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Developing human biomonitoring as a 21st century toolbox within the European exposure science strategy 2020–2030

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ABSTRACT

Human biomonitoring (HBM) is a crucial approach for exposure assessment, as emphasised in the European Commission's Chemicals Strategy for Sustainability (CSS). HBM can help to improve chemical policies in five major key areas: (1) assessing internal and aggregate exposure in different target populations; (2) assessing exposure to chemicals across life stages; (3) assessing combined exposure to multiple chemicals (mixtures); (4) bridging regulatory silos on aggregate exposure; and (5) enhancing the effectiveness of risk management measures.

In this strategy paper we propose a vision and a strategy for the use of HBM in chemical regulations and public health policy in Europe and beyond. We outline six strategic objectives and a roadmap to further strengthen HBM approaches and increase their implementation in the regulatory risk assessment of chemicals to enhance our understanding of exposure and health impacts, enabling timely and targeted policy interventions and risk management. These strategic objectives are: 1) further development of sampling strategies and sample preparation; 2) further development of chemical-analytical HBM methods; 3) improving harmonisation throughout the HBM research life cycle; 4) further development of quality control / quality assurance throughout the HBM research life cycle; 5) obtain sustained funding and reinforcement by legislation; and 6) extend target-specific communication with scientists, policymakers, citizens and other stakeholders.

HBM approaches are essential in risk assessment to address scientific, regulatory and societal challenges. HBM requires full and strong support from the scientific and regulatory domain to reach its full potential in public and occupational health assessment and in regulatory decision-making.

1. Introduction

We live in a world with rapid anthropogenic changes in natural and built environments which introduces substantial risks from chemicals in human populations. Exposure to a large number of highly diverse and biologically active chemicals is extensive, chronic, and multi-faceted (Bernhardt et al. 2017). The need to govern such risks from combined exposures from multiple sources of single, and mixtures of chemicals, as well as other stressors, is a central element of the European Commission's *Chemicals strategy for sustainability towards a toxic-free environment* (CSS) captured in the Staff Working Document (EC, 2020a). The CSS is part of the European Green Deal and its Zero Pollution ambition (EC, 2020a). Risk governance involves multiple steps in order to understand a problem and make decisions on how to address it, in a process often depicted as a cycle as suggested by the International Risk Governance Council, shown in Supplementary Material Figure S1. In this risk governance cycle, human biomonitoring (HBM) has an important role to play. For instance, as shown in Fig. 1, HBM data feed into the risk and socio-economic assessment, the communication of HBM data to address concerns of citizens, and the assessment of the effectiveness of the implementation of exposure reduction policies. One of the main bottlenecks of the current regulation is the lack of data on the actual human exposures to the thousands of chemicals currently on the market.¹ This leads to a lack of exposure knowledge that prevents existing and future health, environment, safety and sustainability legislation from attaining their full protective potential (Bruinen de Bruin et al. 2021).

HBM is a crucial approach to detect and quantify internal exposures,

and hence a key source of evidence in the risk assessment process. HBM datasets are also important in raising awareness about widespread chemical exposures (and other stressors) and their associated health risks. While the monitoring of external exposure sources, such as indoor and outdoor air, workplace air, drinking water, contaminants and pesticide residues in food, is anchored in legislation, human internal exposure as determined by HBM is generally not, except for occupational settings. Although measuring chemicals in consumer products can give additional information on exposure sources (source monitoring), it only reflects potential external exposure (Schindler et al. 2014). In contrast, HBM measures chemicals and their metabolites in internal fluids or other human specimens, and as such by definition reflects the internal exposure, i.e. the amount that has been taken up by the body via inhalation, oral and dermal uptake. Consequently, HBM accounts for the presence of chemicals in the body taken up by all pathways and from multiple sources. Although it is clear that Europe is moving towards improving current systems for risk assessment and risk management of chemicals, a shared understanding on how HBM data can be established as evidence for regulatory decisions, consistent regulatory guidelines on HBM use, and the implementation of HBM in legal frameworks are still lacking. A recent paper gathered information on the use of HBM in risk assessment and showed that examples existed only for a few selected groups of chemicals and that there is a lack of legal enforcement (Louro et al., 2019).

HBM can facilitate the “one substance, one assessment” (1S1A) approach described in the CSS (more coordination and consistency across regulations with a coherent assessment) by using exposure data as a basis for chemicals regulated under different pieces of chemical legislation. This would also support frameworks aimed at attaining optimal health for people on a healthy planet (as envisioned in the Planetary Health concept) (Panorama, 2017). Although significant advances in this direction have already been made during the course of the European Joint Programme HBM4EU (<https://www.hbm4eu.eu/>)

¹ Risk assessed at least to some extent by government authorities before chemicals are allowed onto the market with or without restrictions (e.g. intended use for pesticides) or before ‘REACH restricted’ or ‘REACH authorised’ (i.e. banned except for very specific authorised uses).

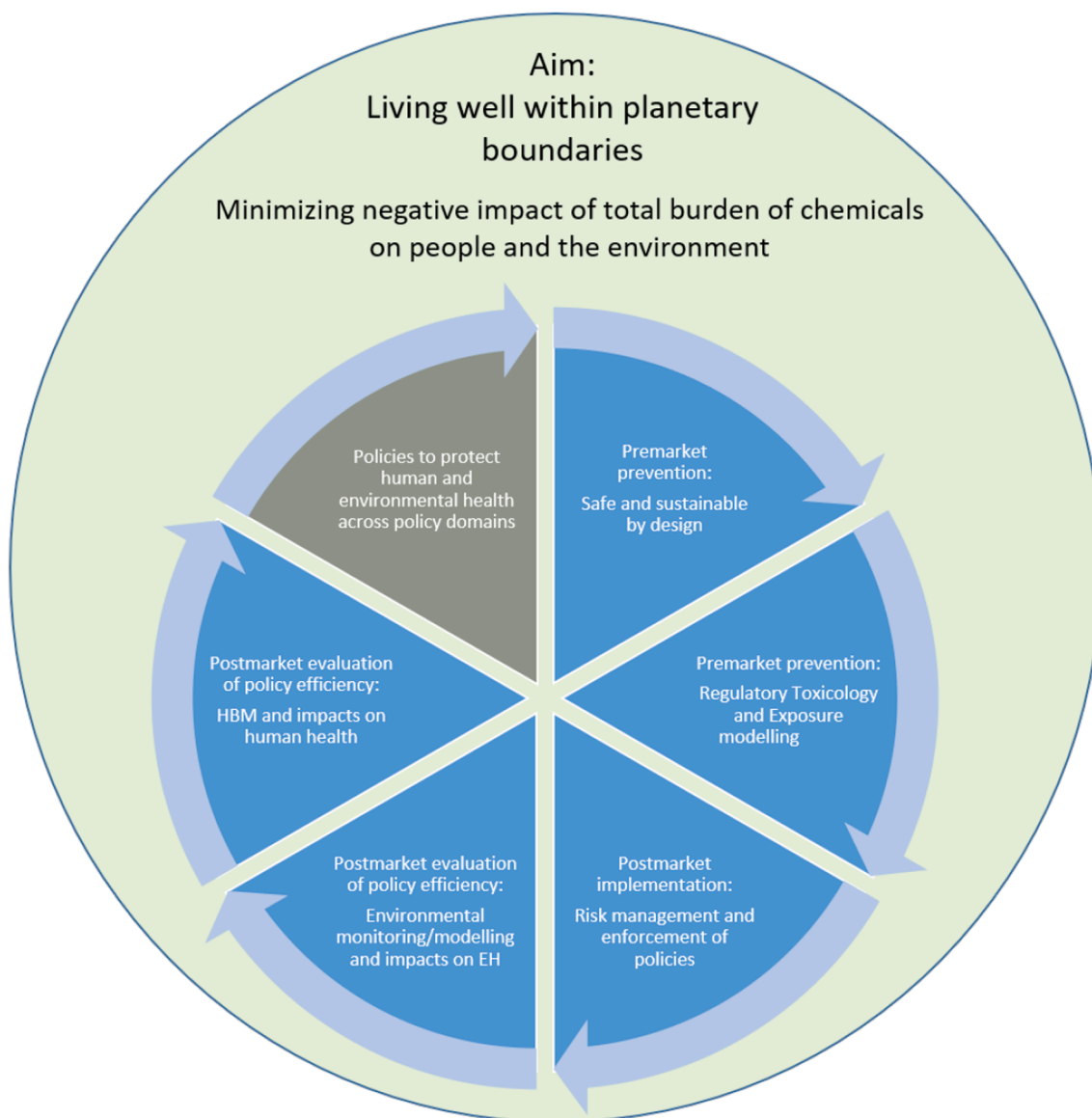


Fig. 1. Risk governance of chemicals relies on monitored, modelled and reported data, from premarket design and evaluation (before a chemical is put on the market), to post-market implementation and evaluation of the effectiveness of policies (credit: [EEA, 2020](#)).

([Ganzleben et al. 2017](#); [Gilles et al. 2021](#)), the use of HBM has not yet reached its full potential to facilitate the transition towards a more integrated approach in chemical risk assessment.

Over the past four years, the 'Europe Regional Chapter of the International Society of Exposure Science' (ISES Europe) has formed an expert working group on "Exposure data production: Human data" (hereafter referred to as the 'HBM expert working group'). This HBM expert working group consists of specialists from different disciplines and policy domains representing over fifteen European countries. The HBM expert working group is committed to working on HBM as one of the priority areas of the European Strategy for Exposure Science 2020–2030 ([Fantke et al. 2020](#)).

The aim of the present activities is to:

- (1) Provide a state-of-the-art overview for HBM, including the advantages and options for its more tailored or wider use in exposure science;
- (2) Translate these findings in strategic HBM objectives, actions, and needs for the 21st century HBM toolbox, which are necessary to strengthen regulatory risk and health impact assessments, and for

decision-making contexts. "The 21st century HBM toolbox" incorporates novel areas (i.e. effect biomarkers, exposure-disease continuum, non-target suspect screening, etc.) where HBM can fill the knowledge gap by associating chemical exposures with diseases.

2. Methods

Three approaches have been used since May 2018 to achieve the above goals:

- a. Expert knowledge elicitation using communication-based methods such as online interviews, roundtable discussions and brainstorming.
- b. A systematic analysis of strengths, weaknesses, opportunities, and threats (SWOT) to identify the opportunities, practical challenges, needs and future requirements for the use of HBM in research, policy and regulatory sectors in Europe. The SWOT analysis was mainly performed using a script and group discussions during the second ISES Europe meeting held in Bilthoven (RIVM) in 2019 ([Fantke et al., 2020](#)).

c. A simplified qualitative Delphi method following a structured group communication process in which a group of individuals jointly discussed and agreed upon complex topics and strategic goals (Drumm et al. 2022). Although it is not necessary for participants to meet face-to-face with the Delphi technique, an expert meeting was organised at the Joint Research Centre (JRC) in Ispra (Italy) in 2020.

The HBM expert working group had dynamic communication and several rounds of online meetings to work further on drafting this strategy paper.

To facilitate the understanding of the discussions that take place in HBM studies, the various phases of an HBM study are presented in Supplementary Material Figure S2.

3. Results

This results section brings together the knowledge and contributions elicited through the aforementioned approaches. The SWOT analysis is presented in Table 1. The advantages of and options for HBM, which includes a discussion on exposure, awareness, time trends, sub-populations and the use of HBM in risk assessment, as well as

monitoring the effectiveness of risk management measures (RMMs), are discussed in Section 3.1. In Section 3.2, the technical/scientific, financial and regulatory requirements for a wider use of HBM to its full potential are presented.

3.1. Advantages and options for HBM

Below, we present the advantages and current options for further developing HBM with respect to nine aspects:

3.1.1. Aggregate exposures

HBM measurements are key in addressing aggregate exposure to one chemical, because HBM integrates all routes (inhalation, skin, ingestion, etc.) and sources of exposure (air, water, soil, food, consumer products, occupational exposure, etc.) and gives information on the internal body burden.

Aggregate exposure is currently considered only in specific chemical regulations (e.g. for carcinogens in the EU Cosmetics Regulation). However, aggregate exposure also occurs for many other substances with the same or different health end points. Consequently, aggregate exposure is increasingly considered in EU risk assessment documents in

Table 1

Results of the SWOT (strengths, weaknesses, opportunities, and threats) analysis addressing applications of human biomonitoring (HBM).

S - Strengths	W - Weaknesses	O - Opportunities	T - Threats
<ul style="list-style-type: none"> HBM is much closer to health effects than external exposure. HBM measures internal exposure (aggregate and combined exposure) HBM can be used to monitor internal exposure trends over time. HBM considers all exposure routes, including e.g., dermal and hands-to-mouth, which cannot be easily measured/modelled. Possibility to compare HBM data with HBM health-based guidance values to assess possible health effects. Effective tool to inform citizens on their level of exposures to chemicals. Previous HBM national campaigns have shown positive results. Exposure assessment during different (vulnerable) life-stages. Less expensive than the costs of health impacting exposures as shown by Burden of Disease approaches. Detecting exposure to emerging new chemicals for e.g. from recycled products (implementing circularity in material work flows) 	<ul style="list-style-type: none"> Detection of the sources, pathways of exposure is not possible without additional questionnaire data or ambient exposure data. For chemicals with a short half-life, exposure assessment by HBM tends to be incomplete. Number of validated exposure and effect biomarkers would benefit from extension. Heterogeneity of HBM data across studies. Number of HBM methods need improving and quantification especially in combined exposure assessment. 	<ul style="list-style-type: none"> Monitoring of need for new measures, compliance and effectiveness of risk management decisions (post-marketing surveillance). HBM may allow for an early warning system combining environmental sources and human exposure. Timely evaluation of effectiveness of regulatory policies. Inclusion of Adverse Outcome Pathways (AOPs) based effect biomarkers possible. Post-incident chemical exposure assessment. Linking external and internal exposure. Findings from HBM could lead to improved health care if considered by physicians in medical treatments. Further development of health-based guidance values allows interpretation of biomarker data in terms of health risk. Timely identification and prioritization of chemicals/stressors of highest concern. Timely detection and evaluation of emerging chemicals and substitutes via untargeted analysis. HBM can elucidate the relationship between exposure and effect biomarkers. Linkage of HBM to external exposure modelling. HBM results may be compared directly to internal exposure in critical animal toxicity studies and in vitro toxicity studies with human cells. HBM is likely to augment significantly epidemiological studies. With appropriate study design and sufficient participants, can help identify causal relations between exposure and health effects. 	<ul style="list-style-type: none"> Lack of regulatory use of HBM data. Lack of specific legal requirement for provision of HBM data. Insufficient consideration of ethical aspects might hamper data use and sharing (HBM data may be considered as sensitive personal information) Variable costs of HBM analysis, depending on number and composition of analytes. Assessment is retrospective (chemicals already on the market and in use). Development of new HBM methods and conducting large-scale HBM studies required considerable investments.

the last decade (Choi et al. 2015; Rousselle et al. 2022). Chemical-related policies and regulations would benefit from systematically including HBM to better address aggregate exposure.

3.1.2. Chemical mixtures

In addition to giving information on the multiple sources of exposure from one chemical, HBM data give insight into co-exposure patterns of multiple chemicals. Consequently, HBM help in assessing combined exposures to chemical mixtures (Socianu et al. 2022). Chemicals and chemical mixtures can be assumed to contribute to the global human burden of diseases (Prüss-Ustün et al. 2011; Scholz et al. 2022). Data on co-exposures can inform source-to-dose models to identify sources of exposure that subsequently can be regulated to lower the burden of disease (Karrer et al. 2020). HBM data can inform the current and future understanding of exposure to real-life mixtures. For this purpose, chemicals measured in individual study participants should be strategically prioritised and the number of measured chemicals should on this basis be expanded in future studies (Bopp et al. 2018).

3.1.3. Emerging chemicals

There is a significant increase in the pace at which new chemicals are introduced, and consequently an increasing need for HBM approaches, particularly in order to achieve a good overview of chemical exposures in different populations. At the moment, only the tip of the exposure iceberg is visible when it comes to the estimated tens to hundreds of thousands of chemicals humans are exposed to throughout their lifetime (EEA, 2019; López et al. 2021; Schindler et al. 2014; Vorkamp et al. 2021). One reason for this is that targeted quantitative analytical methods only exist for a limited number of chemicals. This is partly due to the lack of toxicokinetic information on specific markers, sensitive methods, and commercially available pure analytical standards. For industrial chemicals, it is necessary to identify and quantify chemicals according to the quality standards required for input to risk assessment (EC 657/2002 and ISO 17025). Overall, strategically applied HBM is an excellent approach in the preassessment of risks by screening for exposures to chemicals of emerging concern, using methods such as suspect and non-target screening (Csizsar et al. 2017; Jolliet et al. 2021). This would have societal benefits, as routine HBM would help to prioritise the chemicals of emerging concern with high/relevant exposures and to develop mitigation strategies that can prevent/reduce exposure and associated adverse health effects, as a result of which the impact on health systems and the associated costs would be reduced. For society, this timely intervention is likely to have considerable advantages, also in terms of cost-effectiveness.

Furthermore, as Europe transitions towards a circular economy, HBM can inform the current and future understanding of potential new human exposures resulting from the implementation of circularity in material flows (i.e. recycling of new material flows). Implementing circularity potentially creates new pathways of exposure through which both the general population and workers can be exposed to hazardous chemicals (HBM4EU, 2022). This includes, for instance, consumer exposure to products containing recycled materials (recycled paper, consumer goods made from recycled plastics), dietary exposure to a range of chemicals resulting from the reuse of sewage sludge and waste water on agricultural lands, and workers' exposure to chemicals in recycling installations and production processes using recycled feedstock.

3.1.4. Exposure trends in populations

HBM approaches are excellent ways of following up exposure time trends as well as elucidating the distribution of exposure among sub-populations. This information is important to locate exposure hot spots and exposures among vulnerable groups such as children, the elderly and people with low socio-economic status. Retrospective analysis of (stored) biological samples (biobanks) can detect changes in production, use, and the effectiveness of exposure mitigation measures

(Göen et al. 2018), provided that storage conditions ensure that modifications of the samples are negligible (Lermen et al. 2020). Some EU countries have well-established national HBM programmes. These have demonstrated how HBM can identify trends in chemical exposures, as well as people/groups of high risk, and evaluate any national policy or controls that have been implemented. For example, a HBM study identifying an increasing trend toward ubiquitous exposures to DINCH (diisononylcyclohexane-1,2-dicarboxylate), a phthalate substitute, since it was introduced on the market (Schütze et al. 2014).

Longitudinal prospective HBM studies can be used in identifying sub-populations at risk of higher exposures, as well as in tracking exposures to new chemicals and new biomarkers (Lermen et al. 2020). Thus, a consistent implementation of HBM programmes can identify time-related and/or geographical trends. It is essential to understand regional differences or regional-specific exposures that might exist, as well as potential differences between age groups (i.e. especially vulnerable groups), as consumer and dietary habits differ across age groups. The data from population-representative HBM can also provide a basis for the identification of the exposure of vulnerable groups and to assess if a separate, ad hoc strategy is needed. EU-OSHA is currently implementing a pilot study in six EU Member States collecting data on occupational exposure to cancer risk factors² (EU-OSHA 2018). The survey is aimed at identifying vulnerable groups, such as workers exposed to multiple cancer risk factors. For some substances, in particular those that can be absorbed through the skin or bioaccumulated, including HBM in health surveillance could provide additional insights into the internal exposure and for setting workplace prevention measures.³

HBM is also applied to study spatial distribution in the environment, e.g. to compare exposures by distance to an identified source and to determine to what extent such exposure estimates can be associated with observed health effects that may be clustered around a (suspected) hot spot of environmental pollution (Abecasis et al. 2022; Odabasi et al. 2015; Wilhelm et al. 2005). Contaminated sites may be related to industrial activity, sanitary landfill or certain applications of high-risk chemicals, such as pesticides in agricultural settings (Figueiredo et al. 2021; Silva et al. 2021; Trushna et al. 2022). Exposure studies may help to respond to questions and concerns within society about direct and indirect routes of exposures, particularly if they involve vulnerable groups living at a close distance to (suspected) sources of environmental pollution. In such settings, HBM can be used as an approach to complement other types of data collection and environmental monitoring. This type of use requires the application of contextual data and exposure modelling approaches to understand how environmental pollution may contribute to elevated levels of internal exposures and to identify groups with increased susceptibility (Oerlemans et al. 2018; Schmieid-Tobias et al. 2021).

Overall, conducting well-designed HBM programmes on a routine basis means that changes in exposures (exposure biomarkers) or in populations at increased risk of developing a disease (exposure and effect biomarkers), including vulnerable groups, can be readily identified, enabling timely responses to reduce exposures and remove the exposure source(s).

Therefore, HBM approaches could be utilised, in context, as an early warning system for increasing human exposures to specific chemicals.

3.1.5. Chemical incidents

HBM can be used for retrospective analyses and post-incident chemical exposure assessment (Lemke et al. 2021; Scheepers et al. 2011). Whereas air concentrations decrease below detectable levels soon after the exposure incident, biomarker levels of persistent

² <https://osha.europa.eu/en/facts-and-figures/workers-exposure-survey-cancer-risk-factors-europe>.

³ [https://oshwiki.eu/wiki/Biological_monitoring_\(biomonitoring\)](https://oshwiki.eu/wiki/Biological_monitoring_(biomonitoring)).

substances can still be determined quantitatively for up to weeks or even several months after the exposure event for some chemicals (Aylward et al. 2014). The detection periods after an incident depend on the half-life of the biomarker (Scheepers et al. 2011). Additionally, biobanked samples also allow for a retrospective exposure analysis for non-persistent chemicals (Conrad et al. 2017; Kolossa-Gehring et al. 2012). These HBM data can support retrospective exposure assessment. They enable, *inter alia*, making a distinction between exposed and non-exposed groups. Biomarkers can also provide an estimate of the extent of the exposure, and enable comparison with baseline or background levels in the general population (De Smedt et al. 2014; Scheepers and Smolders 2014). The same principle can be applied in occupational settings as part of an exposure surveillance programme (Bader et al. 2021). HBM data can be used to support risk communication and expectation management in the aftermath of a chemical incident where 'worried well' individuals may not be identifiable, which may enable providing reassurance and may support resilience. Aftercare and support to recover both mentally and physically can be offered to individuals who initially did not have health complaints (Simons et al. 2016), including first responders that need appropriate follow-up (Van Nieuwenhuysse et al. 2014). The use of HBM during and after chemical incidents is supported by a guidance document on a national level (Eggers et al. 2012; Scheepers et al. 2014). HBM has also been adopted as a viable approach in disaster management (Casajus Valles et al. 2020).

3.1.6. Potential onset of adverse health effects

HBM is not limited to exposure data, as HBM can be complemented with data on effect biomarkers (Zare Jeddi et al. 2021a), i.e. evidence of biochemical or physiological changes or responses that can predict the onset of adverse health effects in an organism resulting from a given, multiple exposure (Travis 2013). Effect biomarkers reflect combined biological effects and can serve as an approach for assessing exposures and early effects of both known and unknown chemical mixtures (Rodríguez-Carrillo et al. 2021; Vinggaard et al. 2021; Zare Jeddi et al. 2021a). Therefore, the assessment of effect biomarkers (e.g. DNA damage, oxidative stress, endocrine disruption, altered structure/function) can represent an approach towards solving some of the regulatory challenges regarding exposure to chemical mixtures (Gundacker et al. 2021; Rodríguez-Carrillo et al. 2022; Zare Jeddi et al. 2021a).

The use of toxicological and mechanistic knowledge, such as the adverse outcome pathways (AOP) concept, is important to select relevant and predictive effect biomarkers. The AOP concept can evaluate the biological plausibility of the exposure-outcome associations observed between HBM data and health effects in epidemiological studies (Muster et al. 2022; van den Brand et al. 2022).

HBM measures internal doses and, when used with available epidemiologic, toxicological, and toxicokinetic (modelling) data, help in the estimation of the amount of chemicals absorbed into the body, which could indicate potential health risks and increase the likelihood of detecting an exposure-response relationship (Apel et al. 2020; Schütze et al. 2015). These actual doses found in human populations can also be used to better interpret *in vivo* (i.e. animal data) and animal-to-human extrapolation. Combining HBM data with physiologically-based kinetic (PBK) modelling, which integrates absorption, distribution, metabolism and excretion (ADME) of a chemical, can further help hazard characterisation in combination with toxicological data (Connolly et al. 2020).

3.1.7. Monitoring the effectiveness of risk management measures (RMMs)

As illustrated in Fig. 1, HBM can be used for post-marketing surveillance, monitoring compliance and measuring the effectiveness of RMMs for regulated chemical substances (Kolossa-Gehring et al. 2012). In occupational settings, for example, HBM has been used for many decades and is still regularly used. This may be due to the employers' regulatory obligations, such as compliance with occupational exposure limits aimed at health promotion and disease prevention (Galea et al.

2021; Louro et al. 2019; Viegas et al., 2020). HBM implementation depends on the country's legislation. In some cases, HBM is used as a method for occupational hygiene assessments and in other cases for health surveillance (Viegas et al., 2020). In the latter application, the data are considered medical data, and therefore restrictions may apply to further/other uses, such as in the context of exposure and risk assessment.

HBM can be used to evaluate the success of regulations to lower exposure to chemicals, e.g. by introducing existing regulatory limits in vertical sector policies (e.g. for water, food or consumer products), or banning uses horizontally, e.g. through authorisations and restrictions under REACH. HBM levels may be compared with typically non-regulatory HBM guidance values (HBM-GVs) to calculate the frequency or the exceedance of the HBM-GVs. Plotting the values as a function of time or space can be used to build indicators showing time trends or variances across countries for single or groups of substances (Buekers et al. 2018). The pure presence, e.g. frequency of detection and quantity of a substance, of both currently used and legacy chemicals can provide information on the chemical pressure from legacy, currently used and emerging contaminants. When linked to other descriptors, this may also give insights into possible routes of exposures that would require regulatory attention, and into whether or not the substances are significantly absorbed (Conrad et al. 2017; Koch et al. 2017; Moos et al. 2015; Schütze et al. 2014). In legal disputes, it could also detect exposure in case of unexpected complaints (Buekers et al. 2018). Overall, HBM indicators can be a very useful tool for policymakers and scientists to communicate how well chemical policies have delivered, and to point towards areas where additional policy actions may be needed.

3.1.8. Application in risk assessment

HBM can be used to strengthen exposure assessment in the regulatory risk assessment process for both workers (Santonen et al. 2022) and the general population. When assessing the risk posed by a certain chemical – as equivalent to exposure* hazard – it should be kept in mind that the exposure levels usually drive the differences in risk observed across scenarios and populations. Recently, an occupational study dedicated to occupational Cr(VI) exposure aimed to provide EU relevant exposure data to support the regulatory risk assessment and decision-making. In addition, the capability and validity of different biomarkers for the assessment of Cr(VI) exposure were evaluated (Santonen et al., 2022). This study has enabled us to recognise HBM as an important exposure assessment tool, to identify which exposure scenario implies higher exposure (plating, welding or other surface treatments), and which risk management measures are more effective in controlling workers' exposure (Viegas et al., 2022).

Concrete uses of HBM in regulatory risk assessment processes for REACH restriction and authorisation purposes are limited. They mainly relate to high production volume chemicals (REACH), some well-known environmental contaminants (European Food Safety Authority (EFSA)) (Verhagen et al. 2018), and workers' exposures to pesticides (Louro et al. 2019). The lead, mercury, phthalates and bisphenol A (BPA) restrictions and 2,2'-dichloro-4,4'-methylenedianiline (MOCA) authorisation process provide good examples on how HBM data can be used to strengthen exposure assessment in the regulatory risk assessment underlying and evaluating the effectiveness of RMM (Louro et al. 2019).

In particular, HBM can support model evaluation and/or validation where individual data are strongly preferred. For example, in the case of the BPA restriction in thermal paper (ECHA, 2015), HBM data provided a strong basis for the risk assessment and RMMs (Louro et al. 2019).

Overall, HBM is underused (Viegas et al., 2020) and long-term HBM programmes with comparable and consistent data quality to evaluate the effectiveness of chemical control efforts should be further developed. Very few national and international chemical control strategies have been implemented in legislation to check the effectiveness of regulatory measures. For example, since 2007 a global monitoring plan for POPs has been established to provide comparable biomonitoring information

on the presence of POPs listed in Annexes A, B and C of the Stockholm Convention and to follow temporal changes (UNEP, 2019). In addition, the collection of HBM data to track changes in mercury exposure has been proposed to evaluating the effectiveness of the Minamata convention to ensure that the initiative successfully protects human health and the environment from mercury (Evers et al. 2016; UNEP, 2013).

3.1.9. Priority setting for policy actions based on health endpoints

Integrating HBM data into risk assessment for human health and chemicals regulations in general would further protect the human population (Lange et al. 2021; Ougier et al. 2021; Wilhelm 2021). To this end, it is necessary to develop scientifically sound and up-to-date health-based HBM guidance values (HBM-GVs), which can be used for direct interpretation of HBM data and to protect the general population by integrate them into public health systems.

HBM-GVs are derived from epidemiological and/or toxicological data. They indicate the concentration of a compound or its metabolite(s) in a biological matrix (e.g. blood, urine) at or under which a health risk is not anticipated, according to current knowledge (Apel et al. 2020). In occupational health, these values are set by several expert bodies including the American Conference of Governmental Industrial Hygienists (ACGIH) in the US, the MAK Commission in Germany, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), and the former Scientific Committee on Occupational Exposure Limits [(SCOEL) now in RAC] (ACGIH 2021; ANSES 2020; Forschungsgemeinschaft, 2017; SCOEL 2017). For the general population, different health-related assessment values are established such as HBM-I and HBM-II values from the German HBM Commission, bio-monitoring equivalents (BE) by Summit Toxicology and Health Canada, health-related guidance values (HBM-GVs) referring to the internal body burden set by HBM4EU (Lange et al. 2021).

Health-based HBM-GVs can be used directly for the interpretation of HBM data as a solid scientific basis for chemicals policy and risk communication. These values can help to refine the public health risk assessment by identifying exposures of potential concern, but also indicate potential regulatory priorities and the need for (additional) measures to reduce exposures (Apel et al. 2020).

In addition, HBM data can support derivation of a possible mixture assessment factor (MAF), suggested for single substance risk

assessments, to account for unknown co-exposures (Socianu et al. 2022). It would be of benefit to analyse a wider range of chemicals in the same individuals to better understand true co-exposure patterns.

Overall, the HBM expert working group classified the advantages of HBM in five major key areas (Fig. 2):

Assessing internal and aggregate exposure in different target populations.

Assessing exposure across all life stages – developmental life-stages constitute critical windows of vulnerability. Increased exposure due to a higher food consumption per kg bodyweight (children), underdeveloped or impaired detoxification mechanisms (such as in children, pregnant women, and the elderly), and developmental periods (preconception, prenatal, and early postnatal) account for a higher susceptibility.

Assessing combined exposure to multiple chemicals (mixtures) – An improved exposure assessment using HBM to identify relevant co-exposure patterns (real-life mixtures) will lead to an improved mixture assessment.

Bridging regulatory silos – reflect the aggregate exposure to one chemical used for different purposes and regulated under different legislative frameworks, e.g. a substance used as pesticide, biocide and veterinary medicine. Linked closely with this are the objectives of '1S1A'.

Enhancing monitoring compliance and effectiveness of RMMs – for those substances for which regulatory measures for exposure mitigation are already in place.

3.2. Enabling the use of HBM to its full potential

Making the most of HBM requires ongoing technical, scientific, financial, and regulatory improvement and support. In this paper we discuss nine areas that are important in this context.

3.2.1. Establishing more national surveys in a range of countries

Several countries (inter alia, the United States (US), Canada, Germany, France, Czech Republic, Belgium, South Korea, Japan) have ongoing nationwide HBM programmes to evaluate exposures to existing and emerging pollutants. HBM is a key component in the US National Health and Nutrition Examination Survey (NHANES), which also

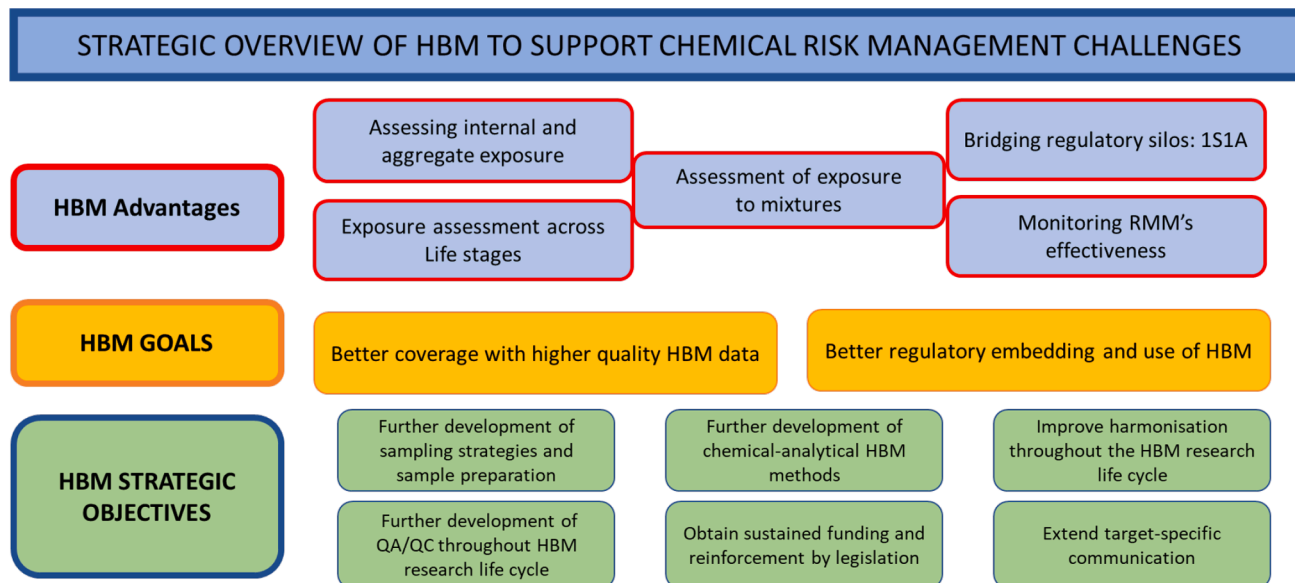


Fig. 2. The role of HBM in addressing the main challenges of risk management of chemicals. Risk Management Measures; 1S1A = one substance once assessment; QA = Quality Assurance; QC = Quality Control.

includes health parameters. NHANES data have provided exposure information to establish reference ranges as well as highlighting specific chemical exposures and inherent factors of variability (e.g. sex, age) (Calafat 2012). The Canadian Health Measures Survey (CHMS) is a HBM survey of the general population. CHMS has established population baseline concentrations levels and informed regulatory risk management decisions for safeguarding public health (Haines et al. 2017). In Germany, two major HBM programmes, the population representative German Environmental Survey and the German Environmental Specimen Bank, provide population HBM data used to identify exposures of concern, identify sources and higher exposed sub-population, control the effectiveness of measures and derive risk reduction measures (Kolossa-Gehring et al. 2012).

These national programmes have demonstrated that HBM can play an important role in evaluating environmental chemical exposures and, in general, health protection policies. In addition, HBM programmes provide population representative datasets, which may be used both to trigger and to provide benchmarks for the assessment of groups deserving special attention. Some examples are for children (Hendryx and Luo 2018) and occupationally exposed groups (Varshavsky et al. 2020).

Many countries, however, lack HBM population studies in general, stand-alone national programmes, to collect HBM data for a wide variety of chemicals over time that are representative of specific characteristics of the populations such as age, sex, community size, and socio-demographic factors. The lack of availability of long term regular consistent monitoring programmes, as well as technological, methodological and biobank resources to monitor human exposure and time trends to various chemical substances in a timely manner pose challenges and limitations to cross-country chemical regulatory assessments (Lermen et al. 2020). Europe would benefit from more nationwide programmes, as well as an EU-wide HBM programme implemented in legislation continuing the work of HBM4EU (<https://www.hbm4eu.eu>).

3.2.2. Developing more chemical standards for biomarkers

Analytical reference standards for the biomarkers of choice are often not (commercially) available. In several cases this is due to the lack of toxicokinetic information which is prerequisite for the identification of specific and sensitive biomarkers. Custom synthesis of the compounds or metabolites used as biomarkers is required for unambiguous identification, development and validation of quantitative methods. An increased use of HBM would create a demand for more toxicokinetic studies and the subsequent production of standards, which might make it lucrative for companies to develop standards for more chemicals at a faster rate.

3.2.3. Promoting routine laboratory analysis

A more regular performance of HBM (i.e. on the basis of regular population studies) with substantial numbers of samples would stimulate the process of establishing HBM analyses as routine procedures in labs. This would increase efficiency and reduce cost. Therefore, a more extended analytical coverage of biomarkers and greater involvement of different laboratories providing tests on a routine basis will be important for further broadening the use of HBM.

3.2.4. Further improving quality assurance (QA) / quality control (QC) for HBM methods

It is not always clear whether HBM results generated by different laboratories are comparable or this comparability may be insufficient, even though quality assurance systems such as G-EQUAS (<https://www.g-equas.de>) and comparable systems in the US and worldwide offer internationally recognised quality assurance systems and regular round robins in which a large number of international HBM laboratories systematically participate. As demonstrated and promoted within the COPHES/DEMOCOPHES projects and more extensively in the European Joint Programme HBM4EU (López et al. 2021), dedicated QA/QC

programmes safeguard comparability of data for a number of biomarkers/biological matrices pairs, and result in a network of competent and highly qualified expert laboratories. Substantial QA/QC efforts have been made within EU-funded research projects and these will continue within the Partnership for Chemicals Risk Assessment (PARC) (Caballero-Casero et al. 2021a; López et al. 2021; Nübler et al. 2022a; Nübler et al., 2022b; Schindler et al. 2014; Vorkamp et al. 2021). Establishing these activities on a permanent basis is important to utilise the full potential of HBM.

3.2.5. Better understanding of toxicokinetics

Better knowledge of biomarker kinetics, including the identity of biotransformation products (e.g. primary and secondary metabolites) and biomarker concentrations in easily obtained biological fluids and/or matrices (e.g. quantification of urinary excretion rates of parent compounds to ensure extrapolation to internal concentrations), is a key factor for the identification of specific and sensitive markers which are a prerequisite for further improving the use of HBM. A more systematic generation and use of toxicokinetic knowledge in view of a better interpretation of HBM data (Carusi et al., 2022), e.g. by enabling the calculation of uptake rates (Koch et al. 2014; Kolossa-Gehring et al. 2017) is another building block of making better use of HBM.

3.2.6. Increasing findability of HBM data suitable for regulatory purpose

The relevance of HBM in a worldwide context is often underestimated, in part due to the unharmonised (heterogeneous) 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). In practice, finding data from studies that are suitable for a specific regulatory purpose is challenging. Some studies are fragmented and heterogeneous in terms of design, terminology, biomarker nomenclature, and data formats (Zare Jeddi et al., 2021b). In addition, policymakers are often required to produce quick responses when problems arise and therefore need timely access to reliable HBM data to come up with sound policy actions (Joas et al. 2017). These shortcomings limit our capacity to compare and integrate data sets retrospectively (i.e. reuse).

As an important step in this direction, HBM4EU has made a big contribution to improving the availability, accessibility and findability of European HBM data (Gilles et al. 2021). More than 61 harmonised datasets from European studies and the HBM4EU Aligned Studies can be found through HBM4EU Dashboard (<https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/>). In order to feed HBM4EU data into the Information Platform for Chemical Monitoring (IPCHEM), HBM4EU has harmonised vocabularies and formats for reporting (meta)data (Bopp et al. 2020). HBM4EU has managed to post-harmonise existing data from former studies and produced harmonised data in the HBM4EU Aligned Studies (Eva et al. 2022). HBM4EU data are also available via IPCHEM.

3.2.7. Promoting holistic exposome approach in HBM studies

A critical feature of the exposome paradigm is that it entails a comprehensive characterisation of exposures an individual experiences over a lifetime (Wild 2012). It relies on interdisciplinary approaches in the characterisation of external exposome as well as internal exposome (biomonitoring and omics) (Vrijheid 2014). Major issues related to human biomonitoring in the exposome context have been extensively discussed (Dennis et al. 2017). The holistic understanding of the internal exposome can be achieved through a combination of approaches, including targeted biomonitoring and agnostic analyses (untargeted/semi-targeted). While both targeted and non-targeted human biomonitoring on their own have limitations in providing a holistic view of the exposome, they can ensure quality assurance / quality control, which has seen significant advancement through large-scale collaborative efforts such as COPHES, DEMOCOPHES and HBM4EU. In the evolving and rather young exposome landscape, such quality assurance

is limited, except through HBM4EU achievements available for agnostic analyses (Caballero-Casero et al. 2021b; Oberacher et al. 2020; Pourchet et al. 2020). The tasks ahead are to overcome pre-analytical and analytical challenges by minimising variability during sample preparation (analyte extraction method) and analysis, as well to develop harmonised semi-quantitative methods.

As gaining a better understanding of the exposome will require evidence amalgamation, the process could be enriched by reusing existing HBM data, analysis (prospective and retrospective) of biobank HBM samples, and federated analysis in line with FAIR (findability, accessibility, interoperability, and reusability) principles, combined with computational and mathematical modelling. The lack of data for exposure and HBM approaches presents a challenge as the exposome assessment involves analysis of life course data. Additional emphasis should be placed on addressing the lack of data through multiple imputation and machine learning approaches. Therefore, exchange and complementarity of the European human biomonitoring projects, programmes and partnerships (ESBIO, COPHES, DEMOCOPHES, HBM4EU, PARC) and the European human exposome initiatives (HELIX, HEALS, EXPOSOMICS and European Human Exposome Network) will be critical to broaden our understanding of environmental exposures and health outcomes. Another approach for combined exposure is to map the spatial coincidence of multiple stressors by overlaying environmental monitoring data from different media, as well as social and demographic data. Both approaches cover not only environmental stressors but also social vulnerability (EEA, 2020). This has also been recognised as a challenge, as combination of data is not easy however artificial intelligence could be a tool to help address this issue. This would also require upfront harmonisation of data frames (Zare Jeddi et al., 2021b).

3.2.8. Inclusion of HBM in chemical regulations against the background of legal requirements

The potential of HBM has not been appropriately recognised in EU chemicals regulations to date and, except for the occupational setting, there is neither a requirement to perform HBM nor are there any specific legal requirements providing for this. One challenge in systematically recognising HBM in the regulatory context is the EU General Data Protection Regulation (GDPR) that came into force in the European Union in 2018. In HBM4EU, (which took place 2017–2022), for instance, it has become clear that compliance with the GDPR required additional efforts. This resulted, for example, in intense discussions about the strengths and limitations of anonymisation and pseudonymisation of individual data, which is particularly relevant when data are to be shared. Further policy input will be necessary to further facilitate HBM in chemical regulations against the background of ethical and legal issues.

3.2.9. Deriving more HBM health-based guidance values

The most informative studies for deriving HBM-GVs are properly conducted human studies adequately reporting measured internal concentration levels of a chemical, metadata (i.e. sampling times, adequate description of the study population, analytical methods used etc.), as well as the relationships between concentrations of a chemical or its metabolites in human biological media and the occurrence of adverse effects. The promotion of scoring systems, such as LaKind or STROBE (Strengthening the Reporting of Observational studies in Epidemiology), could encourage better quality studies and better reporting of quality aspects (LaKind et al. 2014).

As studies in humans are limited, additional means to derive HBM-GVs has been developed, which have been approved at EU level after broad discussion in all 30 HBM4EU partner countries (Apel et al. 2020).

4. Six strategic objectives and an associated action plan

Taking into account advantages of HBM and requirements for a broader use of the HBM approach, we define a twofold goal for the HBM

Strategy to catalyse change in regulatory exposure assessment and policy (Fig. 2):

- I. **High-quality HBM (meta)data** sustained over time covering a broader range of chemical substances and regulatory silos, coverage of sub-populations (more age groups, more regions, more socio-economic groups, etc.), improved significance of HBM data for risk assessment (e.g. through the integrated use of exposure and effect biomarkers, and the derivation of additional toxicologically derived health-based guidance values, such as the HBM-GV (Apel et al. 2020), HBM I, and HBM II-Values (Apel et al. 2017) or the Biomonitoring Equivalents (BEs) (Hays and Aylward 2012).
- II. **Better regulatory use of HBM** approach

The achievement of the following six strategic objectives (Fig. 2) will likely improve the use of HBM, and thus contribute to achieving the goal of better regulatory embedding and the use of HBM, as well as the goal of better coverage:

- (1) further development of sampling strategies and sample preparation towards cost-effectiveness;
- (2) further development of chemical-analytical HBM methods;
- (3) improve harmonisation throughout the HBM research life cycle;
- (4) further development of quality control (QA) / quality assurance (QC) throughout the HBM research life cycle;
- (5) obtain sustained funding and reinforcement by legislation;
- (6) extend target-specific communication.

All six strategic objectives identified in Fig. 2 are translated into clearly identifiable actions to consolidate and expand existing knowledge to support and advance regulatory use and implementation of HBM across current and future EU legislation. In this paper, actions are discussed at a relatively high level, as the scope of this paper is to set a strategy and propose a roadmap (Table 2). Some actions have been or will be the subject of separate papers linked to this HBM strategy paper (Heinemeyer et al. 2021; Zare Jeddi et al. 2021a; Zare Jeddi et al., 2021b).

4.1. Strategic objective 1 – Further development of sampling strategies and sample preparations towards cost-effectiveness

Biological sample collection should be easier, faster and more affordable, while still being reliable. Biosensors, lab-on-a-chip and self-sampling devices are measurement devices that allow for greater ease of collection, as well as smaller volume collection as needed. The availability of these devices should be increased and more widely communicated to the HBM community. A wider implementation of these approaches is likely to lead to increased sample numbers (Arakawa et al. 2020; Hauser et al. 2019; Lenk et al. 2015; Liu et al. 2021; Liu et al. 2019). Blood sampling devices are an interesting new technology being developed to make sampling easier, more affordable and faster in medical settings. This technology might facilitate ‘at home’ sampling that allows participants to self-sample if contamination-free conditions are safeguarded, with the samples then either being collected or sent by the participants to the laboratory for analysis (Seeger and Salzmann 2020; Vorkamp et al. 2021).

Although the chemical-analytical sensitivity has significantly improved in the past decades, a further lowering of the limit of detection (LOD) and limit of quantification (LOQ) might be necessary in some cases, certainly when it comes to promoting low-volume sampling (typically less than 100 µL). Such improvements in detection capability create additional responsibilities in terms of the interpretation of ‘positive’ results.

Ensuring the absence of external background contamination during sampling for ubiquitous chemicals, as well as pre-analytical sample treatment and control of other possible pre-analytical errors, are crucial

Table 2

Strategic objectives, their most relevant associated objectives and more concrete actions as part of the European Exposure Science Strategy for human biomonitoring (HBM) with a roadmap for the mid-term (2022–2025) to long-term (2026–2030), including most relevant stakeholders¹.

Objectives and specific actions	Most relevant stakeholders ²	Timeline*	
Strategic Objective 1: Further develop sampling strategies and sample preparation			
Advancing generation of HBM data	Guidance on harmonisation/optimisation of study designs, research protocols, collection of samples (e.g. standardised terminology)	PARC Agencies ³ OECD/Industry (associations) Academia and RI's NGOs	Mid-term
	Inventory and assessment of available HBM sampling techniques	Academia and RI's	Mid-term
	Further develop protocol and guidance to combine HBM studies with health surveys (HBM coupled with nutrition and health studies)	PARC	Mid-term
Speeding up pre-analytical phase	Less expensive, faster and non-invasive sampling (micro sampling, postal shipping)	Academia and RI's	Mid-term
	Semi-automated sample preparation	Academia and RI's	Mid-term
	Exploring 'point-of-sampling' sensors for effect biomarker determination	Academia and RI's	Long-term
Include toxicokinetics (TK) in humans to improve HBM study design and interpretation and use of HBM data	Parallel use of occupational HBM aligned with high quality personal monitoring (inhalation and dermal exposure) as controlled exposure for establishing basic toxicokinetic (TK) parameters, so-called combined monitoring	Academia and RI's	Long-term
	Human TK knowledge-steered optimisation of HBM sampling protocols	Academia and RI's	Mid-term
	Introducing regulatory requirements for absorption, distribution, metabolism, and excretion (ADME) and TK data ('human-sentinel' ADME and TK)	Agencies European Commission OECD National Authorities	Mid-term
	Better use of animal experiments and introducing requirements to derive TK data from these experiments	OECD	Mid-term
	Exploitation of human in vitro system ADME data to feed human PBK modelling to inform HBM study design and interpretation of HBM data	Academia and RI's	Mid-term
	Accommodate and harmonise the templates for detailed ADME and TK data entry in (e.g. IUCLID in REACH dossiers and OECD harmonised templates), either human in vitro system ADME data, 'human sentinel' ADME and TK data and human volunteer study TK data and combined monitoring TK data)	Agencies OECD	Mid-term
	Guidance on harmonisation of human TK (animal, human volunteer and combined monitoring) data reporting	Academia and RI's	Mid-term
Accommodate registration templates for HBM data	Creating a registry system for human volunteer TK studies	Academia and RI's	Long-term
	Accommodate the templates to include also HBM data, i.e. <i>sec</i> measurement data but also ancillary data such as IUCLID at ECHA	Academia and RI's Agencies	Long-term
Strategic Objective 2: Further develop chemical-analytical HBM methods			
Framework for the analytical performance assessment	Promoting the use of suspect screening (SS) and non-targeted screening (NTS)	Agencies Academia and RI's	Mid-term
	Propose harmonised guidance documents for method performance assessment, and analytical quality control (QA/QC provisions and criteria) for SS/NTS specifically dedicated for HBM analysis and in consideration of the guidelines for food contaminants and environmental contaminants.	OECD National Authorities/Industry (associations) Academia and RI's	Mid-term
	Establish need-based databases and mass spectrometric reference libraries for high throughput and qualitatively consolidated annotation of human biomarkers, linking/collaborating with already existing initiatives (e.g., NORMAN, IPCHEM, HBM4EU and incoming PARC resources and tools)	European Commission, OECD/Industry (associations) Academia and RI's	Long-term
	Build proof-of-concepts to illustrate the applicability/potential of SS/NTS for early warning detection of new and emerging contaminants.	European Commission, OECD Academia and RI's	Mid-term
	Anchor the whole workflow and framework for SS/NTS in a transversal harmonization dynamic across the environment-food safety-HBM communities as well as in a sustainable and scaled-up implementation through a dedicated EU research infrastructure	Academia and RI's European Commission National Authorities	Long-term
	Interface/interaction analytical databases/non-target data files with data repositories	Academia and RI's National Authorities	Long-term
	Stimulate ISO 17025 accreditation (makes participation in EQUAS ⁴ /proficiency testing mandatory), including guidelines for accurate mass spectrometry instrument settings, qualifiers, control tests etc (incentives for certification/accreditation).	OECD Agencies	Long-term
	Routine application of combined quantitative/qualitative analysis of biomarkers using full scan technologies	Academia and RI's	Long-term
	Integrated cross-platform for high-dimension chemical and analytical characterization of chemical exposure signatures	Academia and RI's	Long-term
	Improve analytic chemistry to measure human TK and/at low human exposure (limit of detection), e.g. with tracer techniques for human volunteer studies	Academia and RI's	Long-term
			Mid-term

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Table 2 (continued)

Objectives and specific actions		Most relevant stakeholders ^a	Timeline*
Explore biomarkers of effect, and their regulatory use for mixture exposure assessments	<p>Examine suitability of biomarkers of combined effect/activity for exposure monitoring to relevant (well-known and unknown chemical) human mixtures</p> <p>Set-up selection criteria for best/suitable use of effects biomarkers, which can be also used including as indirect exposure biomarkers (e.g. in occupational studies)</p> <p>Validation (technical, biological/physiological and toxicological) of effect biomarkers, to be used as indirect exposure biomarkers for mixtures exposure</p> <p>Encourage the systematic implementation of effect biomarkers to improve the understanding of exposure-health associations</p> <p>Building Adverse Outcome Pathways (AOPs) based on human biology to validate the use of effect biomarkers</p> <p>Develop guiding principles to set effect biomarker guidance levels to manage potential mixtures exposure for substances affecting that effect biomarker</p>	<p>National Authorities Academia and RI's</p> <p>Academia and RI's</p> <p>Academia and RI's</p> <p>Academia and RI's</p> <p>Academia and RI's</p> <p>Academia and RI's</p>	<p></p> <p>Mid-term</p> <p>Mid-term</p> <p>Mid-term</p> <p>Mid-term</p> <p>Mid-term</p>
Strategic Objective 3: Further develop quality control (QC)/ quality assurance (QA) throughout the HBM research life-cycle	<p>Quality assurance analytical chemistry part</p> <p>Require registrants (producers or importers of the chemical substance) to provide analytical standards/parameters and analytical procedures in the relevant compartments, including degradation products</p> <p>Develop SOPs for sample preparation and chemical analysis and promote their availability and use</p> <p>Guidance for compliance testing</p> <p>Guidance how to set QC/QA requirements</p> <p>Reaching out to laboratories that offer analyses of environmental toxins to align with the HBM standards with the purpose to enable the use of statistical data.</p>	<p>Agencies National Authorities Industry (associations) Academia and RI's Industry (associations) Academia and RI's OECD Agencies Academia and RI's OECD Agencies Academia and RI's</p>	<p>Mid-term</p> <p>Mid-term</p> <p>Long-term</p> <p>Long-term</p> <p>Mid-term</p>
Quality assurance ethics and data protection	<p>Improvement of study design with respects to transparency, ethics and GDPR</p> <p>Development of guidelines for study design and protocols which is fit-for-purpose including compliance with ethical guidelines and GDPR</p>	<p>Academia and RI's</p> <p>Academia and RI's</p>	<p>Mid-term</p> <p>Long-term</p>
Strategic Objective 4: Improve harmonisation throughout the HBM Research Life-cycle	<p>Ensuring/improvement of reliability, comparability and reusability of HBM data</p> <p>Web-based registry with mandatory fields based on web-based templates for the registration process to optimise HBM study designs and standardisation of research protocols (under HBM Global Registry Framework)</p> <p>Guidance how to implement FAIR (Findability, Accessibility, Interoperability, and Reusability) principles in HBM value chain (a FAIRification workflow)</p> <p>Create a FAIR catalog specifically for HBM to promote 'FAIR by design' studies</p> <p>Include research communities to encourage reporting in standard formats useful also for regulatory process</p> <p>Active communication between all stakeholders regarding databases and data repositories</p> <p>Unique coding of analytes (substances and their metabolites) e.g., detailed in codebooks and unique linking to unique identifiers (presumably InChI or InChIKey)</p> <p>Systematic development and coding of relations between chemical substances and their metabolic breakdown products used as biomarker of exposure and harmonised use in registry templates</p> <p>Scientific workshops to harmonise human volunteer studies</p> <p>Guidance how to use HBM in an early warning system (exposure awareness)</p> <p>Federated systems to be able to use data without possessing them at EU level</p>	<p>Academia and RI's National Authorities WHO Agencies Publishers Academia and RI's European Open science could Academia and RI's European Open science could Academia and RI's European Commission Academia and RI's European Commission Academia and RI's Scientific societies Agencies Academia and RI's Scientific societies OECD Academia and RI's Scientific societies Academia and RI's OECD National Authorities Academia and RI's National Authorities</p>	<p>Mid-term</p> <p>Mid-term</p> <p>Mid-term</p> <p>Mid-term</p> <p>Mid-term</p> <p>Long-term</p> <p>Mid-term</p> <p>Long-term</p> <p>Mid-term</p> <p>Mid-term</p> <p>Mid-term</p> <p>Long-term</p> <p>Mid-term</p> <p>Long-term</p>

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Table 2 (continued)

Objectives and specific actions		Most relevant stakeholders ²	Timeline*
Strategic Objective 5: Obtain sustainable funding and reinforcement by legislation			
Promote uptake of HBM data into chemicals management including risk assessment	Developing EU level guidance on the generation, interpretation and use of HBM in regulatory risk assessment	Academia and RI's OECD National Authorities	Mid-term
	Criteria for consideration in the application of HBM data in human health risk assessment for single chemical and priority mixtures of chemicals	Academia and RI's National Authorities	Mid-term
	Approaches for interpreting the HBM data for policy implementation (in relation to various perspectives, e.g. regions, age groups, sex, socio-economic differences, exposure mitigation, risk assessment etc.)	Academia and RI's Agencies National Authorities	Mid-term
	Guidance on HBM data governance (planning, monitoring, and enforcement)	Academia and RI's National Authorities	Long-term
	Advancing integration of HBM into epidemiological studies for chemical risk assessment: Developing an EU level guidance document for defining criteria for best use of epidemiological data and on interpretation of epidemiological studies in risk assessment	Academia and RI's Agencies National Authorities	Mid-term
	Promoting nation-wide HBM programmes	European Commission National Authorities	Long-term
	Promoting sustainable funding for HBM studies	European Commission National Authorities	Long-term
Application of HBM as an exposure assessment tool in occupational safety and health (OSH)-related regulations for single chemical and priority mixtures of chemicals	Use of HBM in the area of chemical incidents and disasters	Agencies National Authorities	Long-term
	Developing guidance under OSH-regulations for HBM as an exposure assessment tool for risk assessment and risk management purposes	Agencies National Authorities Industry (associations)	Mid-term
	Collaborating with OECD on developing HBM guidance values for occupational settings	Academia and RI's OECD	Long-term
	Further exploration of feasibility and existing guidance	Academia and RI's Agencies	Mid-term
	Combining external exposure assessment tools (air and dermal sampling) with HBM (when, how, is it necessary) and interact with occupational hygienists' associations. Evaluation of aggregate exposure (HBM might be more relevant) and use kinetic modelling for interpretation	Academia and RI's Agencies Industry (associations)	Long-term
Development of health-based HBM-guidance values and statistically derived HBM reference values	Develop regulatory guidance for development of HBM guidance value for individual chemical substances and well-defined groups of them (like a few PFAS or a few phthalates)	OECD Academia and RI's Agencies Industry (associations)	Mid-term
	Legal support for establishing general population HBM reference values to be used to interpret occupational HBM results	OECD Academia and RI's Agencies	Long-term
Strategic Objective 6: Extend target specific communication			
Improve the communication of HBM research outputs	Develop communication protocols on how new findings can be applied to different fields of exposure science and how they can support new regulatory actions	Academia and RI's	Mid-term
	Develop communication protocols on how physicians can communicate HBM results (including untargeted substances and the effects of exposure to multiple chemicals) to general public	Academia and RI's Agencies	Mid-term
	Establish a survey of the current number and standards of screenings of patients who test for environmental toxins.	Academia and RI's	Mid-term
	Prepare specific guidance for (interested) regulatory silos on how the new HBM research outputs can be applied and the advantages they bring	Academia and RI's Agencies European Commission	Mid-term
	Develop risk communication schemes	Academia and RI's National Authorities	Mid-term
	Provide medical training at universities regarding the exposure to chemicals and the ongoing professional training	Academia and RI's	Mid-term

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; FAIR = Findability, Accessibility, Interoperability, and Reusability; NGOs = Non-governmental organisations; NTS = non-targeted screening; OECD = Organisation for Economic Co-operation and Development; OSH = Occupational safety and health; PBK = physiologically based kinetic; PFAS = Perfluoroalkyl and Polyfluoroalkyl Substances; RI's = Research Institutions; SOP = standard operating procedures; SS = suspect screening; TK: toxicokinetic; QA = quality assurance; QC = quality control; GDPR - EU General Data Protection Regulation. Timeline: mid-term (2022–2025); long term (2025–2030).

¹ Scientific societies in the area of exposure, occupational hygiene, occupational medicine, environment and health etcetera are not explicitly stated but are relevant for almost all tasks.

² Some of the actions are already in the work plan of ISES Europe HBM working group or European projects such as the European Partnership for the Assessment of Risks from Chemicals (PARC).

³ Agencies such as ECHA, EFSA, US OSHA, EU OSHA, FDA etc.

⁴ EQUAS - external quality assurance scheme.

considering the very large diversity of physicochemical properties and concentration levels encountered in HBM (Fiddicke et al. 2021; Zare Jeddi et al., 2021b). This aspect has not been sufficiently addressed to date, particularly with respect to the new large-scale suspect and non-targeted screening approaches (David et al. 2021; Pourchet et al. 2020).

Reduction of analytical costs will be an important factor for embedding HBM analysis in ongoing and future monitoring programmes at a national or preferably international level. Repeated HBM sampling several times during the day is needed to establish relationships between internal exposure and the intake of food contaminants that leave the body quickly after intake (short half-life). For some studies, depending on their objectives, this requires a different study design and increased resources on many levels. One solution would be a combination of large-scale continuous HBM studies with a reasonable number of HBM samples and small-scale HBM studies with more extensive and diverse biological materials, which cover chemicals with both long and short half-lives in the body. In addition, combining health surveys and HBM studies can have added value for health and exposure monitoring and is cost-effective, as only one infrastructure is needed to collect information and recruit participants (Tolonen et al. 2022). However, this combination of studies might also have its limits, in view of the available amount of biological material and the maximum time for asking participants questions for each arm of the study.

Miniaturisation and automation of sample preparation might help to lower costs and increase sample throughput. However, the usually lower concentrations of metabolites representing the parent compound observed in human specimens (internal exposure) compared to the parent compound in environmental and/or food matrices (external exposure), coupled with small sample amounts (which limits the possibility of concentrating the useful signals of interest), represent a challenge in reaching this goal.

Another course of action would be to plan a rationalised sample preparation specifically dedicated to suspect and non-targeted screening approaches to maximise the number of accessible markers of exposure. This novel and important approach might help to identify unknown or overlooked chemicals, preferably at a time when it becomes feasible to generate reproducible semi-quantitative exposure data.

Another important objective is the optimisation of the sampling strategy (time after potential exposure, blood or urine matrix, parent substance or metabolites), and to consider the dynamic aspects of the exposure and those of the toxicokinetics. When effect biomarkers are integrated into HBM, the same general considerations may apply. However, criteria should be adapted to the nature of effect biomarkers that are usually represented by biochemical (e.g. enzymes), cellular (e.g. DNA adducts) and/or omics (e.g. metabolomic) parameters (Hernández-Mesa et al. 2021).

4.2. Strategic objective 2 – Further development of chemical-analytical HBM methods

Ensuring an extended coverage of chemicals by means of a larger panel of accessible biomarkers, low detection limits and good quantitative performances, while also reducing analytical costs, continues to be a significant objective. One option to reduce analytical costs would be to create large national or international analytical core facilities with a wide range of chemical analytical instruments that provide open access options. This implies the need to develop well-defined guidelines for users and provide the required expertise to ensure the production of robust and reliable data (Andreassen et al. 2021). Obviously, availability of analytical reference standards and the possible need for various HBM protocols are complicating factors. Another option would be to combine multiple biomarker methods to generate more HBM data in a single analysis. For example, many metals have been quantified in one single HBM sample. Approaches used in pesticide and veterinary drug analysis of food and biological matrices (mainly limited to the parent compounds) can now determine hundreds of substances simultaneously and

quantitatively (Heitland and Köster 2006; Morton et al. 2014; Park et al. 2021). Targeted chemical analysis for a range of known chemicals combined with harmonised and reproducible semi-quantitative suspect and non-targeted screening (NTS) might permit documentation on a wider range of substances in an early warning and further prioritisation context. This could significantly boost the generation of HBM analytical data. Generally, sample preparation and data acquisition are similar for suspect screening and NTS whereas data analysis/mining are different. This challenging approach represents a promising strategy to advance the comprehensive characterisation of the human chemical exposome, but several analytical challenges related to sensitivity issues or the annotation process will first have to be overcome (David et al. 2021). The use of NTS requires advanced capabilities and good integration of new cutting-edge data management aspects (advanced data acquisition and processing facilities, bioinformatics, and modelling tools). The elaboration of an extended and qualitatively consolidated reference library for annotation of the detected biomarkers with a sufficiently high level of confidence appears to be a crucial need. There is a need for establishing strong international collaboration and high-level networking to overcome these challenges (David et al. 2021).

In the context of tracing mixtures of concern as well as new single chemicals of concern, Effect-Directed Analysis may be used in a bottom-up approach: First, test fractions of a HBM sample for a single toxicologically relevant activity or a panel of such activities (e.g. interactions with a panel of nuclear receptors) would be tested in a responsive *in vitro* system. Second, if positive, an attempt would be made to identify possible marker(s) of exposure (chemical substances or metabolites) that are responsible for the observed activity (Rodríguez-Carrillo et al. 2021; Vinggaard et al. 2021). While the Effect-Directed Analysis approach is now mature, it is at present clearly less generally applied in HBM (Bjerregaard-Olesen et al. 2019). The application of Effect-Directed Analysis to human samples, such as blood, placenta, amniotic fluid, milk, or meconium, has great potential, as it may provide new insight into chemicals accumulating in the human body (Vinggaard et al. 2021).

4.3. Strategic objective 3 – Further development of QA/QC throughout HBM research life-cycle

Conducting the necessary QA/QC, method performance assessment, and harmonisation ensures a high level of data quality and comparability. It is essential to have insight into the intra- and inter-laboratory precision of HBM data generated by laboratories. We therefore encourage the adoption of common definitions and terminology by the whole community working in this field (Heinemeyer et al. 2021). This would help in harmonising workflows used to treat complex chemical analytical datasets and improving reporting of results. The involvement of multiple laboratories in data generation over time and across different countries is inevitable. One way to gain insight into the comparability of data and inter-laboratory precision is through EQUAS, also known as proficiency tests (PTs). There are very few providers of continuous QA/QC (e.g. G-EQUAS,⁴ OSEQAS⁵) and the scope covered is relatively limited, but perhaps this number of providers could be expanded, if supported by the various, large-scale research initiatives that are ongoing. Therefore, development of a wide network of experts is required that can continue within the PARC framework and other relevant projects, such as EIRENE RI.⁶ This would reduce the investment cost for projects and ensure the long-term viability of commercial schemes.

Existing guidelines and good practices for lists of priority substances from various HBM projects including HBM4EU⁷ (Ougier et al. 2021), as

⁴ <https://app.g-eqas.de/web/>.

⁵ <https://www.inspq.qc.ca/en/ctq/eqas/oqesas/description>.

⁶ <https://www.eirene-ri.eu/>.

⁷ <https://www.hbm4eu.eu/online-library/>.

well as guidance documents and legislation from the food domain, form an excellent basis for the establishment of HBM analysis of various types of biomarkers (EFSA et al. 2017; EFSA et al. 2021; Verhagen and van Loveren 2016). The development of an extended and qualitatively consolidated mass spectrometry detection reference library for annotating markers of exposure will be a key strategical element for operational and harmonised implementation of these approaches at the European level.

Where analytical reference standards are not yet commercially available, there is a need for centralised custom synthesis and distribution amongst HBM laboratories. It is also important to harmonise collection and the use of repeated samples (analysed separately or pooled) to assess exposure to non-persistent chemicals. Collaborations must be encouraged to use complementary analytical techniques between laboratories to cover the very large diversity of physicochemical properties of the chemicals of emerging concern.

The HBM4EU lab network (<https://www.hbm4eu.eu>), which is continued in PARC, represents an important step towards a “map” of the existing laboratories (both nationally and internationally) and their domain of activities. In addition, there is a need for networking and collaboration between laboratories and large-scale pooling of comparable HBM data to identify relevant emerging research questions in addition to providing data for chemicals-related policies and regulations.

4.4. Strategic objective 4 – Improve harmonisation throughout the HBM research life-cycle

For HBM to become useable as evidence for regulatory decisions and policy, **optimisation, harmonisation, and guidance** are three domains where improvements will be necessary. Recently, HBM4EU has been working on systematisation and optimisation of the choices that need to be made before starting an HBM campaign (Fiddicke et al. 2021). These choices are framed as questions and include: which biomarkers best reflect certain external exposures; what is the best matrix to sample in; and what is the most appropriate sampling time, dependent on the absorption, half-life and metabolism of the parent substance? Mostly, these optimisations have been completed for one programme or project and perhaps for the validation of the analytical methods for only a few chemicals. Germany has an ongoing programme for occupational human biomonitoring to optimise HBM campaigns (Göen et al. 2012). An ongoing OECD project aims to summarise the current state of knowledge in occupational HBM and support a harmonisation of deriving health based human biomarker guidance values and using biomonitoring in exposure assessment and risk management in occupational health.⁸ There may be different solutions for optimisation, which depend on the goal, the chemical of interest, and the various exposure scenarios. Therefore, optimisation and development of **guidance on how to implement optimisation** is needed. However, beyond this need for optimisation to support consolidation and improvement of data comparability, flexibility and innovation must be preserved, as HBM (including non-target screening and other front-of-science fields) continues to require capabilities in discovery and exploratory research (Pourchet et al. 2020).

Harmonisation of HBM (meta)data is key in supporting and advancing regulatory risk assessments and management of chemicals in environmental and occupational health domains, as well as supporting IS1A and One Health policy needs. One Health is an umbrella concept that involves the evaluation and monitoring of the impact of chemical exposures on human health and the environment. To promote the generation of comparable HBM data, the ISES Europe HBM expert group recently proposed the development of an HBM Global Registry

Framework (HBM GRF) implementing FAIR principles and Open Science practices as the solution to several of the current challenges hampering the (re)use of HBM (meta)data. The HBM GRF aims to develop a global, host-independent platform (FAIRHBM) for the preregistration of HBM studies. This platform provides HBM specific metadata catalogues, harmonised terminologies, ontologies, and harmonised open-access protocol templates for better designing HBM studies, (Zare Jeddi et al., 2021b). Regulatory enforcement of HBM harmonisation is also conceivable.

Along with the rapidly evolving HBM programmes and advanced omics technologies, large amounts of data are generated. Statistical (or other advanced) models help in establishing associations between exposure and health-related outcomes. Such relationships will only be elucidated when HBM data are (re)usable and comparable.

Overall, for each step of conducting an HBM study, there is a need for developing relevant guidance. Further research and guidance are also needed on how to store HBM data in a database adhering to FAIR principles (Zare Jeddi et al., 2021b). (Meta)data should be easy to find for both humans and computers. Machine-readable metadata are essential for automatic discovery of datasets and services, so this is an essential component of the FAIRification process. In all the activities of data sharing, data protection plays an important role. If HBM data are aggregated, they can be considered anonymous and are not considered personal data under the European GDPR (EC, 2018; Eva et al., 2022). Single measurement HBM data must be handled in a stringent way to prevent the risk of re-identification of data subjects. GDPR requirements need to be strictly followed when processing such pseudonymised data. One solution would be to establish federated FAIR database systems (Collins et al., 2018) in which data contained in constituent databases can be used for further analyses by researchers or policy makers without holding or storing the data themselves on an in-house server. In addition, data transfer agreements need to be established for processing personal health data. This means that in many cases the study participants must have agreed at the beginning of the study in the consent form that data are shared with a pre-defined list of institutions. Data users need to demonstrate compliance with the original consent form and the research questions described therein. Therefore, the design of the study forms (data catalogues) at the beginning of the study is crucial to make the best possible use of the data later (Fiddicke et al. 2021). Furthermore, the availability and accessibility of HBM data repositories should be considered.

Harmonisation of HBM data will facilitate this process of developing HBM-GVs. The HBM-GVs need to be derived for a specific population and/or country and regularly updated to be meaningful on a national or regional level. HBM-GVs will also stimulate the harmonised use of effect biomarkers. Furthermore, it would be beneficial if spatial and temporal trends in chemical body burden could be correlated with time trend assessments of chemicals in occupational and environmental exposure (Buekers et al. 2018). Most of the available guidance values are derived from data showing external dose/health effect relationships. However, for persistence chemicals, information on body burdens may provide a more accurate understanding of their toxicity (Pohl et al. 2007).

There are new and evolving tools and advances to equip the HBM toolbox for a better use of HBM. Two approaches are mentioned in Box 1 as an example.

4.5. Strategic objective 5 – Obtain sustained funding and reinforcement by legislation

Without more regulatory backing, the growth of HBM as an imperative exposure assessment tool will be slow. Lack of regulatory requirement and enforcement is one of the key obstacles in using biomonitoring in an occupational context (Louro et al. 2019). Legislation needs to mandate HBM where appropriate (such as for blood lead under EU law for the protection of workers). In addition, it should provide guidance as to how HBM data can be added to substance dossiers

⁸ <https://www.oecd.org/env/ehs/risk-assessment/occupational-biomonitoring.htm>.

Box 1

New tools and advancement for HBM toolbox for 21st century.

Analysis of published texts/papers.

Moving toward advancements in the application of machine learning, a subset of artificial intelligence in risk assessment process such as AOP-helpFinder will support and facilitate the first time-consuming steps in literature search, classification and organising HBM data (Wittwehr et al. 2020). Automatic and reliable classification of large amounts of textual data could potentially be useful in future decision-making. In particular, big data can be used for identifying and prioritising problems, gathering and analysis of information, facilitating expert evaluation/judgement and cognitive models (Ali et al. 2021; Brandon et al. 2020; Ciallella and Zhu 2019).

Promoting a more data-based exposome approach.

Promoting a more data-based exposome approach can help in assessing the effects of exposures to chemical mixtures and their role in specific biological pathways, but experimental data is still needed to establish causal relationships. The causal relationships will enable policymakers to identify the chemicals that need to be prioritised to design targeted preventive measures to reduce health care and socio-economic costs (Bijlsma and Cohen 2016). At the same time, the knowledge about associations between exposure and health effects will help in identifying mitigation measures for people that are already exposed. Exposure to harmful substances, that are subject to the toxicologically relevant dose–response principle or that have a primarily sensitising effect, can be tracked by the physician by means of evaluating the patient’s medical history, anamnesis, and specific laboratory tests (if relevant) (EC, 2018; Eva et al., 2022). Regular physical exams can provide additional information about the onset and diagnosis of the disease. If restrictions on the use of medical data are followed, such data may also be used for scientific purposes. This approach of data collection from the disease point of view would complement the HBM approach (starting from the stressor) with cohorts covering the entire lifetime. This knowledge can bridge the ambitions of the CSS and the EU Green deal and drive the development of upcoming policies.

submitted by industry under chemicals regulations. Although REACH recognises the possibility of adding HBM data to the exposure assessment, detailed guidance, including on how to deal with ethical issues, is lacking (Louro et al. 2019). In addition, a statement on harmonisation of legislative requirements (as in 1S1A) would be helpful. The recognition of the importance of the toxicokinetic data and its inclusion in the data requirements for high production volume chemicals are also essential for growing the use of HBM. Fortunately, the value of HBM has been clearly emphasised recently by the EC in the CSS and the Zero Pollution Action Plan as an important approach to produce a long-term data collection as a HBM-baseline against which to measure progress (Bonzini et al. 2022; EC 2020b). This provides an insight into overall pollution levels and their impacts, as well as post-monitoring of policy implementation at national and EU levels (EC 2020b; 2021).

More emphasis on specifying exposures (both external and internal) in various legislative frameworks is expected to facilitate the increased use of HBM-based data. Internal exposures in humans (HBM data) can be directly compared to internal exposure in critical animal toxicity studies and in vitro toxicity studies with human cells. HBM is therefore key in implementing expected policy requirements to move away from animal testing and to invest in the HBM potential (and thus the proposed HBM 21st century toolbox), which is expected to reduce future problems.

HBM can be linked up to a ‘multiple silo exposure-based risk assessment’ for a more comprehensive picture of the overall exposure. While scientists need to continue producing more high-quality HBM data that will enable cross-regulatory work on aggregate and mixture exposure, the various regulatory processes need to integrate internal exposure based assessments (i.e. rather than only external exposures) and develop regulatory guidance for the use of exposure and effect HBM. Although the HBM approach is already well developed in some areas, other aspects are still lacking (e.g. EU-level guidance) and others require further development. Maturation to a full and sophisticated toolbox will be a process that needs substantial investments. Significant funding, such as in PARC, will be needed in this decade for both general methods (e.g. guidance for the generation and use of HBM in a risk assessment context) and specific requirements (e.g. effect biomarkers predicting increased risks for specific, high-concern health effects such as specific cancer types or neurodevelopmental effects).

In addition, development must respect ethical considerations, with due consideration of differences between countries. In some countries, HBM data can be used and reused for research purposes to investigate

health effects, while in other countries, reuse is not possible for purposes where no specific written consent has been provided. European harmonisation in this area will likely help to generate Europe-wide exposure data.

4.6. Strategic objective 6 – Extend target specific communication

The field of the communication between policy-makers, scientific activities and communities and societal stakeholders is complex and evolving; in this paper only some essential points relevant to HBM development are mentioned. Communication plans (between scientists / risk assessors and risk managers / policymakers and between science and society) should be developed during the study design and updated (and revised as necessary) within the life course of the study. The materials required and adapted for each audience – where public communication media can also have a place – and a timeframe for releasing each material should be part of such a communication plan (Exley et al. 2015).

There are several communication principles that professionals are advised to follow. Covello et al. 1992 and Exley et al. 2015 suggested including the following: accept and involve the concerned populations as a legitimate partner; plan carefully and evaluate outcomes; listen to the citizens’ specific concerns; be honest, frank, and open; coordinate and collaborate with other credible sources; meet the needs of the media; and speak clearly and with compassion. Communicating early with the workers involved in occupational studies can address their concerns, prevent rumours and misinformation, encourage participation and improve participation rates and compliance with the protocol and improve the overall quality of the investigation (Decker et al. 2013).

Conversely, early communication with key stakeholders is essential to achieve maximum efficacy of any policy developments. This last aspect is relevant when there is a particular interest in supporting new policy actions or to evaluate policies that are already in place (Sepai et al. 2008).

Overall, validated and trustful dissemination of results is key in empowering citizens to act and take informed decisions to reduce chemical exposure and promote the concepts of citizens in shaping collaborative knowledge between citizens’, experts, scientists, and policy makers on equal terms (Uhl et al. 2021).

In addition, information on exposure levels should, where possible, be accompanied by information on the health relevance of such

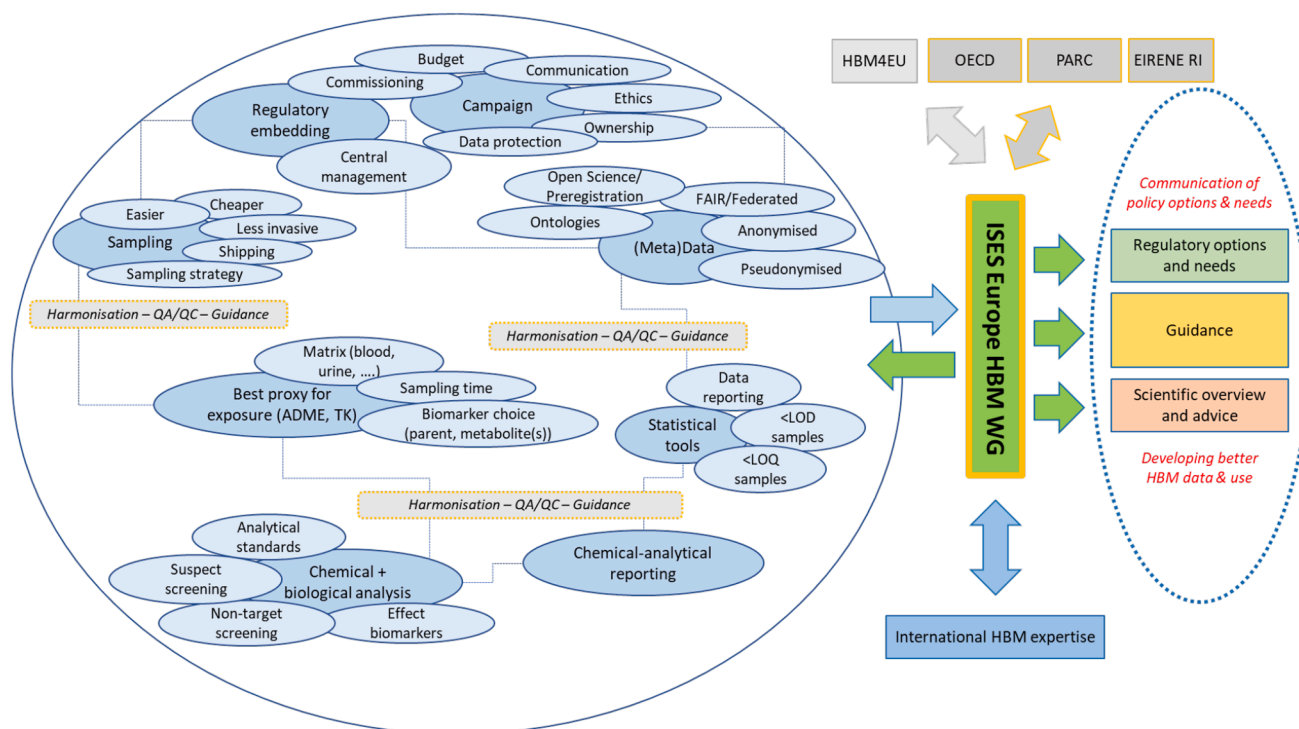


Fig. 3. Relevant interlinked human biomonitoring (HBM) objectives and concrete scientific, technology and regulatory interactions to increase scale, usefulness, relevance and uptake of HBM for integrated real-life measurement of exposure. Main topics (dark blue), sub-topics (light blue) and the pivotal role of harmonisation, quality control (QA) / quality assurance (QC) and guidance. HBM4EU: European Human Biomonitoring Initiative; OECD: Organisation for Economic Co-operation and Development; PARC: European Partnership for the Assessment of Risks from Chemicals; EIRENE RI: Environmental Exposure Assessment Research Infrastructure; ADME: absorption, distribution, metabolism, and excretion; TK: Toxicokinetic. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

exposures. As stated by Stokstad, “HBM makes pollution personal” (Stokstad 2004). Communication of HBM results to the public might enable individuals to take personal actions to reduce their exposure to potentially harmful chemicals (EC 2020b).

5. Conclusion and recommendations

A shared, comprehensive, and long-term vision for exposure science, including the role of HBM therein, is essential for the protection of human health (Bruinen de Bruin et al. 2021; Fantke et al. 2020). Six strategic objectives have been translated into a roadmap (Table 2) of the most prominent and concrete actions for which a tentative timeline and the most relevant and interested stakeholders have been defined. Low-cost approaches to achieve the outlined objectives include fostering scientific exchange, cross-cultural dialogue, interdisciplinary engagement, and international collaboration between regulators, industry, academia, and other societal stakeholders. This will help bridge the gap between regulators and researchers, as well as support the ‘science to policy’ interface and ensure that the most promising aspects of the use of HBM data are identified and applied, especially in informing individual and public health decisions. The European Joint Programme HBM4EU, which ended in June 2022, has contributed greatly to this cross-sectional dialogue and regulatory uptake of research data. Fortunately, this effort will be continued and further developed in the PARC initiative.⁹ This process includes applying the very recent results of HBM4EU and continuously developing them in new activities in PARC. The research data generated in PARC will be an integrator of different policy trends, particularly in relation to the Zero Pollution Action Plan

for a non-toxic environment and the chemicals strategy. Although the HBM4EU initiative and PARC are laying foundations for collaborative and harmonised approaches to HBM in Europe, it is necessary to put in place legislative and policy requirements to ensure an adoption of HBM programmes throughout the EU, and to improve standards and have access to the required facilities and resources, all this to enhance the protection of human and environmental health. Unlocking the full potential of HBM is an ongoing process that requires a concerted effort by all stakeholders in society. HBM experts involved in the ISES Europe HBM working group will continue to work on different actions outlined in the roadmap for the six strategic objectives (Table 2). The multidisciplinary nature of the ISES Europe HBM working group allows for connection between relevant fields and linking up various projects to find synergies as a driver for integrated work streams enabling researchers to answer new, exciting, interdisciplinary research questions and to investigate existing questions in novel ways. The ISES Europe HBM working group plans to help set up training and workshops at the European level as well as globally, using the ISES network. In the ISES Annual meetings, integrative initiatives can be communicated in symposia especially organised to advance knowledge, enable experts to work together in tackling the identified challenges. The same applies for current OECD guidance activities for Occupational Biomonitoring,¹⁰ which will help to facilitate the international regulatory uptake in using HBM for worker protection.

Using the analysis provided in this strategy paper, it is recommended that policymakers and regulators within Europe (in both EU member states and non-member states) as well as the European Parliament, funding organisations and (inter)national scientists, review and consider

⁹ https://ec.europa.eu/info/sites/default/files/research_and_innovation_funding/documents/ec_rtd_he-partnerships-chemical-risk-assessment.pdf.

¹⁰ <https://www.oecd.org/env/ehs/risk-assessment/occupational-biomonitoring.htm>.

Box 2

Needs for the 21st century HBM Toolbox.

- Recognition of human biomonitoring (HBM) as an approach to monitor progress in the protection of both the general and occupationally exposed populations by chemicals legislation.
- Development of:
 - harmonised guidance for 'FAIR by design' HBM studies, and implementation of Open Science Practices.
 - guidance on application, use and interpretation of HBM as a complementary regulatory chemical risk assessment approach.
 - guidance on HBM data governance (planning, monitoring, and enforcement).
 - health-based guidance values and population-based reference values.
 - guidance on communication of measured biomonitoring data to individuals, companies, organisations and stakeholders including its ethical aspects.
 - internationally harmonised terminologies on exposure science including HBM and updating of the terminology in a timely manner.
 - HBM specific ontologies.
 - structural networks of European institutions (possibly coordinated by the governance structure) to support HBM throughout EU, providing HBM training and guidance.
- Harmonisation of:
 - approaches on advanced effect biomarkers and/or statistical methods to deal with potential exposure to mixtures;
 - HBM data sharing by including governance structure that takes into account national and European ethical, legal and societal implications as well as confidentiality of data.
- Integration of:
 - exposure biomarkers data with effect biomarkers data and appropriate health and environmental data;
 - epidemiology in which HBM and external exposure assessment are included with non-animal testing results (in vitro, in silico) and computational modelling to generate more reliable information enhancing assessment of risks posed by exposure to single chemical and chemical mixtures.
- Increase research and innovation capacity to ensure continuation of HBM initiatives in Europe and sustained country-specific funding according to needs.
- Implementation of education in exposure science for the scientific community, as well as the public, emphasising the importance of biomonitoring, its strengths and limitations.
- Positioning HBM as a solution integrating exposure knowledge into companies' chemical innovation and management systems.

the identified strategic objectives and associated actions (Fig. 3). A vision for the 21st century HBM toolbox that may aid in developing these objectives is provided in Box 2. The presented strategic objectives are a starting point to drive future research in science and technology, as well as to encourage policymakers to develop and implement necessary revisions at regulatory level. This is supported by the obvious need for transitions to more safe and sustainable by design production and use of chemicals in this decade (Caldeira et al. 2022). A close dialogue between the researchers and policymakers will be required to ensure adequate and timely uptake of HBM data into policy. Such an implementation would give citizens better information regarding their actual exposures to chemicals. A structured network and sustained long-term funding are needed to develop the strategic objectives identified in this paper.

We expect that HBM will be of considerable added value to chemicals risk assessments, management, and policy challenges with HBM stakeholders engaging constructively and fully considering and implementing the outlined strategy. These strategies address the European Commission's ambition of a toxic-free environment and the United Nations' Sustainable Development Goals. Establishing HBM in all EU states as a legislative and/or mandatory requirement would enrich the HBM data, and consequently, create a lucrative market for developing HBM standards and assist for creating necessary toxicokinetic data using standardised protocols. HBM needs to be positioned as a solution integrating exposure knowledge into companies' chemical innovation and management systems.

CRedit authorship contribution statement

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

- Abecasis, L., Gamelas, C.A., Justino, A.R., Dionísio, I., Canha, N., Kertesz, Z., Almeida, S. M., 2022. Spatial distribution of air pollution, hotspots and sources in an urban-industrial area in the Lisbon Metropolitan Area, Portugal—a biomonitoring approach. *Int. J. Environ. Res. Public Health* 19, 1364.
- ACGIH. TLVs and BEIs. 2021.
- Ali, I., Dreij, K., Baker, S., Högberg, J., Korhonen, A., Stenius, U., 2021. Application of text mining in risk assessment of chemical mixtures: a case study of polycyclic aromatic hydrocarbons (PAHs). *Environ. Health Perspect.* 129, 067008.
- Andreasen, B., van Bavel, B., Fischer, S., Haglund, P., Rostkowski, P., Reid, M.J., Samanipour, S., Schlabach, M., Veenas, C., Dam, M., 2021. Maximizing output from non-target screening ed'eds. Nordic Council of Ministers.
- ANSES. ANSES COLLECTIVE EXPERT APPRAISAL: SUMMARY AND CONCLUSIONS - Regarding the "expert appraisal on recommending occupational exposure limits for chemical agents" - On the evaluation of biomarkers of exposure and recommendation for biological limit values and biological reference values for trichloroethylene (n° CAS 79-01-6). 2020.
- Apel, P., Angerer, J., Wilhelm, M., Kolossa-Gehring, M., 2017. 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* 220, 152–166.
- Apel, P., Rousselle, C., Lange, R., Sissoko, F., Kolossa-Gehring, M., Ougier, E., 2020. Human biomonitoring initiative (HBM4EU)-Strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment. *Int. J. Hyg. Environ. Health* 230, 113622.
- Arakawa, T., Aota, T., Iitani, K., Toma, K., Iwasaki, Y., Mitsubayashi, K., 2020. Skin ethanol gas measurement system with a biochemical gas sensor and gas concentrator toward monitoring of blood volatile compounds. *Talanta* 219, 121187.
- Aylward, L.L., Green, E., Porta, M., Toms, L.-M., Den Hond, E., Schulz, C., Gasull, M., Pumarega, J., Conrad, A., Kolossa-Gehring, M., 2014. Population variation in biomonitoring data for persistent organic pollutants (POPs): an examination of multiple population-based datasets for application to Australian pooled biomonitoring data. *Environ. Int.* 68, 127–138.
- Bader, M., Bäcker, S., Jäger, T., Webendörfer, S., Van Bortel, G., Van Mieghem, F., Van Weyenbergh, T., 2021. Preparedness as a key factor for human biomonitoring programs after chemical incidents. *J. Exposure Sci. Environ. Epidemiol.* 1–9.
- Bernhardt, E.S., Rosi, E.J., Gessner, M.O., 2017. Synthetic chemicals as agents of global change. *Front. Ecol. Environ.* 15, 84–90.
- Bijlsma, N., Cohen, M.M., 2016. Environmental chemical assessment in clinical practice: Unveiling the elephant in the room. *Int. J. Environ. Res. Public Health* 13, 181.
- Bjerregaard-Olesen, C., Bach, C.C., Long, M., Wielsøe, M., Bech, B.H., Henriksen, T.B., Olsen, J., Bonefeld-Jørgensen, E.C., 2019. Associations of fetal growth outcomes with measures of the combined xenoestrogenic activity of maternal serum perfluorinated alkyl acids in Danish pregnant women. *Environ. Health Perspect.* 127, 017006.
- Bonzini, M., Leso, V., Iavicoli, I., 2022. Towards a toxic-free environment: perspectives for chemical risk assessment approaches. *La Medicina del Lavoro* 113.
- Bopp, S.K., Barouki, R., Brack, W., Dalla Costa, S., Dorne, J.-L.-C., Drakvik, P.E., Faust, M., Karjalainen, T.K., Kephapopoulos, S., van Klaveren, J., 2018. Current EU research activities on combined exposure to multiple chemicals. *Environ. Int.* 120, 544–562.
- Bopp, S., Franco, A., Cusinato, A., Kephapopoulos, S., Ceridono, M. Information Platform for Chemical Monitoring IPCHEM 2020 – Update on the state of play of IPCHEM, European Commission, Ispra 2020;JRC123154.
- Brandon, N., Dionisio, K.L., Isaacs, K., Tornero-Velez, R., Kapraun, D., Setzer, R.W., Price, P.S., 2020. Simulating exposure-related behaviors using agent-based models embedded with needs-based artificial intelligence. *J. Exposure Sci. Environ. Epidemiol.* 30, 184–193.
- Bruinen de Bruin, Y., Franco, A., Ahrens, A., Morris, A., Verhagen, H., Kephapopoulos, S., Dulio, V., Slobodnik, J., Sijm, D.T., Vermeire, T., 2021. Enhancing the use of exposure science across EU chemical policies as part of the European Exposure Science Strategy 2020–2030. *J. Exposure Sci. Environ. Epidemiol.* 1–13.
- Buekers, J., David, M., Koppen, G., Bessems, J., Scheringer, M., Lebret, E., Sarigiannis, D., Kolossa-Gehring, M., Berglund, M., Schoeters, G., 2018. Development of policy relevant human biomonitoring indicators for chemical exposure in the European population. *Int. J. Environ. Res. Public Health* 15, 2085.
- Caballero-Casero, N., Belova, L., Vervliet, P., Antignac, J.-P., Castano, A., Debrauwer, L., Lopez, M.E., Huber, C., Klanova, J., Krauss, M., 2021a. Towards harmonized criteria in Quality Assurance and Quality Control of suspect and non-target LC-HRMS analytical workflows for screening of emerging contaminants in human biomonitoring. *TrAC, Trends Anal. Chem.* 116201.
- Caballero-Casero, N., Belova, L., Vervliet, P., Antignac, J.-P., Castano, A., Debrauwer, L., Lopez, M.E., Huber, C., Klánová, J., Krauss, M., 2021b. Towards harmonised criteria in quality assurance and quality control of suspect and non-target LC-HRMS analytical workflows for screening of emerging contaminants in human biomonitoring. *TrAC, Trends Anal. Chem.* 136, 116201.
- Calafat, A.M. The U.S. National Health and Nutrition Examination Survey and human exposure to environmental chemicals. *International Journal of Hygiene and Environmental Health* 2012;215:99-101.
- Caldeira, P., Farcial, R., Moretti, C., Mancini, L., Rauscher, H., Rasmussen, K., Riego Sintes, J., Sala, S. Safe and Sustainable by Design chemicals and materials Review of safety and sustainability dimensions, aspects, methods, indicators, and tools, EUR 30991. Publications Office of the European Union. Luxembourg; 2022.
- Carusi, A., Wittwehr, C., Whelan, M. Addressing evidence needs in chemicals policy and regulation. Publications Office of the European Union. Luxembourg; JRC126724; 2022.
- Casajus Valles, A., Marin Ferrer, M., Poljanšek, K., Clark, I., 2020. Science for Disaster Risk Management 2020: acting today, protecting tomorrow, EUR 30183 EN. Publications Office of the European Union, Luxembourg.
- Choi, J., Aarøe Morcer, T., Polcher, A., Knudsen, L.E., Joas, A., 2015. 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 Publications 12, 724E.
- Ciallella, H.L., Zhu, H., 2019. Advancing computational toxicology in the big data era by artificial intelligence: Data-driven and mechanism-driven modeling for chemical toxicity. *Chem. Res. Toxicol.* 32, 536–547.
- Connolly, A., Coggins, M.A., Koch, H.M., 2020. Human biomonitoring of glyphosate exposures: State-of-the-art and future research challenges. *Toxics* 8, 60.
- Conrad, A., Schröter-Kermani, C., Hoppe, H.-W., Rütther, M., Pieper, S., Kolossa-Gehring, M., 2017. Glyphosate in German adults—Time trend (2001 to 2015) of human exposure to a widely used herbicide. *Int. J. Hyg. Environ. Health* 220, 8–16.
- Covello, V.T., Allen, F.W., Covello, V.T., 1992. Seven cardinal rules of risk communication ed'eds. US Environmental Protection Agency.
- Csiszar, S.A., Ernststoff, A.S., Fantke, P., Jolliet, O., 2017. Stochastic modeling of near-field exposure to parabens in personal care products. *J. Exposure Sci. Environ. Epidemiol.* 27, 152–159.
- David, A., Chaker, J., Price, E.J., Bessonneau, V., Chetwynd, A.J., Vitale, C.M., Klánová, J., Walker, D.I., Antignac, J.-P., Barouki, R., 2021. Towards a comprehensive characterisation of the human internal chemical exposome: challenges and perspectives. *Environ. Int.* 156, 106630.
- De Smedt, T., De Cremer, K., Vlemingcx, C., Fierens, S., Mertens, B., Van Overmeire, I., Bader, M., De Paepe, P., Göen, T., Nemery, B., 2014. Acrylonitrile exposure in the general population following a major train accident in Belgium: a human biomonitoring study. *Toxicol. Lett.* 231, 344–351.
- Decker, J.A., DeBord, D.G., Bernard, B., Dotson, G.S., Halpin, J., Hines, C.J., Kiefer, M., Myers, K., Page, E., Schulte, P., 2013. Recommendations for biomonitoring of emergency responders: focus on occupational health investigations and occupational health research. *Mil. Med.* 178, 68–75.

- Dennis, K.K., Marder, E., Balshaw, D.M., Cui, Y., Lynes, M.A., Patti, G.J., Rappaport, S. M., Shaughnessy, D.T., Vrijheid, M., Barr, D.B., 2017. Biomonitoring in the era of the exposome. *Environ. Health Perspect.* 125, 502–510.
- Drum, S., Bradley, C., Moriarty, F., 2022. 'More of an art than a science'? The development, design and mechanics of the Delphi Technique. *Res. Soc. Administrative Pharmacy* 18, 2230–2236.
- Collins, S., Genova, F., Harrower, N., Hodson, S., Jones, S., Laaksonen, L., Mietchen, D., Petrauskaitė, R., Wittenburg, P., 2018. Turning FAIR into reality: Final report and action plan from the European Commission expert group on FAIR data.
- EC. Protection of your personal data; Processing operation: Information Platform for Chemical Monitoring (IPCHEM). in: DPR-EC-00213, ed. JRC; 2018. Available at: https://ipchem.jrc.ec.europa.eu/documents/Privacy_Statement_IPCHEM_General_Processing.pdf.
- EC. European Commission Proposal for a decision of the European Parliament and of the council on a General Union Environment Action Programme to 2030. 2020a;COM (2020) 652 final.
- EC. European Commission, Chemicals Strategy for Sustainability Towards a Toxic-Free Environment. Brussels; 2020b. Available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2020%3A667%3AFIN>.
- ECHA, E. Committee for Risk Assessment (RAC) Committee for Socio-economic Analysis (SEAC) Background document to the Opinion on the Annex XV dossier proposing restrictions on 4,4'-isopropylidenediphenol (Bisphenol A; BPA). ECHA/RAC/RES-O-0000001412-86-56/F; ECHA/SEAC/RES-O-0000001412-86-82/F; 2015.
- EEA, 2020. Healthy environment, healthy lives: how the environment influences health and well-being in Europe. In: 21/2019 E.R.N., ed. Publications Office of the European Union, Luxembourg.
- EEA, 2019. The European Environment State and Outlook 2020. Knowledge for transition to a sustainable Europe, Chapter 10, Chemical Pollution. the European environment agency. doi: 10.2800/96749. Available at: <https://www.eea.europa.eu/publications/soer-2020>.
- EFSA, Hardy, A., Benford, D., Halldorsson, T., Jeger, M.J., Knutsen, H.K., More, S., Naegeli, H., Noteborn, H., Ockleford, C. Guidance on the assessment of the biological relevance of data in scientific assessments. *Efsa Journal* 2017;15:e04970.
- EFSA, More, S., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T., Hougaard Bennekou, S., Koutsoumanis, K., Machera, K., Naegeli, H. Statement on the derivation of Health-Based Guidance Values (HBGV s) for regulated products that are also nutrients. *EFSA Journal* 2021;19:e06479.
- Eggen, M.L., Bos, P., Grievink, L., Nijhuis, N., Scheepers, P., van de Weerd, D., Wientjes, A., van der Woude, I. GGD-richtlijn medische milieukunde: Biomonitoring bij kleinschalige (chemische) incidenten. 2012.
- EU-OSHA. Feasibility study on the development of a computer-assisted telephone survey to estimate workers' exposure to carcinogens in the European Union. Publications Office of the European Union. Luxembourg; 2018.
- Eva, G., Liese, G., Stephanie, B., Petr, H., Leslie, M., Roel, V., Martine, V., Sergi, B., Mette, H., Sarah, J., Laura, R.M., 2022. Position paper on management of personal data in environment and health research in Europe. *Environ. Int.* 107334.
- Evers, D.C., Keane, S.E., Basu, N., Buck, D., 2016. Evaluating the effectiveness of the Minamata Convention on Mercury: principles and recommendations for next steps. *Sci. Total Environ.* 569, 888–903.
- Exley, K., Cano, N., Aerts, D., Biot, P., Casteleyn, L., Kolossa-Gehring, M., Schwedler, G., Castaño, A., Angerer, J., Koch, H.M., 2015. Communication in a Human biomonitoring study: Focus group work, public engagement and lessons learnt in 17 European countries. *Environ. Res.* 141, 31–41.
- Fantke, P., Von Goetz, N., Schlüter, U., Bessems, J., Connolly, A., Dudzina, T., Ahrens, A., Bridges, J., Coggins, M.A., Conrad, A., 2020. Building a European exposure science strategy. *J. Exposure Sci. Environ. Epidemiol.* 30, 917–924.
- Fiddicke, U., Pack, L.K., Tolonen, H., Sepai, O., López, M.E., Castaño, A., Schoeters, G., Kolossa-Gehring, M., 2021. A Phased Approach for preparation and organization of human biomonitoring studies. *Int. J. Hyg. Environ. Health* 232, 113684.
- Figueiredo, D.M., Krop, E.J., Duyzer, J., Gerritsen-Ebben, R.M., Gooijer, Y.M., Holterman, H.J., Huss, A., Jacobs, C.M., Kivits, C.M., Kruijne, R., 2021. Pesticide Exposure of residents living close to agricultural fields in The Netherlands: protocol for an observational study. *JMIR Res. Prot.* 10, e27883.
- Forschungsgemeinschaft, D. List of MAK and BAT Values 2017: Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. Report 53. Print ISBN:9783527343904 |Online ISBN:9783527812127 | DOI:10.1002/9783527812127. 2017 WILEY-VCH Verlag GmbH & Co. KGaA.
- Galea, K.S., Porras, S.P., Viegas, S., Bocca, B., Bousoumah, R., Duca, R.C., Godderis, L., Iavicoli, L., Janasik, B., Jones, K., 2021. HBM4EU chromates study-Reflection and lessons learnt from designing and undertaking a collaborative European biomonitoring study on occupational exposure to hexavalent chromium. *Int. J. Hyg. Environ. Health* 234, 113725.
- Ganzleben, C., Antignac, J.-P., Barouki, R., Castaño, A., Fiddicke, U., Klánová, J., Lebre, E., Olea, N., Sarigiannis, D., Schoeters, G.R., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. *Int. J. Hyg. Environ. Health* 220, 94–97.
- Gilles, L., Govarts, E., Rambaud, L., Vogel, N., Castano, A., López, M.E., Martin, L.R., Koppen, G., Remy, S., Vrijheid, M., 2021. HBM4EU combines and harmonises human biomonitoring data across the EU, building on existing capacity—The HBM4EU survey. *Int. J. Hyg. Environ. Health* 237, 113809.
- Göen, T., Eckert, E., Schäferhenrich, A., Hartwig, A., 2012. Allocation of reliable analytical procedures for human biomonitoring published by the DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area. *Int. J. Hyg. Environ. Health* 215, 233–237.
- Göen, T., Lermen, D., Hildebrand, J., Bartel-Steinbach, M., Weber, T., Kolossa-Gehring, M., 2018. Discovering time-trends of the German populations exposure to contaminants by analysis of human samples of the German Environmental Specimen Bank (ESB). *Toxicol. Lett.* 298, 194–200.
- Gundacker, C., Forsthuber, M., Szigeti, T., Kakucs, R., Mustieles, V., Fernandez, M.F., Bengtson, E., Vogel, U., Hougaard, K.S., Saber, A.T., 2021. Lead (Pb) and neurodevelopment: a review on exposure and biomarkers of effect (BDNF, HDL) and susceptibility. *Int. J. Hyg. Environ. Health* 238, 113855.
- Haines, D.A., Saravanabhavan, G., Werry, K., Khoury, C., 2017. An overview of human biomonitoring of environmental chemicals in the Canadian Health Measures Survey: 2007–2019. *Int. J. Hyg. Environ. Health* 220, 13–28.
- Hauser, J., Lenk, G., Ullah, S., Beck, O., Stemme, G.R., Roxhed, N., 2019. An autonomous microfluidic device for generating volume-defined dried plasma spots. *Anal. Chem.* 91, 7125–7130.
- Hays, S.M., Aylward, L.L., 2012. Interpreting human biomonitoring data in a public health risk context using Biomonitoring Equivalents. *Int. J. Hyg. Environ. Health* 215, 145–148.
- HBM4EU. Chemicals in a circular economy: Using human biomonitoring to understand potential new exposures. 2022. Available at: <https://www.hbm4eu.eu/wp-content/uploads/2022/07/ChemicalsCircularEconomy.pdf>.
- Heinemeyer, G., Connolly, A., von Goetz, N., Bessems, J., Bruinen de Bruin, Y., Coggins, M.A., Fantke, P., Galea, K.S., Gerding, J., Hader, J.D., 2021. Towards further harmonization of a glossary for exposure science—an ISES Europe statement. *J. Exposure Sci. Environ. Epidemiol.* 1–4.
- Heitland, P., Köster, H.D., 2006. Biomonitoring of 30 trace elements in urine of children and adults by ICP-MS. *Clin. Chim. Acta* 365, 310–318.
- Hendryx, M., Luo, J., 2018. Children's environmental chemical exposures in the USA, NHANES 2003–2012. *Environ. Sci. Pollut. Res.* 25, 5336–5343.
- Hernández-Mesa, M., Le Bizet, B., Dervilly, G., 2021. Metabolomics in chemical risk analysis – a review. *Anal. Chim. Acta* 1154, 338298.
- Joas, A., Schwedler, G., Choi, J., Kolossa-Gehring, M., 2017. Human biomonitoring: science and policy for a healthy future, April 17–19, 2016, Berlin, Germany. *Int. J. Hyg. Environ. Health* 220, 299–304.
- Jolliet, O., Huang, L., Hou, P., Fantke, P., 2021. High throughput risk and impact screening of chemicals in consumer products. *Risk Anal.* 41, 627–644.
- Karrer, C., Andreassen, M., von Goetz, N., Sonnet, F., Sakhi, A.K., Hungerbühler, K., Dirven, H., Husøy, T., 2020. The EuroMix human biomonitoring study: Source-to-dose modeling of cumulative and aggregate exposure for the bisphenols BPA, BPS, and BPF and comparison with measured urinary levels. *Environ. Int.* 136, 105397.
- Koch, H., Bader, M., Weiss, T., Koslitz, S., Schütze, A., Kafferlein, H.-U., Brüning, T., 2014. Metabolism and elimination of N-ethyl-2-pyrrolidone (NEP) in human males after oral dosage. *Arch. Toxicol.* 88, 893–899.
- Koch, H.M., Rütger, M., Schütze, A., Conrad, A., Pälme, C., Apel, P., Brüning, T., Kolossa-Gehring, M., 2017. 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. *Int. J. Hyg. Environ. Health* 220, 130–141.
- Kolossa-Gehring, M., Becker, K., Conrad, A., Schröter-Kermani, C., Schulz, C., Seiwert, M., 2012. Environmental surveys, specimen bank and health related environmental monitoring in Germany. *Int. J. Hyg. Environ. Health* 215, 120–126.
- Kolossa-Gehring, M., Fiddicke, U., Leng, G., Angerer, J., Wolz, B., 2017. New human biomonitoring methods for chemicals of concern—the German approach to enhance relevance. *Int. J. Hyg. Environ. Health* 220, 103–112.
- LaKind, J.S., Sobus, J.R., Goodman, M., Barr, D.B., Fürst, P., Albertini, R.J., Arbuckle, T. E., Schoeters, G., Tan, Y.-M., Teeguarden, J., 2014. A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument. *Environ. Int.* 73, 195–207.
- Lange, R., Apel, P., Rousselle, C., Charles, S., Sissoko, F., Kolossa-Gehring, M., Ougier, E., 2021. The European Human Biomonitoring Initiative (HBM4EU): Human biomonitoring guidance values for selected phthalates and a substitute plasticizer. *Int. J. Hyg. Environ. Health* 234, 113722.
- Lemke, N., Murawski, A., Lange, R., Weber, T., Apel, P., Dębiak, M., Koch, H.M., Kolossa-Gehring, M., 2021. Substitutes mimic the exposure behaviour of REACH regulated phthalates – a review of the German HBM system on the example of plasticizers. *Int. J. Hyg. Environ. Health* 236, 113780.
- Lenk, G., Sandkvist, S., Pohanka, A., Stemme, G., Beck, O., Roxhed, N., 2015. A disposable sampling device to collect volume-measured DBS directly from a fingerprick onto DBS paper. *Bioanalysis* 7, 2085–2094.
- Lermen, D., Gwinner, F., Bartel-Steinbach, M., Mueller, S.C., Habermann, J.K., Balwir, M.-B., Smits, E., Virgolino, A., Fiddicke, U., Berglund, M., 2020. Towards harmonized biobanking for biomonitoring: a comparison of human biomonitoring-related and clinical biorepositories. *Biopreserv. Biobanking* 18, 122–135.
- Liu, H., Dao, T.N.T., Koo, B., Jang, Y.O., Shin, Y., 2021. Trends and challenges of nanotechnology in self-test at home. *TrAC, Trends Anal. Chem.* 116438.
- Liu, J., Geng, Z., Fan, Z., Liu, J., Chen, H., 2019. Point-of-care testing based on smartphone: the current state-of-the-art (2017–2018). *Biosens. Bioelectron.* 132, 17–37.
- López, M.E., Göen, T., Mol, H., Nübler, S., Haji-Abbas-Zarrabi, K., Koch, H.M., Kasper-Sonnenberg, M., Dvorakova, D., Hajšlova, J., Antignac, J.-P., 2021. The European human biomonitoring platform-Design and implementation of a laboratory quality assurance/quality control (QA/QC) programme for selected priority chemicals. *Int. J. Hyg. Environ. Health* 234, 113740.
- Louro, H., Heinälä, M., Bessems, J., Buekers, J., Vermeire, T., Woutersen, M., Van Engelen, J., Borges, T., Rousselle, C., Ougier, E., 2019. Human biomonitoring in health risk assessment in Europe: current practices and recommendations for the future. *Int. J. Hyg. Environ. Health* 222, 727–737.

- Moos, R.K., Koch, H.M., Angerer, J., Apel, P., Schröter-Kermani, C., Brüning, T., Kolossa-Gehring, M., 2015. Parabens in 24 h urine samples of the German Environmental Specimen Bank from 1995 to 2012. *Int. J. Hyg. Environ. Health* 218, 666–674.
- Morton, J., Tan, E., Leese, E., Cocker, J., 2014. Determination of 61 elements in urine samples collected from a non-occupationally exposed UK adult population. *Toxicol. Lett.* 231, 179–193.
- Mustieles, V., Rodríguez-Carrillo, A., Vela-Soria, F., D’Cruz, S.C., David, A., Smagulova, F., Mundo-López, A., Olivás-Martínez, A., Reina-Pérez, I., Olea, N., 2022. BDNF as a potential mediator between childhood BPA exposure and behavioral function in adolescent boys from the INMA-Granada cohort. *Sci. Total Environ.* 803, 150014.
- Nübler, S., Esteban López, M., Castano, A., Mol, H., Haji-Abbas-Zarrabi, K., Schäfer, M., Müller, J., Hajslova, J., Dvorakova, D., Antignac, J.-P. Interlaboratory Comparison Investigations (ICI) and External Quality Assurance Schemes (EQUAS) for Human Biomonitoring of Perfluoroalkyl Substances (PFASs) in Serum as Part of the Quality Assurance Programme Under HBM4EU. 2022a.
- Nübler, S., Schäfer, M., Haji-Abbas-Zarrabi, K., Marković, S., Marković, K., López, M.E., Castaño, A., Mol, H., Koch, H.M., Antignac, J.-P., 2022b. Interlaboratory Comparison Investigations (ICIs) for human biomonitoring of chromium as part of the quality assurance programme under HBM4EU. *J. Trace Elem. Med. Biol.* 70, 126912.
- Oberacher, H., Sasse, M., Antignac, J.-P., Guitton, Y., Debrauwer, L., Jamin, E.L., Schulze, T., Krauss, M., Covaci, A., Caballero-Casero, N., 2020. A European proposal for quality control and quality assurance of tandem mass spectral libraries. *Environ. Sci. Eur.* 32, 1–19.
- Odabasi, M., Özgünerge Falay, E., Tuna, G., Altioik, H., Kara, M., Dumanoglu, Y., Bayram, A., Tolunay, D., Elbir, T., 2015. Biomonitoring the spatial and historical variations of persistent organic pollutants (POPs) in an industrial region. *Environ. Sci. Technol.* 49, 2105–2114.
- Oerlemans, A., van Dael, M., Vermeulen, R., Russel, F., Scheepers, P., 2018. Urine collection methods for non-toilet-trained children in biological monitoring studies: Validation of a disposable diaper for characterization of tebuconazole exposure. *Toxicol. Lett.* 298, 201–206.
- Ougier, E., Ganzleben, C., Lecoq, P., Bessems, J., David, M., Schoeters, G., Lange, R., Meslin, M., Uhl, M., Kolossa-Gehring, M., 2021. Chemical prioritisation strategy in the European Human Biomonitoring Initiative (HBM4EU)—Development and results. *Int. J. Hyg. Environ. Health* 236, 113778.
- Panorama. The Panorama Perspectives: Conversations on Planetary Health, Planetary Health 101, Information and Resources, Report I. 2017.
- Park, E., Lee, J., Lee, J., Lee, J., Lee, H.S., Shin, Y., Kim, J.-H., 2021. Method for the simultaneous analysis of 300 pesticide residues in hair by LC-MS/MS and GC-MS/MS, and its application to biomonitoring of agricultural workers. *Chemosphere* 277, 132015.
- Pohl, H.R., Abadin, H.G., Jones, D.E., De Rosa, C.T., 2007. The role of exposure versus body burden data in deriving health guidance values. *J. Toxicol. Environ. Health, Part B* 10, 401–415.
- Pourchet, M., Debrauwer, L., Klanova, J., Price, E.J., Covaci, A., Caballero-Casero, N., Oberacher, H., Lamoree, M., Damont, A., Fenaille, F., 2020. Suspect and non-targeted screening of chemicals of emerging concern for human biomonitoring, environmental health studies and support to risk assessment: From promises to challenges and harmonisation issues. *Environ. Int.* 139, 105545.
- Prüss-Ustün, A., Vickers, C., Haefliger, P., Bertollini, R., 2011. Knowns and unknowns on burden of disease due to chemicals: a systematic review. *Environ. Health* 10, 1–15.
- Rodríguez-Carrillo, A., Mustieles, V., d’Cruz, S.C., Legoff, L., Gil, F., Olmedo, P., Reina-Pérez, I., Mundo, A., Molina, M., Smagulova, F., 2022. Exploring the relationship between metal exposure, BDNF, and behavior in adolescent males. *Int. J. Hyg. Environ. Health* 239, 113877.
- Rodríguez-Carrillo, A., Rosenmai, A.K., Mustieles, V., Couderq, S., Fini, J.-B., Vela-Soria, F., Molina-Molina, J.M., Ferrando-Marco, P., Wielsøe, M., Long, M., 2021. Assessment of chemical mixtures using biomarkers of combined biological activity: a screening study in human placentas. *Reprod. Toxicol.* 100, 143–154.
- Rousselle, C., Meslin, M., Berman, T., Woutersen, M., Bil, W., Wildeman, J., Chaudhry, Q., 2022. Using human biomonitoring data to support risk assessment of cosmetic ingredients—a case study of benzophenone-3. *Toxics* 10, 96.
- Santonen, T., Porras, S.P., Bocca, B., Bousoumah, R., Duca, R.C., Galea, K.S., Godderis, L., Göen, T., Hardy, E., Iavicoli, I., 2022. HBM4EU chromatates study—Overall results and recommendations for the biomonitoring of occupational exposure to hexavalent chromium. *Environ. Res.* 204, 111984.
- Scheepers, P.T., Bos, P.M., Konings, J., Janssen, N.A., Grievink, L., 2011. Application of biological monitoring for exposure assessment following chemical incidents: a procedure for decision making. *J. Exposure Sci. Environ. Epidemiol.* 21, 247–261.
- Scheepers, P.T., Smolders, R., 2014. Identifying a role for human biomonitoring in incidents involving hazardous materials. Elsevier.
- Scheepers, P.T., van Brederode, N.E., Bos, P.M., Nijhuis, N.J., van de Weerd, R.H., van der Woude, I., Eggen, M.L., 2014. Human biological monitoring for exposure assessment in response to an incident involving hazardous materials. *Toxicol. Lett.* 231, 295–305.
- Schindler, B.K., Esteban, M., Koch, H.M., Castano, A., Koslitz, S., Cañas, A., Casteleyn, L., Kolossa-Gehring, M., Schwedler, G., Schoeters, G., 2014. The European COPHES/DEMOCOPHES project: towards transnational comparability and reliability of human biomonitoring results. *Int. J. Hyg. Environ. Health* 217, 653–661.
- Schmid-Tobies, M.L., Murawski, A., Rucic, E., Schwedler, G., Bury, D., Kasper-Sonnenberg, M., Koslitz, S., Koch, H.M., Brüning, T., Kolossa-Gehring, M., 2021. Alkyl pyrrolidone solvents N-methyl-2-pyrrolidone (NMP) and N-ethyl-2-pyrrolidone (NEP) in urine of children and adolescents in Germany—human biomonitoring results of the German Environmental Survey 2014–2017 (GerES V). *Environ. Int.* 146, 106221.
- Schol, S., Brack, W., Escher, B.I., Hackermüller, J., Liess, M., von Bergen, M., Wick, L.Y., Zenclussen, A.C., Altenburger, R., 2022. The EU chemicals strategy for sustainability: an opportunity to develop new approaches for hazard and risk assessment. *Arch. Toxicol.* 1–6.
- Schütze, A., Kolossa-Gehring, M., Apel, P., Brüning, T., Koch, H.M., 2014. Entering markets and bodies: increasing levels of the novel plasticizer Hexamoll® DINCH® in 24 h urine samples from the German Environmental Specimen Bank. *Int. J. Hyg. Environ. Health* 217, 421–426.
- Schütze, A., Lorber, M., Gawrych, K., Kolossa-Gehring, M., Apel, P., Brüning, T., Koch, H.M., 2015. Development of a multi-compartment pharmacokinetic model to characterize the exposure to Hexamoll® DINCH®. *Chemosphere* 128, 216–224.
- SCOEL. Methodology for Derivation of Occupational Exposure Limits of Chemical Agents. The General Decision-Making Framework of the Scientific Committee on Occupational Exposure Limits (SCOEL). 2017:.
- Seeger, C., Salzmann, L., 2020. After another decade: LC-MS/MS became routine in clinical diagnostics. *Clin. Biochem.* 82, 2–11.
- Sepai, O., Collier, C., Van Tongelen, B., Casteleyn, L., 2008. Human biomonitoring data interpretation and ethics; obstacles or surmountable challenges? *Environ. Health* 7, 1–5.
- Silva, V., Alaoui, A., Schlüssens, V., Vested, A., Graumans, M., Van Dael, M., Trevisan, M., Suci, N., Mol, H., Beekmann, K., 2021. Collection of human and environmental data on pesticide use in Europe and Argentina: field study protocol for the SPRINT project. *PLoS ONE* 16, e0259748.
- Simons, K., De Smedt, T., Stove, C., De Paep, P., Bader, M., Nemery, B., Vleminckx, C., De Cremer, K., Van Overmeire, I., Fierens, S., 2016. Short-term health effects in the general population following a major train accident with acrylonitrile in Belgium. *Environ. Res.* 148, 256–263.
- Socianu, S., Bopp, S.K., Govarts, E., Gilles, L., Buekers, J., Kolossa-Gehring, M., Backhaus, T., Franco, A., 2022. Chemical mixtures in the EU population: composition and potential risks. *Int. J. Environ. Res. Public Health* 19, 6121.
- Stokstad, E., 2004. Pollution gets personal. *Science* 304, 1892.
- Tolonen, H., Moore, S., Lermen, D., Virgolino, A., Knudsen, L.E., Andersson, A.-M., Rambaud, L., Ancona, C., Kolossa-Gehring, M., 2022. What is required to combine human biomonitoring and health surveys? *Int. J. Hyg. Environ. Health* 242, 113964.
- Travis, C.C., 2013. Use of biomarkers in assessing health and environmental impacts of chemical pollutants ed’eds. Springer Science & Business Media.
- Trushna, T., Dhiman, V., Aher, S.B., Raj, D., Ahirwar, R., Shubham, S., Nandi, S.S., Tiwari, R.R. Environmental monitoring and health assessment in an industrial town in central India: A cross-sectional study protocol. medRxiv 2022:.
- Uhl, M., Santos, R.R., Costa, J., Santos, O., Virgolino, A., Evans, D.S., Murray, C., Mulcahy, M., Ubong, D., Sepai, O., 2021. Chemical exposure: European citizens’ perspectives, trust, and concerns on human biomonitoring initiatives, information needs, and scientific results. *Int. J. Environ. Res. Public Health* 18, 1532.
- UNEP. Minamata Convention on Mercury. 2013. Available at: <https://www.unep.org/r/esources/report/minamata-convention-mercury>.
- UNEP. Draft Guidance on the Global Monitoring Plan for Persistent Organic Pollutants, United Nations Environment Programme (UNEP). United Nations Environment Programme (UNEP), Geneva, Switzerland 2019. Available at: <https://www.unep.org/explore-topics/chemicals-waste/what-we-do/persistent-organic-pollutants/global-monitoring>.
- van den Brand, A.D., Bajard, L., Steffensen, I.-L., Brantsæter, A.L., Dirven, H.A., Louise, J., Peijnenburg, A., Ndaw, S., Mantovani, A., De Santis, B., 2022. Providing biological plausibility for exposure-health relationships for the mycotoxins deoxynivalenol (DON) and fumonisin B1 (FB1) in humans using the AOP framework. *Toxins* 14, 279.
- Van Nieuwenhuyse, A., Fierens, S., De Smedt, T., De Cremer, K., Vleminckx, C., Mertens, B., Van Overmeire, I., Bader, M., De Paep, P., Göen, T., 2014. Acrylonitrile exposure assessment in the emergency responders of a major train accident in Belgium: a human biomonitoring study. *Toxicol. Lett.* 231, 352–359.
- Varshavsky, J.R., Morello-Frosch, R., Harwani, S., Snider, M., Petropoulos, S.-S.-E., Park, J.-S., Petreas, M., Reynolds, P., Nguyen, T., Quach, T., 2020. a pilot biomonitoring study of cumulative phthalates exposure among Vietnamese american nail salon workers. *Int. J. Environ. Res. Public Health* 17, 325.
- Verhagen, H., Merten, C., Chiusolo, A., Arcella, D., Binaglia, M. Human Biomonitoring Requires Validation. *The Analytical Scientist* 2018.
- Verhagen, H., van Loveren, H., 2016. Status of nutrition and health claims in Europe by mid 2015. *Trends Food Sci. Technol.* 56, 39–45.
- Viegas, S., Zare Jeddi, M., B Hopf, N., Bessems, J., Palmen, N., S Galea, K., Jones, K., Kujath, P., Duca, R.-C., Verhagen, H., 2020. Biomonitoring as an underused exposure assessment tool in occupational safety and health context—Challenges and way forward. *International Journal of Environmental Research and Public Health* 17: 5884.
- Viegas, S., Martins, C., Bocca, B., Bousoumah, R., Duca, R.C., Galea, K.S., Godderis, L., Iavicoli, I., Janasik, B., Jones, K., Leese, E., 2022. HBM4EU Chromates Study: Determinants of Exposure to Hexavalent Chromium in Plating, Welding and Other Occupational Settings. *Int. J. Environ. Res. Public Health* 19 (6), 3683.
- Vinggaard, A.M., Bonfeld-Jørgensen, E.C., Jensen, T.K., Fernandez, M.F., Rosenmai, A. K., Taxvig, C., Rodríguez-Carrillo, A., Wielsøe, M., Long, M., Olea, N., 2021. Receptor-based in vitro activities to assess human exposure to chemical mixtures and related health impacts. *Environ. Int.* 146, 106191.
- Vorkamp, K., Castaño, A., Antignac, J.-P., Boada, L.D., Cequier, E., Covaci, A., López, M. E., Haug, L.S., Kasper-Sonnenberg, M., Koch, H.M., 2021. Biomarkers, matrices and analytical methods targeting human exposure to chemicals selected for a European human biomonitoring initiative. *Environ. Int.* 146, 106082.
- Vrijheid, M., 2014. The exposome: a new paradigm to study the impact of environment on health. *Thorax* 69, 876–878.

- Wild, C.P., 2012. The exposome: from concept to utility. *Int. J. Epidemiol.* 41, 24–32.
- Wilhelm, M., 2021. Human biomonitoring: its importance in toxicological regulation. *Regulatory Toxicology* 375–393.
- Wilhelm, M., Eberwein, G., Hölzer, J., Begerow, J., Sugiri, D., Gladtko, D., Ranft, U., 2005. Human biomonitoring of cadmium and lead exposure of child–mother pairs from Germany living in the vicinity of industrial sources (hot spot study NRW). *J. Trace Elem. Med Biol.* 19, 83–90.
- Wittwehr, C., Blomstedt, P., Gosling, J.P., Peltola, T., Raffael, B., Richarz, A.-N., Sienkiewicz, M., Whaley, P., Worth, A., Whelan, M., 2020. Artificial Intelligence for chemical risk assessment. *Comput. Toxicol.* 13, 100114.
- Zare Jeddi, M., Hopf, N.B., Viegas, S., Price, A.B., Paini, A., van Thriel, C., Benfenati, E., Ndaw, S., Bessems, J., Behnisch, P.A. Towards a systematic use of effect biomarkers in population and occupational biomonitoring. *Environment International* 2021a; 146:106257.
- Zare Jeddi, M., Virgolino, A., Fantke, P., Hopf, N.B., Galea, K.S., Remy, S., Viegas, S., Mustieles, V., Fernandez, M.F., von Goetz, N., 2021b. A human biomonitoring (HBM) Global Registry Framework: Further advancement of HBM research following the FAIR principles. *Int. J. Hyg. Environ. Health* 238, 113826.

Further reading

- EC. European Commission, Progress report on the assessment and management of combined exposures to multiple chemicals (chemical mixtures) and associated risks. in: Brussels, ed. SWD(2020) 250 final; 2020c.