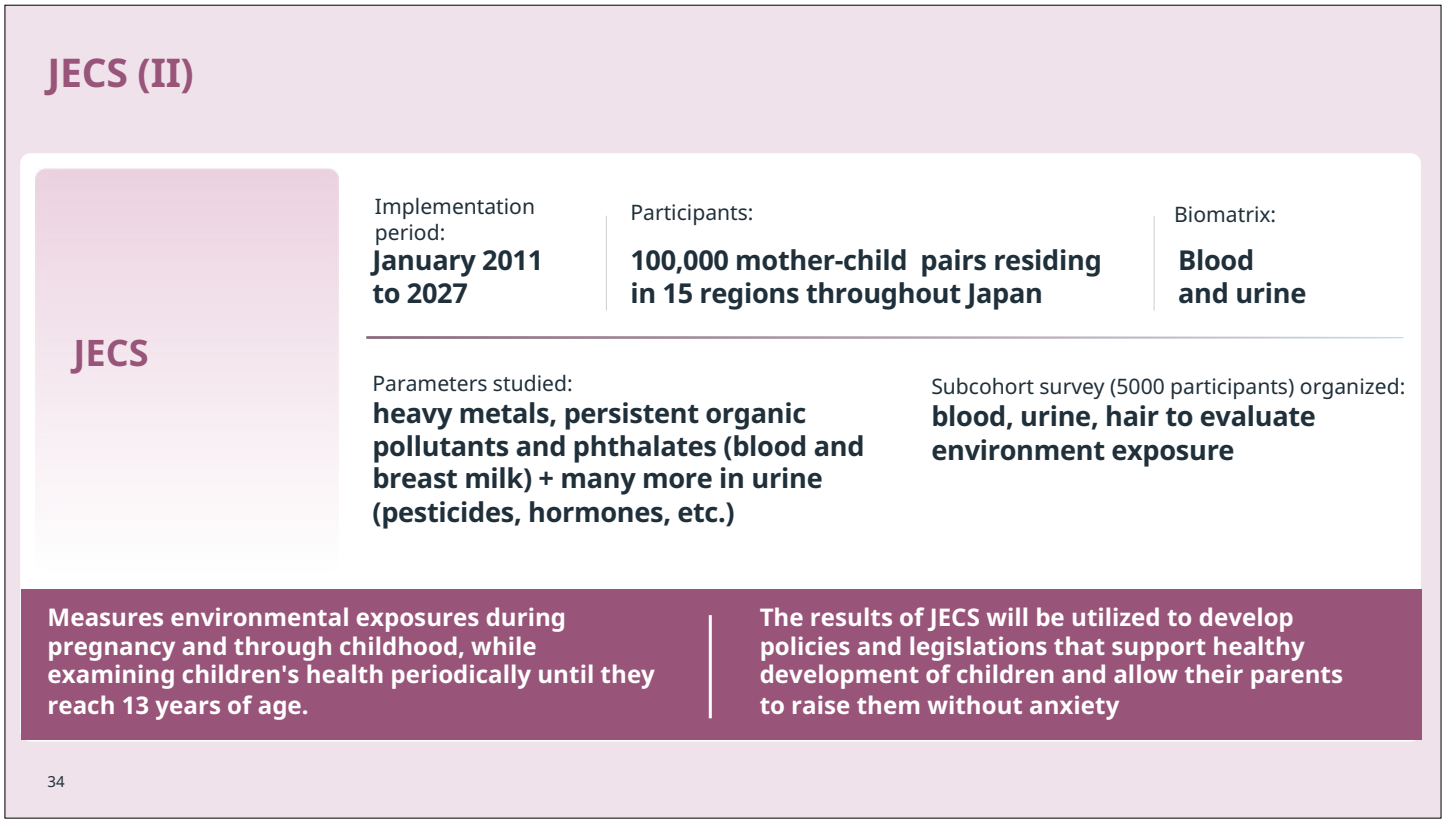
The JECS is a longitudinal cohort study that will follow the same participants for many years.

Notes: JECS: Japan Environment and Children's Study; RA: risk assessment.

Sources

Japan Environment and Children's Study [website]. Tokyo: Ministry of the Environment Government of Japan; 2022 (https://www.env.go.jp/chemi/ceh/en/, accessed 10 November 2022).

Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M et al. Rationale and study design of the Japan Environment and Children's Study (JECS). BMC Public Health. 2014;14:25. doi: 10.1186/1471-2458-14-25.



The JECS consists of:

- the main study, which includes all the participants recruited;
- a subcohort study with 5000 participants randomly extracted from the main study;
- a pilot study that examines validity and feasibility of study protocols before they are applied to the main study; and
- adjunct studies conducted by each or any combination of JECS organization(s) using extramural funding targeting all or some of the main study participants; these studies must be approved by the Ministry of the Environment.

Extensive biological sample collections are performed at a variety of time points in the main study.

Notes: JECS: Japan Environment and Children's Study.

Sources

Japan Environment and Children's Study [website]. Tokyo: Ministry of the Environment Government of Japan; 2022 (https://www.env.go.jp/chemi/ceh/en/, accessed 10 November 2022).

Japan Environment and Children's Study: study protocol. Tokyo: Ministry of the Environment Government of Japan; 2022 (https://www.env.go.jp/chemi/ceh/en/about/advanced/material/jecs-study_protocol_14_en.pdf, accessed 10 November 2022).

KoNEHS
Korean National Environmental Health Survey

Aims

- Assess exposure to environmental chemicals
- Identify sources and exposure factors

Design

- Population-representative sample survey
- Cross-sectional survey in 3-year cycle

Contents

- Specimen (urine, blood) collection
- Self-administered questionnaire survey
- Clinical test

- **Ministry of Environment, National Institute of Environmental Research**
- **The Environmental Health Act**

35

Notes: KoNEHS: Korean National Environmental Health Survey.

Sources

Jung SK, Choi W, Kim SY, Hong S, Jeon HL, Joo Yet al. Profile of environmental chemicals in the Korean population: results of the Korean National Environmental Health Survey (KoNEHS) cycle 3, 2015−2017. Int J Environ Res Public Health. 2022;19(2):626. doi: 10.3390/ijerph19020626.

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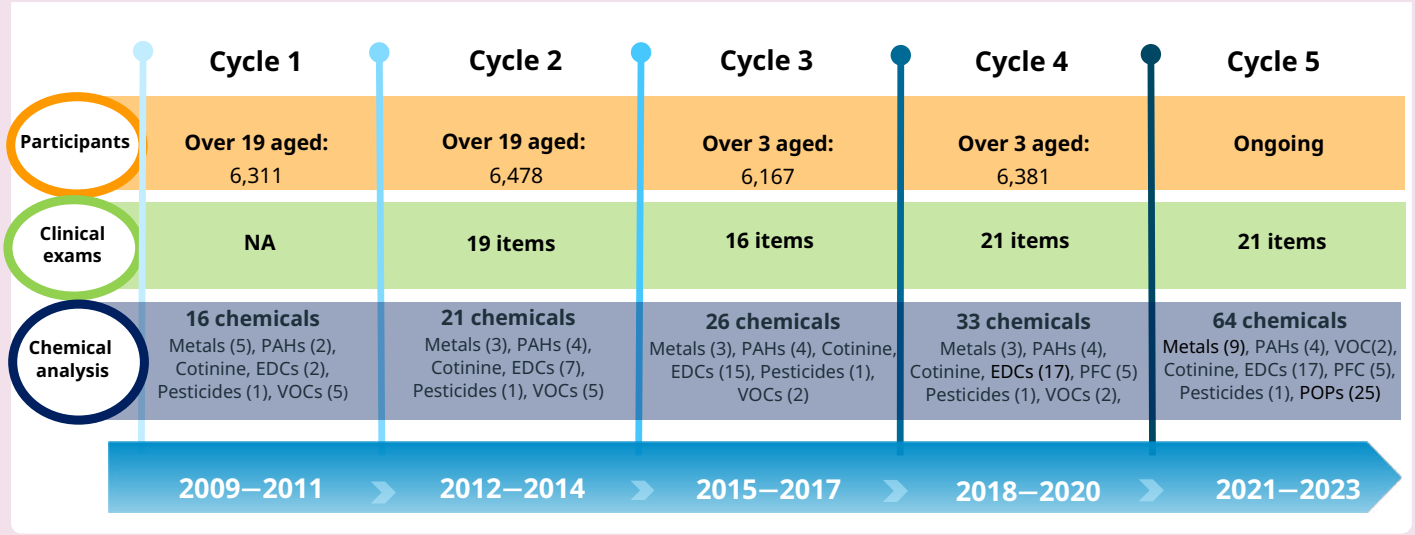


36 *Source*: Kim and Baek, 2016. Reproduced with permission from National Institute of Environmental Research at the Ministry of Environment.

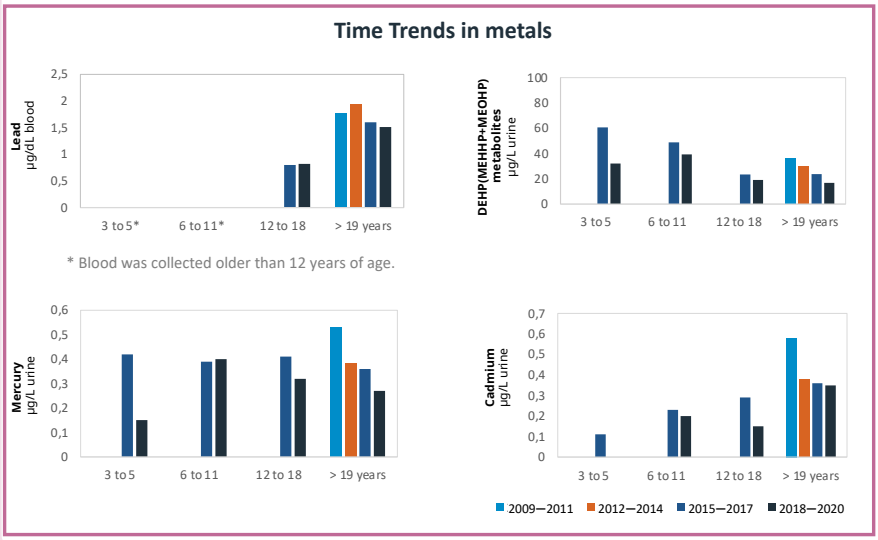
Notes: EDCs: endocrine-disruptiing chemical; KoNEHS: Korean National Environmental Health Survey; PAHs: polycyclic aromatic hydrocarbons; PFC: perfluorinated compounds; POPs: persistent organic pollutants; VOCs: organic compounds.

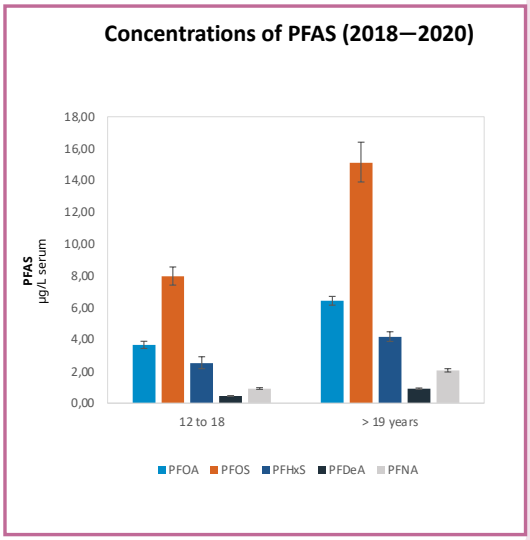
Sources

Kim S, Baek Y-W. Korean National Environmental Health Survey (KoNEHS): the past, present and future of human bio-monitoring in Korea. In: Korean National Environmental Health Survey (KoNEHS) 2nd International Conference on Human Biomonitoring, Berlin 2016. Dessau-Roßlau: German Environment Agency; 2016 (https://www.umweltbundesamt.de/sites/default/files/medien/378/dokumente/suejin_kim_korean_national_environmental_health_survey_konehs.pdf, accessed 10 November 2022).

Korean population exposure to chemicals

Result of KoNEHS





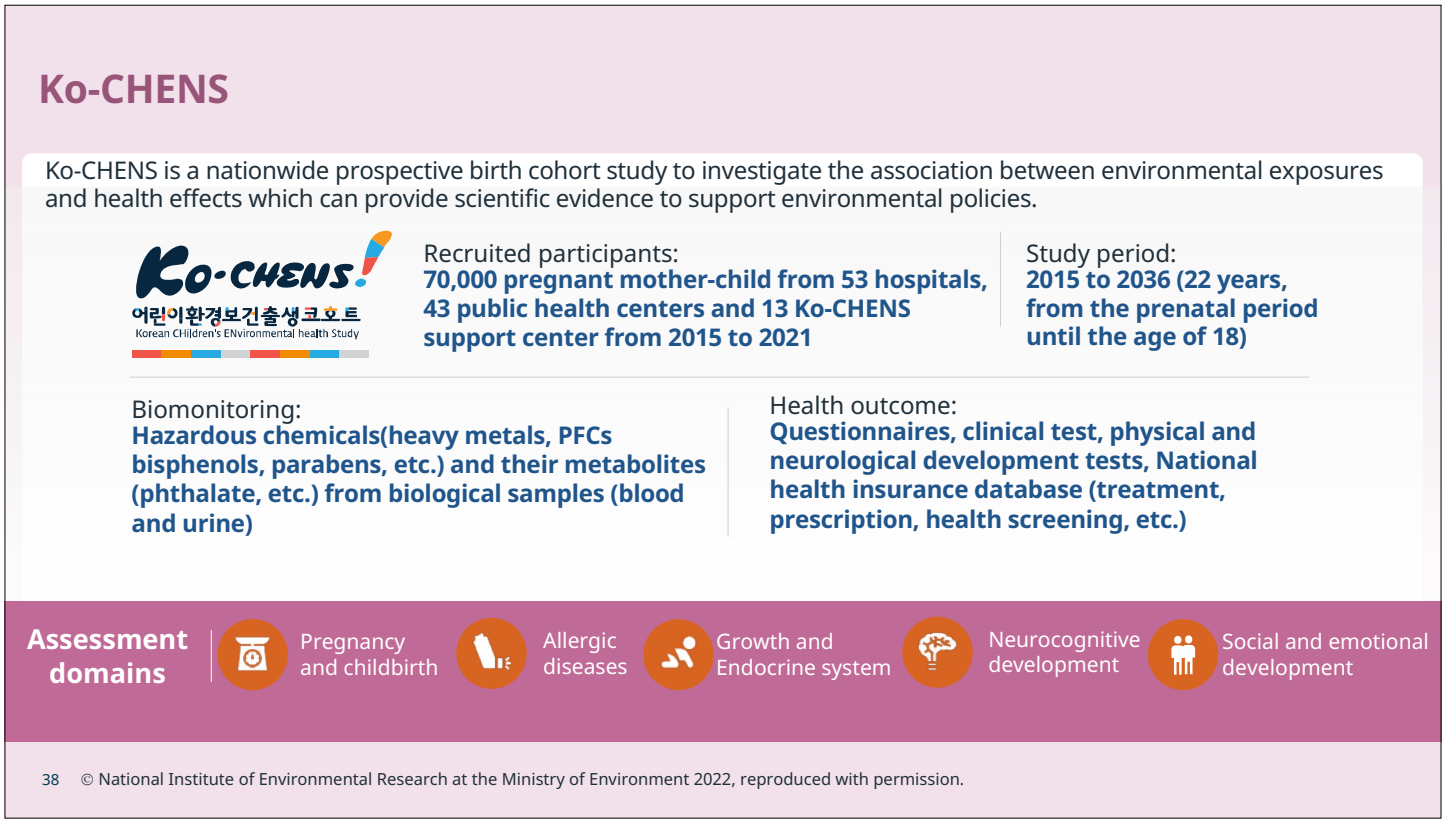
37 *Source*: (left) Lee et al., 2021. Reproduced with permission from National Institute of Environmental Research at the Ministry of Environment. (right) Data taken from Lee et al., 2021.

The Korean National Environmental Health Study has performed in cycles with results of the fourth cycle reported to the public in December in 2021. Results are uploading in the KOSIS by the National Institute of Environment and Ministry of Environment.

Notes: Cd: cadmium; DEHP: Di(2-ethylhexyl)phthalate; Hg: mercury: KoNEHS: Korean National Environmental Health Survey; KOSIS: Korean Statistical Information Service; MEHHP: moho(2-ethyl-5-oxohexyl) phthalate; MEOHP: mono(2-ethyl-5-hydroxyl) phthalate; Pb: lead; PFAS: Per- and polyfluoroalkyl substances; PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulfonate; PFDeA: perfluorodecanoic acid; PFHxS: perfluorohexanesulfonic; PFNA: perfluorononanoic acid.

Sources

Lee CW, Kil JH, Kim JY, Kang TS. Concentrations of environmentally hazardous substances in Koreans were mostly down from three years ago. Seoul: Ministry of Environment, National Institute of Environmental Research, Government of the Republic of Korea; 2021 (press release 032-560-7103/7129/7138).



Notes: Ko-CHENS: Korean CHildren's ENvironmental health Study; PFCs: perfluorinated compounds.

Sources

Jeong KS, Kim S, Kim WJ, Kim HC, Bae J, Hong YC et al. for the Ko-CHENS Study Group. Cohort profile: Beyond birth cohort study: the Korean CHildren's ENvironmental Health Study (Ko-CHENS). Environ Res. 2019;172:358-66. doi: 10.1016/j.envres.2018.12.009.

HBM in Slovenia

Phase I

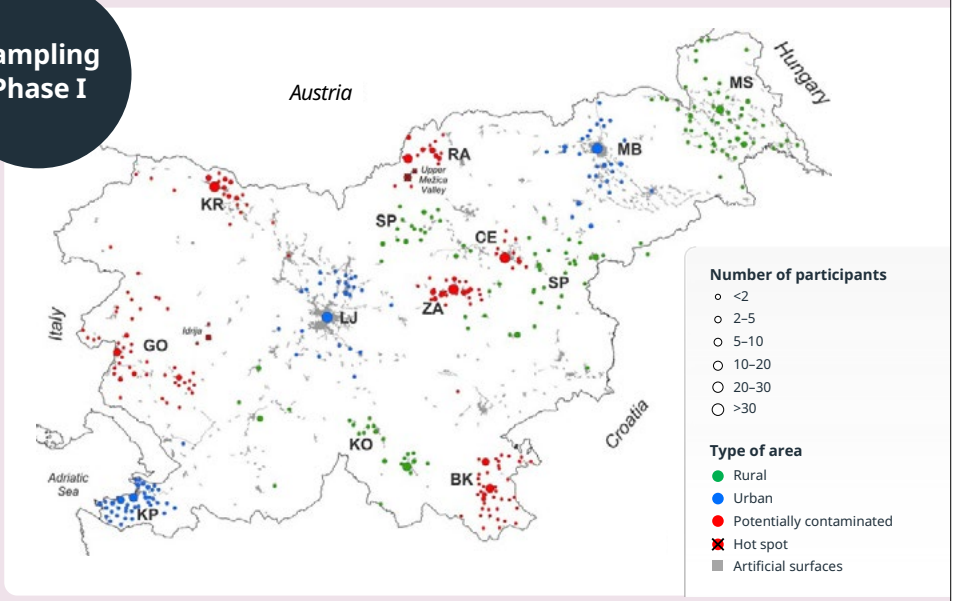
2007—2009 pilot phase

2011—2014 full scale
Men and lactating women

Phase II

2016—2019 pilot phase

2019—2022 full scale
Additional chemicals from Phase I Children and adolescents



39 *Source*: Snoj Tratnik et al., 2019. Reproduced with permission from Elsevier.

Notes: HBM: human biomonitoring.

Sources

Snoj Tratnik J, Falnoga I, Mazej D, Kocman D, Fajon V, Jagodic M et al. Results of the first national human biomonitoring in Slovenia: trace elements in men and lactating women, predictors of exposure and reference values. Int J Hyg Environ Health. 2019;222(3):563-82. doi: 10.1016/j.ijheh.2019.02.008.

Stajnko A, Falnoga I, Tratnik JS, Mazej D, Jagodic M, Krsnik M et al. Low cadmium exposure in males and lactating females-estimation of biomarkers. Environ Res. 2017;152:109-119. doi: 10.1016/j.envres.2016.09.025.

Jagodic M, Potočnik D, Snoj Tratnik J, Mazej D, Pavlin M, Trdin A et al. Selected elements and fatty acid composition in human milk as indicators of seafood dietary habits. Env Res. 2020;180:108820. doi: 10.1016/j.envres.2019.108820.

HBM in Slovenia: phase I results (I)

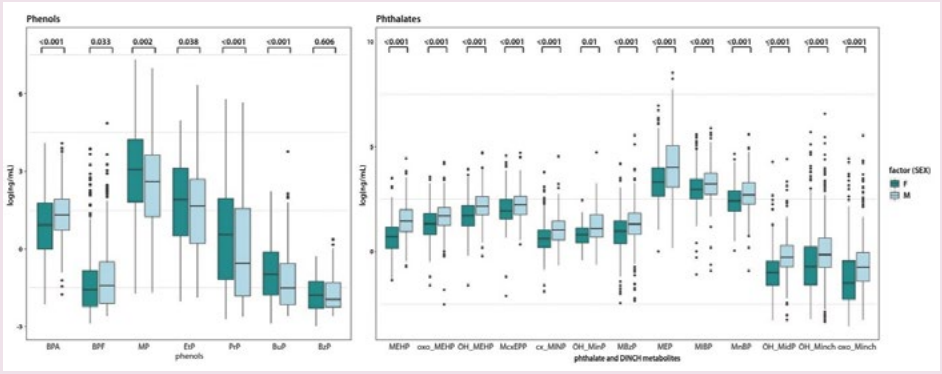
Reference values

Cd in urine	n	P95 [95% CI]	RV_{95}
Lactating women, non-smoking	410	0.75 [0.65 – 0.87]	0.8 µg/g crt
Men, non-smoking	453	0.41 [0.36 – 0.47]	0.4 µg/g crt
Hg in blood	**n**	***P95 [95% CI]***	***RV_{95}***
Lactating women consuming fish ≤ 3 times/month	431	3.65 [3.17 - 4.20]	4.0 µg/L
Men consuming fish ≤ 3 times/month	479	4.78 [4.10 – 5.58]	5.0 µg/L
Pb in blood	**n**	***P95 [95% CI]***	***RV_{95}***
Lactating women, Pb-smelter area excluded	506	33.1 [30.5 – 36.0]	35 µg/L
Men, Pb-smelter area excluded	499	42.4 [37.9 – 47.4]	45 µg/L

Spatial distribution

Exposure determinants

Phthalates and DINCH, bisphenols, parabens and triclosan



40 *Sources:* (left) Snoj Tratnik et al., 2019. Reproduced with permission from Elsevier. (right) Runkel et al., 2022. Reproduced with permission from Elsevier.

The HBM results demonstrated that increased seafood consumption in the coastal study area contributed to higher Hg and arsenobetaine As levels. Extensive sample size of the database accompanied by lifestyle and environmental data improved the prediction of exposure patterns, set the reference values for the child-bearing population living in Slovenia and provided a strong basis for evaluating spatial and temporal trends in exposure. To our best knowledge, this is the first study to establish reference values for lactating primiparous women.

Notes: As: arsenic; BPA: bisphenol A; BPF: bisphenol F; BuP: butyl paraben; BzP: benzyl paraben; Cd: cadmium; cx-MINP: monocarboxy-isononyl phthalate; DINCH: 1,2-cyclohexane dicarboxylic acid diisononyl ester; EtP: ethyl paraben; HBM: human biomonitoring; Hg: mercury; MBzP: mono-benzyl phthalate; MEHP: mono (2-ethylhexyl) phthalate; MnBP: mono-n-butyl phthalate; MP: methyl paraben; OH-MEHP: mono (2-ethyl-5-hydroxyhexyl) phthalate monohydroxy isodecyl phthalate; OH-MINCH: cyclohexane-1,2-dicarboxylic acid-mono (hydroxyl – isononyl) ester; oxo-MEHP: mono (2-ethyl-5-oxohexyl) phthalate; oxo-MINCH: cyclohexane-1,2-dicarboxylic acid-mono (oxo-isononyl) ester; P95: 95th percentile; Pb: lead; PrP: propyl paraben; RV: reference value.

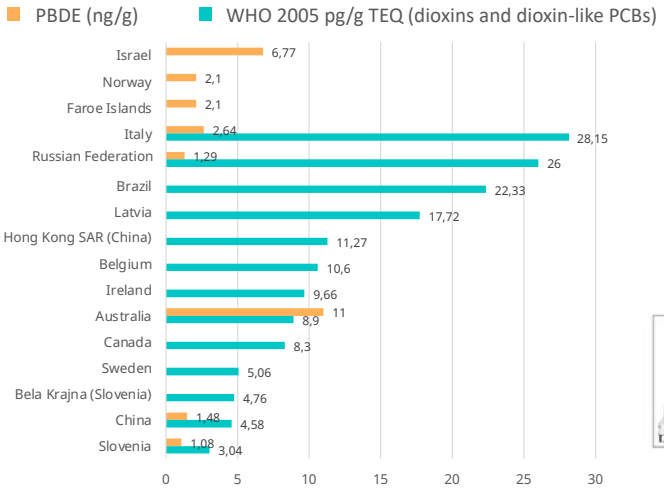
Sources

Snoj Tratnik J, Falnoga I, Mazej D, Kocman D, Fajon V, Jagodic M et al. Results of the first national human biomonitoring in Slovenia: trace elements in men and lactating women, predictors of exposure and reference values. Int J Hyg Environ Health. 2019;222(3):563-82. doi: 10.1016/j.ijheh.2019.02.008.

Jagodic M, Potočnik D, Snoj Tratnik J, Mazej D, Pavlin M, Trdin A et al. Selected elements and fatty acid composition in human milk as indicators of seafood dietary habits. Env Res. 2020;180:108820. doi: 10.1016/j.envres.2019.108820.

Runkel AA, Mazej D, Tratnik JS, Tkalec Z, Kosjek T, Horvat M. Exposure of men and lactating women to environmental phenols, phthalates, and DINCH. Chemosphere. 2022;286:131858. doi: 10.1016/j.chemosphere.2021.131858.

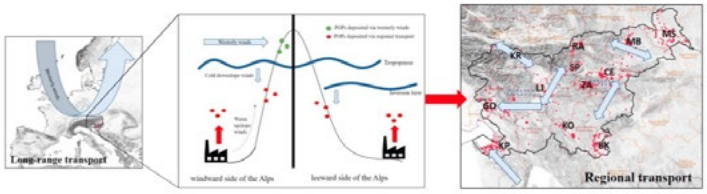
HBM in Slovenia: phase I results (II)



Reference values

Spatial distribution

Protective role of Alps from long-range transport of POPs



41 *Source*: Runkel et al., 2021. Reproduced with permission from Elsevier.

The study findings suggest the occurrence of low exposure in men and in lactating women to legacy pollutants in Slovenia, which gave rise to the hypothesis that Slovenia's geographical location might provide shelter from the long-range transport of POPs via westerly winds. This hypothesis remains to be confirmed within future studies.

Notes: HBM: human biomonitoring; PCB: polychlorinated biphenyls; PDDE: polybrominated diphenyl ethers; POPs: persistent organic pollutants; TEQ: toxic equivalents.

Sources

Runkel AA, Križanec B, Lipičar E, Baskar M, Hrženjak V, Kodba ZC et al. Organohalogens: A persisting burden in Slovenia? Environ Res. 2021;198:111224. doi: 10.1016/j.envres.2021.111224.

The United States NHANES

The largest ongoing cross-sectional survey to assess the health and nutritional status of adults and children in the United States

Administered by the National Center for Health Statistics of the Centers for Disease Control and Prevention

Select environmental chemicals including lead in blood measured for the first time in NHANES II (1976–1980)

Beginning in 1999, NHANES began sampling the United States population annually and releasing the data in 2-year cycles

- Interviews: demographic, socioeconomic, dietary, and health-related questions
- Physical examinations: medical, dental, and physiological measurements, as well as laboratory tests

NHANES

Goals of HBM

- Determine which chemicals are getting into people's bodies and how much of those chemicals are in blood and urine
- Monitor the number of people who have levels of a chemical above a known toxicity level (e.g. blood lead levels)
- Track exposure trends and impacts of public health programmes
- Provide body burden data to inform public health practice and research
- Minimize RA uncertainty

42

NHANES is conducted to help developing sound public health policy, direct and design health programmes and services, and expand the health knowledge of the nation. This is the biggest HBM survey globally.

Risk factors addressed are aspects of a person's lifestyle, constitution, heredity or environment; smoking; alcohol consumption; drug use; sexual practices; physical fitness and activity; weight; and dietary intake. Data on certain aspects of reproductive health, such as use of oral contraceptives and breastfeeding practices, are also collected.

An advanced computer system (using high-end servers, desktop computers and wide-area networking) collects and processes all the NHANES data, nearly eliminating the need for paper forms and manual coding operations. This system allows interviewers to use tablet computers with electronic pens. The staff at the mobile centres can automatically transmit data into databases through such devices as digital scales and stadiometers. In each location, local health and government officials are notified of the upcoming survey. Local media may feature stories about the survey.

Participants each receive compensation and a report of their medical findings. All information collected in the survey is kept confidential. Information from NHANES is made available through an extensive series of publications and articles in scientific and technical journals. For data users and researchers throughout the world, survey data are available on the Internet.

Notes: HBM: human biomonitoring; NHANES: National Health and Nutrition Examination Survey; RA: risk assessment.

Sources

National Health and Nutrition Examination Survey: overview. Atlanta (GA): US Centers for Disease Control and Prevention National Center for Health Statistics; 2022 (https://www.cdc.gov/nchs/nhanes/index.htm, accessed 10 November 2022).

Choi J, Mørck TA, Joas A, Knudsen LE. Major national human biomonitoring programs in chemical exposure assessment. Environ Sci. 2015;3:782-02. doi: 10.3934/environsci.2015.3.782.

NHANES (II)

Two main measurements:

1. nutrition indicators of public health concern
2. exposure to select environmental chemicals known or suspected to cause cancer, reproductive dysfunction, and respiratory, neurological, endocrine, immunologic, heart or renal diseases

Measures more than 450 environmental chemicals and nutritional indicators in humans (pollutants and nutrients)

Chemicals that are measured include: phenols, metals, organochlorine pesticides, phthalates, cotinine, PBDEs and other brominated flame retardants, PCB and dioxin-like chemicals, PAHs, PFAS and VOCs

Number of compounds monitored since 1999

43

As one of the components of NHANES, analysis of chemical exposure in the general American population is performed using blood and urine samples collected from the participants.

A wide range of chemicals or classes of chemicals is analysed in the recent NHANES, including acrylamide and its metabolite glycidamide, dioxins (PCDDs, PCDFs), PCBs, PBDEs, pesticides (e.g. carbamates, organophosphorates, pyrethroids) and their metabolites, metals (e.g. As, Cd, Co, Cu, Pb, Hg, Se, Tl, W, U, Zn), phenols such as BPA and parabens, trihalomethanes, tobacco smoke (e.g. cotinine as a metabolite of nicotine), PFCs, phthalate metabolites, PAHs metabolites, phytoestrogens and metabolites, and VOCs and metabolites, industrial chemicals (e.g. PBDEs, PFCs, BPA), and by-products of chemical reactions such as acrylamide.

Notes: As: arsenic; BPA: bisphenol A; Cd; cadmium; Cu; copper; Co: cobalt; Hg: mercury; NHANES: National Health and Nutrition Examination Survey; PAHs: polycyclic aromatic hydrocarbons; Pb: lead; PBDE: polybrominated diphenyl ethers; PCB: polychlorinated biphenyls; PCDD: dibenzo-p-dioxin; PCDF: dibenzofuran; PFAS: per- and polyfluoroalkyl substances; PFC: perfluorinated compounds; Se: selenium; Tl: thallium; OC: organochlorine; VOCs: organic compounds; W: wolframe; U: uranium; Zn: zinc.

Sources

National biomonitoring program [website]. Atlanta (GA): US Centers for Disease Control and Prevention; 2022 (www.cdc.gov/biomonitoring/, accessed 10 November 2022).

National Health and Nutrition Examination Survey [website]. Atlanta (GA): US Centers for Disease Control and Prevention National Center for Health Statistics; 2022 (http://www.cdc.gov/nchs/nhanes/about_nhanes.htm, accessed 10 November 2022).

National report on human exposure to environmental chemicals. Atlanta (GA): US Centers for Disease Control and Prevention; 2022 (https://www.cdc.gov/exposurereport/index.html, accessed 10 November 2022).

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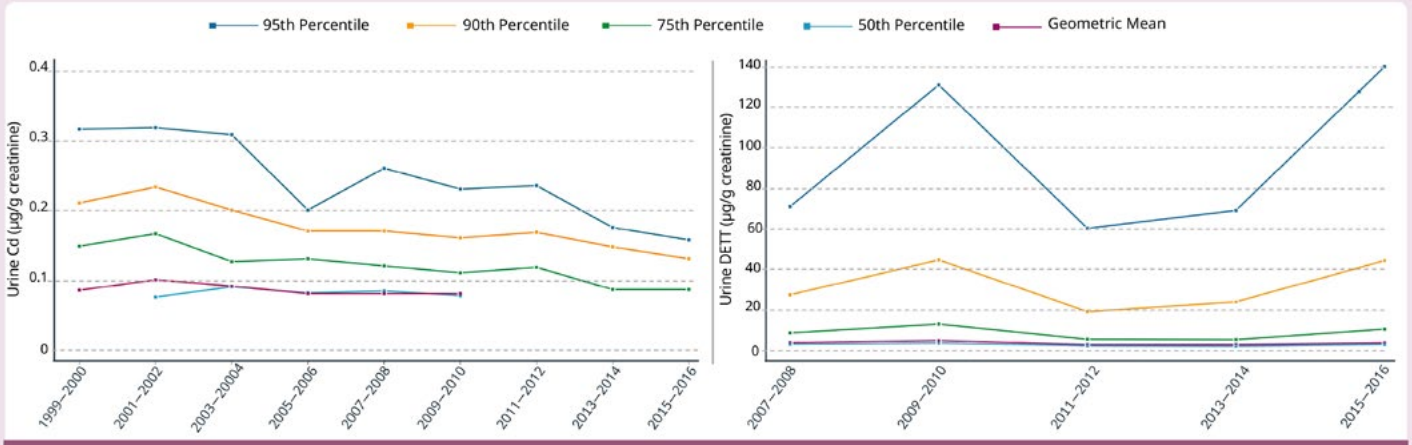
NHANES: example of time trends of exposure of population to selected chemicals



Urinary cadmium (creatinine corrected) in children of 6–11 years old (1999–2016)

Geometric mean and selected percentiles of urine Cd (µg/g creatinine) for the United States population from the NHANES

Geometric mean and selected percentiles of urine concentrations of DCBA, metabolite of DEET (µg/g of creatinine) for the United States population from the NHANES (2007–2016)

44 *Source*: data taken from Centers for Disease Control and Prevention, 2022.

Notes: Cd: cadmium; DCBA: 3-(diethylcarbamoyl)benzoic acid; DEET: n,n-diethyl-meta-toluamide; NHANES: National Health and Nutrition Examination Survey.

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The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations creted in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

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