



Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

A human biomonitoring (HBM) Global Registry Framework: Further advancement of HBM research following the FAIR principles

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ARTICLE INFO

Keywords:

Human biomonitoring
Regulatory risk assessment

ABSTRACT

Data generated by the rapidly evolving human biomonitoring (HBM) programmes are providing invaluable opportunities to support and advance regulatory risk assessment and management of chemicals in occupational and environmental health domains. However, heterogeneity across studies, in terms of design, terminology,

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<https://doi.org/10.1016/j.ijheh.2021.113826>

Received 7 January 2021; Received in revised form 30 July 2021; Accepted 6 August 2021

Available online 25 September 2021

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Data value chain
Data governance
Harmonisation
Registry

biomarker nomenclature, and data formats, limits our capacity to compare and integrate data sets retrospectively (reuse). Registration of HBM studies is common for clinical trials; however, the study designs and resulting data collections cannot be traced easily. We argue that an HBM Global Registry Framework (HBM GRF) could be the solution to several of challenges hampering the (re)use of HBM (meta)data. The aim is to develop a global, host-independent HBM registry framework based on the use of harmonised open-access protocol templates from designing, undertaking of an HBM study to the use and possible reuse of the resulting HBM (meta)data. This framework should apply FAIR (Findable, Accessible, Interoperable and Reusable) principles as a core data management strategy to enable the (re)use of HBM (meta)data to its full potential through the data value chain. Moreover, we believe that implementation of FAIR principles is a fundamental enabler for digital transformation within environmental health.

The HBM GRF would encompass internationally harmonised and agreed open access templates for HBM study protocols, structured web-based functionalities to deposit, find, and access harmonised protocols of HBM studies. Registration of HBM studies using the HBM GRF is anticipated to increase FAIRness of the resulting (meta)data. It is also considered that harmonisation of existing data sets could be performed retrospectively. As a consequence, data wrangling activities to make data ready for analysis will be minimised. In addition, this framework would enable the HBM (inter)national community to trace new HBM studies already in the planning phase and their results once finalised. The HBM GRF could also serve as a platform enhancing communication between scientists, risk assessors, and risk managers/policy makers. The planned European Partnership for the Assessment of Risk from Chemicals (PARC) work along these lines, based on the experience obtained in previous joint European initiatives. Therefore, PARC could very well bring a first demonstration of first essential functionalities within the development of the HBM GRF.

1. Introduction

Human biomonitoring (HBM) is defined as the method for assessing human exposure to chemicals or their effects by measuring chemicals, their metabolites or reaction products (and/or their effects biomarkers) in human specimens (WHO, 2015a). HBM is a valuable tool to support the environment and health policy-making process because it provides quantitative actual distribution of exposures in a population. Environmental pollutants can then be mapped for emerging pollutants, as well as data regarding their resulting health effects, and/or population susceptibility.

HBM has a long history serving health surveys with well-known national programs such as the German Environmental Surveys (GerES), the US National Health and Nutrition Examination Survey (NHANES), the Canadian Health Measures Survey (CHMS), and the Korean National Environmental Health Survey (KoNEHS). (Becker et al., 2003; Choi et al., 2017; Cox, 1992; Haines et al., 2017). However, only recently HBM has become more widely used in risk assessment and management frameworks. HBM is considered the “gold standard” for assessing people’s exposure to environmental chemical agents (Sexton et al., 2004). The increased availability of exposure and effect biomarkers is helping HBM to become an even more valuable tool to investigate associations between internal exposures and health outcomes. This approach presents well-known complementary information on and advantages over cell-based and experimental animal studies (Burns et al., 2019; Mustieles and Fernández, 2020). In the current article, we define HBM studies as “all observational studies that apply HBM as a tool to collect data” (WHO, 2015a). These might include studies where the main scope is a health survey, health surveillance, as well as biomonitoring programmes in both general and occupational populations.

HBM research in combination with results from human and/or animal toxicological studies, for example in the form of hypothesized Adverse Outcome Pathway (AOP) networks or the use of biomonitoring equivalents, can provide interpretation tools for human hazard and risk assessment (Baken et al., 2019; Faure et al., 2020; Mustieles et al., 2020; St-Amand et al., 2014; Zare Jeddi et al., 2020). Moreover, HBM provides a holistic perspective, enabling an integrative measurement of combined exposures from all routes (ingestion, inhalation, and dermal uptake) and all environmental sources (air, water, soil, dust, food), the results of toxicokinetic processes and individual differences in combination with signs of (early) responses with effect biomarkers (Mustieles et al., 2020; Zare Jeddi et al., 2020). If combined with health surveys and cohorts,

HBM (meta)data can also provide opportunities to investigate the relationship between internal exposure and health effects, promote risk-reduction measures, monitor exposure trends, and evaluate the effectiveness of implemented national and global policies (e.g., (Eykelbosh et al., 2018; Romano et al., 2020)). Overall, the use of HBM (meta) data increases the value of exposure information in risk assessment and management context (Wilhelm, 2020).

Given the multiple benefits of using HBM at national and global levels, the use of HBM is a recognized priority in chemical safety. HBM can increase the robustness of regulatory long-term decisions for marketed chemicals, and in particular, the increased importance of mixture risk assessment of chemicals and grouping approaches, as echoed at national, supranational, and intergovernmental level such as UN, WHO, OECD and EU (EC, 2020a; OECD, 2018; SAICM, 2013; WHO, 2015b). To serve this role, methodologies should be harmonised and HBM (meta) data should be easily findable, accessible, interoperable, secure, shared and reused by default (EC, 2020a).

Regrettably, HBM has received little regulatory application to date which is partly due to a lack of sufficient, reliable, quality-assured, and well-structured (meta)data. HBM is an important and useful tool, yet quite complicated in terms of its design, application, and interpretation. The existing legislative frameworks on chemicals do not currently provide clear harmonised guidance for developing a comprehensive and integrated assessment of (combined) internal exposures to chemicals from different sources and routes. Any available guidance has evolved separately in different regulatory frameworks (Bopp et al., 2018; Drakvik et al., 2020; Evans et al., 2016; Fantke et al., 2020a; Louro et al., 2019).

This article aims to describe the challenges and needs to drastically increase the use and possible reuse of HBM data. It describes requirements to make HBM study information (metadata as wells as measurement data) more FAIR (Findable, Accessible, Interoperable, and Reusable) (Wilkinson et al., 2016). In this article, these four principles are grouped in the coupled cornerstones of findability/accessibility and interoperability/reusability. Findability/accessibility is a system to store HBM (meta)data. Interoperability/reusability is how the (meta)data themselves should be expressed (and stored in HBM data repositories). For both cornerstones, harmonisation is critical. Harmonisation of storage systems for HBM (meta)data helps to find and better access HBM (meta)data (better findability and quicker access) where harmonisation of the HBM (meta)data generation itself enables reuse and interoperability. This article attempts to scrutinise whether a framework for harmonised, web-based HBM study registries, as so called HBM Global

Registry Framework (HBM GRF), could accommodate existing needs.

2. Harmonisation and FAIRification of HBM studies, needs, challenges and opportunities

Systematic harmonisation and FAIRification of HBM (meta)data production through the data value chain can improve all aspects of HBM. First, results from several HBM studies could be compared easier to delineate e.g., exposure patterns. This refers to challenges for instance regarding differences in the definition of age groups (teenagers e.g., 10–18 years old or 13–19 years old), lifestyle parameters measured, biological matrices used, and of sampling methods, storage conditions as well as analytical procedures (Ågerstrand et al., 2018; Bocato et al., 2019; Joas et al., 2012). Moreover, the metadata including information about the studies are not always readily available. Even when such data are accessible, data are often scattered and/or incomplete thereby undermining the proper understanding, interpretation, and final use of the HBM data collected to support chemical risk assessment. Second, it could facilitate performing combined (meta)analyses of data from different HBM studies, aiming for increased statistical power, to find e.g., correlations between exposure biomarkers and effect biomarkers to support exposure to outcome assessments (Boyden and Walnicki, 2021). The use of systematic reviews and (meta)analyses is gaining acceptance in exposure science to transparently synthesize and evaluate a body of scientific evidence to answer research or policy questions (Hubal, 2019; Wikoff et al., 2020; Wolffe et al., 2019). Nevertheless, handling and comparing heterogeneous data generated across multiple scientific disciplines is challenging. This is especially true when a high degree of variability across studies is expected in terms of study aims and designs, population characteristics, exposure assessment procedures, data analysis and reporting (Burns et al., 2019; Goodman et al., 2019; Hubal, 2019). Third, it would also enable data sharing and data integration which are of particular relevance for decision making in environmental and occupational health policies (Kromerová and Bencko, 2019; Louro et al., 2019). It is clear that there is an increasing use purpose for HBM data in compliance to the FAIR (Findable, Accessible, Interoperable, Reusable) data principles.

Currently, the abovementioned opportunities are unfortunately hindered by problems with data comparability due to lack of harmonisation. Based on a survey regarding national practices in risk assessment and risk assessors' views on HBM use in Europe (Louro et al., 2019), the European Human Biomonitoring Initiative HBM4EU¹ recognized that regulatory practices related to HBM still vary across different countries. HBM data should be collected using harmonised study protocols to a significant extent to facilitate data interpretation (Fiddicke et al., 2021). In addition, the need for harmonised coding of substances and metabolites measured and the statistical analysis such as aggregation of individual data to percentiles of a distribution of HBM levels has received particular attention under recent HBM research projects. Harmonised study designs and structured study registries could counter these problems.

The HBM community would profit from global sharing of information of existing, new, and planned HBM studies. The authors envisage that any registry system should be globally useable and legislative framework independent, be it national legislation such as in the USA, Canada, Japan, Korea, Germany, France, or regional legislations in the EU or a framework like the OECD. Given that, we hereby present the concept for a web-based system based on modern IT-technology and independent of any website host requirements as part of an overarching HBM GRF.

The HBM GRF would facilitate and promote prospective (a priori) harmonisation of HBM study designs and thus the resulting HBM data would follow the FAIR data principals. As a consequence, data

wrangling activities to make data ready for analysis will be minimised. Therefore, prospective (a priori) harmonisation of foreseen or already planned HBM studies is recommended rather than focusing on retrospective (post-hoc) harmonisation. The prospective (a priori) harmonisation leads to a higher degree of data homogeneity in an effective way. It should be noted that aligning in terms of harmonisation is essential but is different from standardization. HBM is not science in the sense of duplicating experiments based on standardised methods. It is a tool for field studies where some parts obviously could be standardised in the future, such as analytical chemical methods while the process of defining study population and the sampling process can be harmonised but not standardised. The HBM GRF should facilitate a step-by-step harmonisation process but not necessarily standardization using a scientifically and technically sound and viable system. Fig. 1 provides a general overview of the HBM GRF concepts and potentials.

3. Existing initiatives towards verification of HBM data

Comparability and combination of results and interoperability of data are often difficult due to a lack of harmonisation, even when different HBM studies have investigated similar research questions (Joas et al., 2012; Lermen et al., 2020). In the last 10–15 years, significant efforts have been made towards harmonising HBM studies prospectively such as in the European Commission funded projects COPHES, DEMO-COPHES and HBM4EU (Ganzleben et al., 2017) as well as the European Cooperation in Science and Technology (COST) Action DiMoPEx (DiMoPEx, 2015). Codebooks were developed for both the HBM exposure data as well as accompanying variables important for interpretation (age, sex, gender, NUTS [Nomenclature of Territorial Units for Statistics] codes, season of sampling, etc.) in a harmonised structure and format. Statistical analysis protocols scripted in R were used to extract comparable and machine-readable summary statistics or “aggregated data” that can be compared across data collections of the HBM4EU aligned studies and also across existing studies that share similarities in design. This has allowed the development of an interactive dashboard to display the data of the HBM4EU project (<https://www.hbm4eu.eu/eu-hbm-dashboard/>). Work on occupational exposure under the HBM4EU project is also directed to harmonise methodologies and data collection by developing standard operating procedures (SOPs), that can be used in multiple countries and analysed in an integrative approach (Santonen et al., 2019).

Registries containing some (meta)data on HBM studies or studies containing an HBM part exist such as the WHO International Clinical Trials Registry Platform², the US Clinical Trials database³. In addition, registries exist in which planned work is registered before the execution of the study. PROSPERO⁴ is an example of such an international database of prospectively registered systematic reviews with a health-related outcome. Others such as the EU Clinical Trials Register⁵, already contains human intervention studies.

Moreover, there are several initiatives as listed in Table 1 regarding data collections containing mainly environmental monitoring and external exposure monitoring data. The Information Platform for Chemical Monitoring (IPCHEM⁶), the NORMAN network⁷, the Elixir community (ELIXIR, 2017), the BBMRI-ERIC⁸ and the Hazchem@work for occupational exposure data have been created to tackle the lack of harmonised information (EU, 2016). Most of these portals have their own challenges, some of which are highlighted in Table 1. In addition,

² <https://www.who.int/clinical-trials-registry-platform>.

³ <https://clinicaltrials.gov/>.

⁴ <https://www.crd.york.ac.uk/prosperso/>.

⁵ <https://www.clinicaltrialsregister.eu/>.

⁶ <https://ipchem.jrc.ec.europa.eu/>.

⁷ <https://www.norman-network.net>.

⁸ <https://www.bbMRI-eric.eu>.

¹ <https://www.hbm4eu.eu/>.

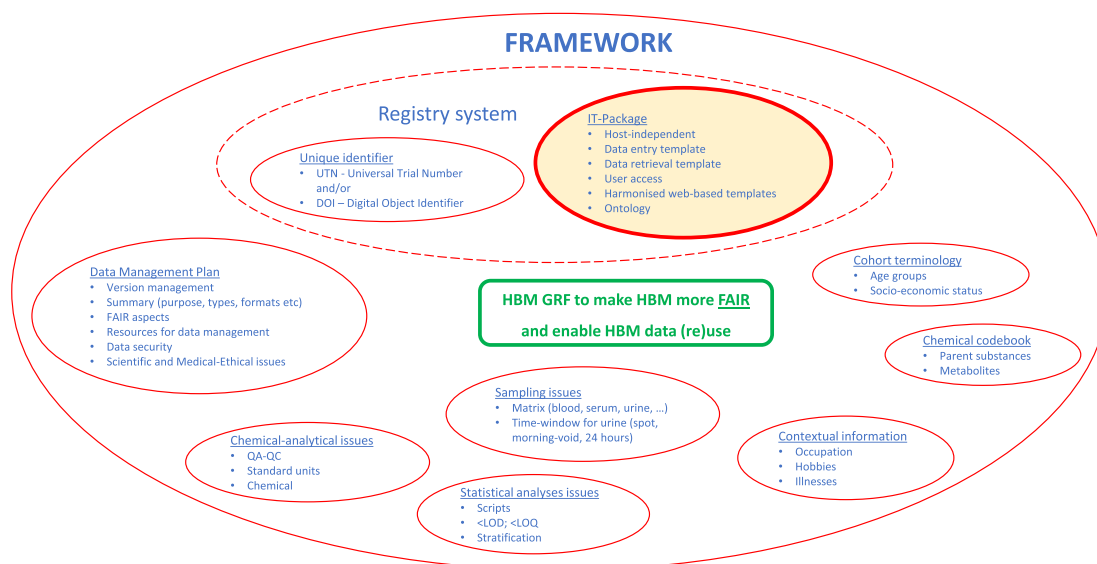


Fig. 1. HBM Global Registry Framework (HBM GRF).

there are many health surveys and HBM studies at national, regional and/or international levels which are not typically integrated into these platforms despite their potential for enhancing informed decision making in environment, public and occupational health.

IPCHEM was established by the European Commission (EC) to support a coordinated approach for collecting, storing, sharing, and assessing data on the occurrence of chemicals and chemical mixtures in humans and the environment. It is structured in four thematic modules: ‘environmental monitoring’, ‘human biomonitoring’, ‘food and feed’ and ‘products and indoor air.’ IPCHEM is designed to specifically provide access to chemical monitoring data and underlying (meta)data currently not readily accessible, making them findable and accessible and to a certain extent interoperable and reusable (Comero et al., 2020; Knetsch and Ruether, 2016; Wilkinson et al., 2016). IPCHEM is intended to assist scientists and risk managers/policy makers to discover and access chemical monitoring data on existing, new, emerging and less-investigated chemicals, covering a wide range of matrices and media (Comero et al., 2020). It is however not intended to register study designs ex ante. IPCHEM is the European Commission’s reference access point for searching, accessing and retrieving chemical occurrence data collected and managed in Europe. IPCHEM is a distributed infrastructure. Data owners/data providers can decide on the level of detail to which the different IPCHEM user groups can access their data. As shown in Fig. 2, the volume of HBM datasets uploaded to the IPCHEM platform has increased by over 400% in the last two years. It includes now more than 100 (meta)data for HBM data collections gathered under the HBM4EU project (EC, 2020b).

The platform already includes particularly useful (meta)data, containing crucial information concerning study design, population size and age, sampling, analytics, and substances/biomarkers monitored, etc., amongst others. However, it is not able (yet) to quickly upload new data from data collections as the data collections themselves and the preceding study designs are lacking sufficient harmonisation. This limits easy and wider reuse and meta-analyses. There is for example currently not yet an optimal use of ontologies to facilitate linking different biomarker metabolites measured in different data collections but originating from the same parent substance to that parent substance.

4. Remaining challenges to be addressed by development of the HBM registry system under the HBM GRF

The current absence of harmonised study design templates makes

searching HBM studies and their (meta)data cumbersome, and retrospective information validation processes time-consuming and often subject to errors. Data and metadata data harmonisation, at least from a retrospective point of view, requires access to a lot of information on each study including objectives, measured biomarkers and biological matrices, sampling methods, protocols, questionnaires, etc., which needs to be validated. Moreover, retrospective harmonisation processes are, to some extent, subjective processes and can thus present an inherent risk of biased (meta)data in a ‘post-hoc harmonised’ repository.

In addition, researchers typically provide the data, including the (meta)data, quite some time after study completion. This can be problematic as other researchers and regulatory risk assessors, providing scientific advice to risk managers/policy makers, are often looking for fast and user-friendly access to information as well as protocols regarding planned and ongoing studies. Early-on registration of the plan for an HBM study, even in draft form, would enable other researchers to prepare for (re)using the new data once available.

Another main issue is the lack of harmonisation in reporting of the chemical compounds investigated in HBM studies. Hundreds of non-endogenous compounds are found in HBM samples, some of them being known chemicals with a Chemical Abstract Services Registry Number (CAS RN), but many are unknown. Even known metabolites do not have CAS RNs as usually only the parent substance has been registered. Beyond this, even the use of a CAS RN for known compounds can be ambiguous (Williams and Yerin, 2013). Therefore, it is essential to harmonise how chemical compounds (parents and metabolites) are identified and findable (fulfil the FAIR criteria) in HBM studies. The InChI/InChIKey framework of IUPAC (IUPAC, 2018) is, to our knowledge, the only system for unique identification of chemical substances with a known structure (including stereochemistry). Ontologies based on fragmentation in molecular structure might help in linking metabolites to parent compounds.

Although several environmental exposure studies have been registered in existing platforms (e.g., Study number NCT03440307 in the US ClinicalTrials database⁹), these platforms currently lack the design to enhance and optimize the dialogue between the scientific disciplines of epidemiology, HBM, toxicology and risk assessment. Most of these platforms merely make HBM-related studies findable. The harmonisation of HBM would also be useful for prospective cohorts. Indeed,

⁹ <https://www.bbmri-eric.eu>.

Table 1

Examples of existing platforms related to chemical monitoring data.

| Platform | Coverage | Funding | Main aim(s) | Limitation(s) |
|--|---------------------------------|---|---|---|
| IPCHEM (Information Platform for Chemical Monitoring) https://ipchem.jrc.ec.europa.eu/ | Europe | EC | <ul style="list-style-type: none"> Assisting policy makers and scientists to discover and access chemical monitoring data on chemicals covering a range of matrices and media (environment, food and feed, human biomonitoring, indoor air, and products) Hosting data currently not readily accessible (e.g., outcomes of research projects, off-line stored monitoring data) Providing chemical monitoring data and information of defined quality in terms of spatial, temporal, methodological and metrological traceability | <ul style="list-style-type: none"> Differences in data quality Differences in representativeness of populations^a Discrepancies in reporting formats (harmonised for the essential fields but leaving room for data collection specific fields) Only occurrence data from targeted, quantitative analyses |
| Canada Open Government, 2020 Canadian Health Measures Survey (CHMS) Human Biomonitoring Data for Environmental Chemicals Health Canada, Ottawa, ON (2020) http://open.canada.ca/data/en/dataset/8cc88229-8132-4ccd-a3dd-b456579158c6 | Canada | Canada government | <ul style="list-style-type: none"> Present HBM results of the 5 cycles of the Canadian Health Measures Survey (2007–2017). Tabulated CSV-downloadable results | <ul style="list-style-type: none"> Metadata not directly available in the app |
| NORMAN Association https://www.norman-network.com/ | Europe, North America, and Asia | Not for profit network; self-funded by its members | <ul style="list-style-type: none"> Enhancing the exchange of information and collection of data on emerging environmental substances Encouraging the validation and harmonisation of common measurement methods and monitoring tools Ensuring that knowledge on emerging pollutants is maintained and developed by stimulating coordinated, interdisciplinary projects on problem-oriented research and knowledge transfer to address identified needs | <ul style="list-style-type: none"> Focus only on environment Absence of information regarding human data |
| BBMRI-ERIC (Biobanking and Biomolecular Resources Research Infrastructure) https://www.bbmri-eric.eu/ | Europe | European Research Infrastructure Consortium funded by its members | <ul style="list-style-type: none"> Collecting and making available information about biobanks throughout Europe that are willing to share their data and/or samples, and to collaborate with other research groups | <ul style="list-style-type: none"> Only puts in contact people who search information on biobanks Sample query processing missing |
| Elixir community https://elixir-europe.org/ | Europe | National funding in each country (hubs) | <ul style="list-style-type: none"> Managing and safeguarding the increasing volume of data being generated by publicly funded life sciences research | <ul style="list-style-type: none"> Currently mostly focussed on human endogenous compounds (DNA, proteins, small molecules) |
| HazChem@work https://www.certifico.com/sicurezza-lavoro/documenti-sicurezza/68-documenti-ue/3859-hazchem-work-project-to-estimate-occupational-exposure-chemicals | Europe | European Commission (DG Employment) | <ul style="list-style-type: none"> Create a database and developing a model to estimate the occupational exposure for a list of hazardous chemicals in EU countries and in the EFTA/EEA countries. | <ul style="list-style-type: none"> Discontinued Dedicated only to specific chemicals |

EC-European Commission; EFTA - European Free Trade Association; EEA – European Economic Area.

^a E.g., samples in one 'national' HBM cohort might be taken in 50 different locations in that country where another cohort in the same country might be taken at only 10 different locations.

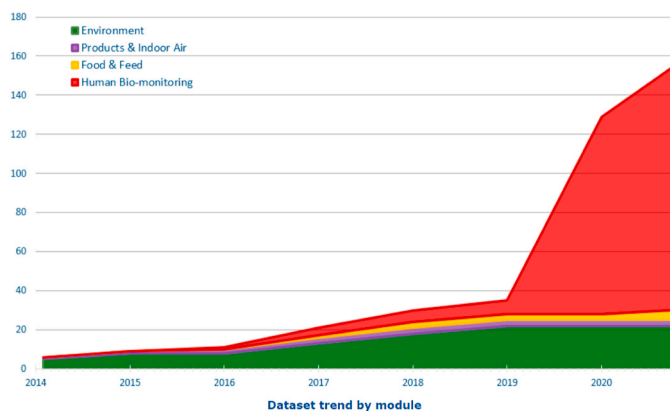


Fig. 2. Time trend of monitoring data included in IPCHEM.

the proposed HBM GRF should promote a dialogue between organisers of HBM surveys and cohort studies since cohort data add a longitudinal component to better investigate exposure-effect-outcome relationships. Beyond this, a dialogue with the fields of toxicology and risk assessment must also be fostered. Toxicological data, preferably organized through AOPs (Adverse Outcome Pathways), help prioritise the most relevant effect biomarkers and adverse health outcomes to be investigated. Effect biomarkers are at the intersection of toxicology, epidemiology and HBM, and a more systematic use of effect biomarkers in HBM studies has been proposed (Zare Jeddi et al., 2020). Notwithstanding, given the complexity and diversity of effect biomarkers, a prospective harmonisation of the type of biological samples collected (e.g., blood, urine), their processing (e.g., whole blood with or without RNA preservation, DNA isolation, serum, plasma, red blood cells, white blood cells) and their storage and biobanking are crucial for an optimal evaluation.

Pourchet et al. (2020) in their recent publication on suspect and non-targeted screening of biomarkers in human matrices highlighted that harmonisation of quality assurance/quality control (QA/QC)

criteria and structure of reporting results appear necessary for better comparability of results produced by different laboratories (Pourchet et al., 2020). In addition, Galea et al. highlighted in their lessons learned from undertaking the HBM4EU chromates study that users must receive training and instruction to ensure that harmonised templates used to collect study data are populated correctly (Galea et al., 2021). A rigorous structure for reporting of screening-level monitoring data in environmental matrices is already incorporated in the NORMAN Database System in the EMPODAT (Environmental Monitoring of Pollutants DATabase) module (Dulio et al., 2020) and the first prototype for structured collection of non-target and suspect screening data has been developed in its Digital Sample Freezing Platform module (DSFP (Alygizakis et al., 2019)). Another critical issue is how to deal with observations below the LOD (limit of determination) or LOQ (limit of quantification) in the statistical analyses and aggregation of the individual data. Obviously, these are issues that could be included in the harmonisation efforts as part of the HBM GRF.

In addition, policy support is not a strong component of existing platforms, which tend to function primarily as a repository of scientific information for researchers and not as an easily useable source of information for regulatory risk assessors, providing advice to risk managers/policy makers.

Existing platforms should be scrutinized for their strengths and weaknesses when developing the HBM GRF. Overall, user friendly web-based platforms would be key to facilitate further use of HBM (meta) data available or accessible via HBM GRF for regulatory risk assessment of chemicals and their mixtures.

5. Aim and objectives of the HBM Global Registry Framework (HBM GRF)

The aim of the HBM GRF is to make HBM research FAIR (Fig. 1). Only by doing so, the ethical imperative to make the most out of human volunteer data would be met.

Based on crucial needs, a series of underlying objectives can be defined that, when accomplished, will increase wider use of HBM (meta) data. An HBM GRF is expected to be able to contribute to the following objectives:

1. Creating an open-access web-based registry system that allows researchers to register HBM studies.
2. Improving data management infrastructure that will meet the FAIR principles by facilitating registrations of HBM studies. For example, assigning a unique reference ID for each study, which can be referred to in any research using data from that study. This would simplify the identification of studies generating new data or reusing data (original study).
3. Harmonising identifiers for chemical substances, including parent substances, metabolites, and effect biomarkers. Examples of effect biomarkers are hormones, specific DNA methylation, markers for gene expression of specific nuclear receptor, cholesterol, liver enzymes.
4. Facilitating multidisciplinary interaction among research scientists, regulatory risk assessors and risk managers/policy makers in the domain of HBM, epidemiology, toxicology, and risk assessment.

As an HBM GRF would benefit many stakeholders (national, EU, international), Table 2 summarises suggested intended audiences for the proposed HBM GRF including other regulatory frameworks and risk assessment processes, as well as for demonstrating regulatory efficacy (Louro et al., 2019). In addition, policy initiatives foreseen under the European Green Deal might benefit from an HBM GRF. A tabulated overview as prepared by the HBM4EU project indicates where HBM data could support directly and indirectly the European Green Deal (see Annex A, unpublished HBM4EU deliverable).

Table 2

Description of potential users and foreseen advantages of the HBM Global Registry Framework (HBM GRF).

| Users/Regulatory Frameworks | More specific data/information to be provided by the registries ^a | Advantages |
|---|--|---|
| HBM and epidemiological researchers/REACH ^b , OSH ^c , Food safety | Questionnaires; Informed consent templates; Sampling templates; Analytical methods, QC/QA; Guidelines for ethics, monitoring and reporting; Methods description; Harmonised Standard Operating Procedures (SOPs) describing some of the above; Statistical analysis plan; Biological sample processing and biobanking. | Harmonised approaches; Comparability of the data; Awareness of data requirements; Identification of gaps and needs for further research; Discovery of chemical analytical methods available; Use of HBM data for building and evaluating exposure models. |
| Exposure researchers and regulatory exposure assessors/REACH, OSH, Food safety | Harmonised SOPs; Methods description; Guidelines for ethics, monitoring and reporting; Statistical analysis plan. | Harmonised approaches; Comparability of the data; Data available to support modelling; Awareness for data requirements; Support for defining new HBM campaigns/programmes. |
| Regulatory risk assessors and competent authorities/REACH, OSH, Food safety | Access to planned HBM-related studies (measuring exposure as well as effect biomarkers) also pointing at contextual data of studies; HBM results might enable setting of HBM guidance and limit values. | Definition of priorities for RMMs (risk management measures) implementation; identification of new RMMs; Risk assessment options; Identification of needs for further regulatory actions to be supported by robust and available scientific knowledge. |
| Industry and trade associations/REACH and OSH | Access to planned HBM-related studies also pointing at contextual data of studies. | Definition of priorities for RMMs implementation; identification of new RMMs. |

^a The registries aimed at are not about results, but about the contextual data, and information on the study (sampling plan, study population, QC/QA, research hypotheses etc).

^b EU Regulation on Registration, Evaluation and Authorisation of Chemicals.

^c Occupational Safety and Health.

6. How to make the HBM Global Registry Framework (HBM GRF) happen?

In Europe there is an opportunity to bring the outlined concepts to fruition. In the coming years, the EU-wide research and innovation program PARC (Partnership for the Assessment of Risks from Chemicals) will run (see intermezzo overleaf). We think that this provides an excellent opportunity to investigate feasibility and options for development of such a registry framework. The current organisations involved in the preparation of the Partnership represent 28 EU and non-EU countries and include ministries (for research, health, and environment), national and EU agencies and research organisations as well as academia and research institutions. We believe that this broad set-up is very well suited and capable of developing further the HBM GRF as advocated by the authors of in this article from various parts of the world. The stimulus could very well come from Europe under PARC. Global input during the process could be processed through the international PARC Advisory Board. Global contributions where possible along the process would be essential to ensure worldwide use of the HBM GRF to enhance registration of new and ongoing HBM studies e.g.,

NHANES in the USA, the CHMS in Canada, KNEHS in Korea and JECS in Japan. Additionally, support from and cooperation with UN, WHO and OECD would help global implementation of this initiative.

PARC – Partnership for the Assessment of Risks from Chemicals

PARC is an EU-wide research and innovation programme that will run 2022–2028. The Partnership will promote harmonisation of data and exchange between different actors (scientific community, health agencies, regulators, policymakers etc.) and disciplines (e.g., exposure science, toxicology) to promote transparency, support risk assessment, and facilitate wider reuse of obtained data. To achieve this, it will build on existing data platforms included in or collaborating with the Partnership and contribute to extend their usability for risk assessors and managers. It will ensure data and associated information is FAIR and addresses the GDPR (EU General Data Protection Regulation) related challenges for data exchange. Important will be that all relevant EU Agencies can duly contribute to and access relevant PARC activities and outputs, and the most relevant European Commission Directorates General will be involved as well.

The Partnership will strive towards fostering European leadership at the international level for research and innovation in chemical risk assessment and will promote cooperation and collaboration across Europe and internationally. The Partnership will contribute to international fora, dealing with chemicals, pollution, and the SDGs (UN Sustainable Development Goals), such as the World Health Organisation (WHO) (e.g., International Programme on Chemical Safety IPCS Chemical Risk Assessment Network) and Strategic Approach to International Chemicals Management (SAICM), UN Environment Programme (UNEP) and OECD, dealing with chemicals, pollution, and the SDGs. Bilateral relations with major international risk assessment agencies (e.g., U. S. Environmental Protection Agency) and research institutions (e.g., U.S. National Toxicology Program) will also be envisaged. Member States are already contributing as single entity to many of these networks. Collaboration of MS in the Partnership will strengthen the influence of the EU in addressing global challenges associated with chemical risk assessment and place the EU as the front runner of the international community in this area.

Dialogue and collaboration with the international community is essential for mutual support and for the identification of needs and opportunities for harmonisation actions and development of tools that support the collaboration. Connecting this Partnership with the international community will foster the dissemination of results and will promote the importance of data and knowledge sharing among international networks. An international board consisting of experts from other international chemical risk assessment platforms, scientific advisory boards or scientific societies, or experts in related EU or international activities will contribute to ensuring the Partnership establishes links and dialogue with relevant international activities.

7. Summary and conclusion

Overall, we propose to develop an HBM Global Registry Framework (HBM GRF) aiming at harmonising the design and structuring the registration of HBM studies and by such, making the ultimate HBM (meta)data more FAIR (Findable, Accessible, Interoperable and Reusable). Consequently, this will improve the assessment, comparability and combination, reuse, and interpretation of HBM-study results. Preparing HBM study protocols would be facilitated with such a web-based system as they would be based on digitised and harmonised templates. This would result in harmonised data entries into registries.

The ultimate objective could be to make HBM (meta)data accessible in a virtual, federated, infrastructure, so that data with the right

credentials become instantaneously accessible for human and machine interactions. Implementing the FAIR principles in the HBM domain could act as fundamental enabler for digital transformation in the environment and health domain.

HBM GRF would facilitate the process of data creation and use to its final use and reuse (the data value chain). This is expected to better channel knowledge on the internal exposure of chemicals (exposure biomarkers) and early warnings of effects (effects biomarkers) in human samples into regulatory risk assessment and risk management (Burns et al., 2019).

The HBM GRF would help to close the science to policy interface gap between scientific ambitions and regulatory and policy requirements resulting in an added value in protecting human health (Burns et al., 2019). This knowledge transfer is of particular relevance for the European Chemicals Sustainability Strategy, which needs more and better exposure data, as well as in the scope of international conventions aiming to protect human health from chemical exposures. Creating the HBM GRF as proposed here would advance exposure science and would ultimately support a better protection of citizen's health throughout the world (Fantke et al., 2020b).

Disclaimer

The contents, including any opinions and/or conclusions expressed of this manuscript, are those of the authors alone and do not necessarily reflect the opinions or policy of the organisations to which they are employed.

Acknowledgements

Stephanie Bopp (European Commission, DG Joint Research Centre) is acknowledged to provide valuable information regarding the IPCHEM Platform. The VITO HBM data management team is acknowledged for providing specific input. The HBM expert working group of the European Chapter of the International Society for Exposure Science (ISES Europe) is acknowledged for their great support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijheh.2021.113826>.

References

- Ågerstrand, M., Christiansen, S., Hanberg, A., Rudén, C., Andersson, L., Andersen, S., Appelgren, H., Borge, C., Clausen, I.H., Eide, D.M., 2018. A call for action: improve reporting of research studies to increase the scientific basis for regulatory decision-making. *J. Appl. Toxicol.* 38, 783–785.
- Alygizakis, N.A., Oswald, P., Thomaidis, N.S., Schymanski, E.L., Aalizadeh, R., Schulze, T., Oswaldova, M., Slobodnik, J., 2019. NORMAN digital sample freezing platform: a European virtual platform to exchange liquid chromatography high resolution-mass spectrometry data and screen suspects in “digitally frozen” environmental samples. *Trac. Trends Anal. Chem.* 115, 129–137.
- Baken, K.A., Lambrechts, N., Remy, S., Mustieles, V., Rodríguez-Carrillo, A., Neophytou, C.M., Olea, N., Schoeters, G., 2019. A strategy to validate a selection of human effect biomarkers using adverse outcome pathways: proof of concept for phthalates and reproductive effects. *Environ. Res.* 175, 235–256.
- Boyden J., and Walnicki D., *Leveraging the Power of Longitudinal Data: Insights on Data Harmonisation and Linkage from Young Lives.* (2021).
- Becker, K., Schulz, C., Kaus, S., Seiwert, M., Seifert, B., 2003. German Environmental Survey 1998 (GerES III): environmental pollutants in the urine of the German population. *Int. J. Hyg Environ. Health* 206, 15–24.
- Bocato, M.Z., Bianchi Ximenez, J.P., Hoffmann, C., Barbosa, F., 2019. An overview of the current progress, challenges, and prospects of human biomonitoring and exposome studies. *J. Toxicol. Environ. Health, Part B* 22, 131–156.
- Bopp, S.K., Barouki, R., Brack, W., Dalla Costa, S., Dorne, J.-L.C., Drakvik, P.E., Faust, M., Karjalainen, T.K., Kephelopoulou, S., van Klaveren, J., 2018. Current EU research activities on combined exposure to multiple chemicals. *Environ. Int.* 120, 544–562.
- Burns, C.J., LaKind, J.S., Mattison, D.R., Alcalá, C.S., Branch, F., Castillo, J., Clark, A., Clougherty, J.E., Darney, S.P., Erickson, H., 2019. A matrix for bridging the epidemiology and risk assessment gap. *Global Epidemiology* 1, 100005.

- Choi, W., Kim, S., Baek, Y.-W., Choi, K., Lee, K., Kim, S., Do Yu, S., Choi, K., 2017. Exposure to environmental chemicals among Korean adults—updates from the second Korean National Environmental Health Survey (2012–2014). *Int. J. Hyg Environ. Health* 220, 29–35.
- Comero, S., Dalla Costa, S., Cusinato, A., Korytar, P., Kephelopoulou, S., Bopp, S., Gawlik, B.M., 2020. A conceptual data quality framework for IPCHEM—the European commission information platform of chemical monitoring. *Trac. Trends Anal. Chem.* 115879.
- Cox, C.S., 1992. Plan and Operation of the NHANES I Epidemiologic Followup Study, 1987. US Department of Health and Human Services, Public Health Service, Centers.
- DiMoPEX, 2015. **Diagnosis, Monitoring and Prevention of Exposure Related Non-communicable Diseases, DiMoPEX (CA 15129)**. <http://dimopex.eu/>.
- Drakvik, E., Altenburger, R., Aoki, Y., Backhaus, T., Bahadori, T., Barouki, R., Brack, W., Cronin, M.T., Demeneix, B., Bennekou, S.H., 2020. Statement on advancing the assessment of chemical mixtures and their risks for human health and the environment. *Environ. Int.* 134, 105267.
- Dulio, V., Koschorreck, J., van Bavel, B., van den Brink, P., Hollender, J., Munthe, J., Schlabach, M., Aalizadeh, R., Agerstrand, M., Ahrens, L., 2020. The NORMAN association and the European partnership for chemicals risk assessment (PARC): let's cooperate! *Environ. Sci. Eur.* 32, 1–11.
- Ec, 2020a. European Commission Chemicals Strategy for Sustainability—Towards a Toxic-free Environment. Brussels, COM(2020) 667 Final.
- Ec, 2020b. European Commission, Information Platform for Chemical Monitoring (IPCHEM) Data Integration.
- ELIXIR, 2017. Position Paper on FAIR Data Management in Life Sciences.
- EU, 2016. Service Contract to Create a Database and Develop a Model to Estimate the Occupational Exposure for a List of Hazardous Chemicals in the Member States of the European Union and in the EFTA/EEA Countries No VT/2013/079. Publications Office of the European Union, Luxembourg, ISBN 978-92-79-45435-6.
- Evans, R.M., Martin, O.V., Faust, M., Kortenkamp, A., 2016. Should the scope of human mixture risk assessment span legislative/regulatory silos for chemicals? *Sci. Total Environ.* 543, 757–764.
- Eykelbosh, A., Werry, K., Kosatsky, T., 2018. Leveraging the Canadian health measures survey for environmental health research. *Environ. Int.* 119, 536–543.
- Fantke, P., Aurisano, N., Provoost, J., Karamertzanis, P.G., Hauschild, M.Z., 2020a. Toward effective use of REACH data for science and policy. *Environ. Int.* 135.
- Fantke, P., Von Goetz, N., Schlüter, U., Bessems, J., Connolly, A., Dudzina, T., Ahrens, A., Bridges, J., Coggins, M.A., Conrad, A., 2020b. Building a European exposure science strategy. *J. Expo. Sci. Environ. Epidemiol.* 30, 917–924.
- Faure, S., Noisel, N., Werry, K., Karthikeyan, S., Aylward, L.L., St-Amand, A., 2020. Evaluation of human biomonitoring data in a health risk based context: an updated analysis of population level data from the Canadian Health Measures Survey. *Int. J. Hyg Environ. Health* 223, 267–280.
- 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.
- Galea, K.S., Porras, S.P., Viegas, S., Bocca, B., Bousoumah, R., Duca, R.C., Godderis, L., Iavicoli, I., Janasik, B., Jones, K., 2021. HBM4EU chromatates 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.
- Goodman, K.J., Geary, J., Walker, E., Fagan-Garcia, K., Archie, B., Lennie, C., Munday, R., McAlpine, L., Colquhoun, A., Chang, H.-J., 2019. Community-driven epidemiologic research: guiding principles. *Global Epidemiology* 1, 100013.
- 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.
- Hubal, E.A.C., 2019. PFAS: Insights from Past Actions to Inform Today's Decisions. Nature Publishing Group.
- IUPAC, 2018. What on Earth Is InChI?.
- Joas, R., Casteleyn, L., Biot, P., Kolossa-Gehring, M., Castano, A., Angerer, J., Schoeters, G., Sepai, O., Knudsen, L.E., Joas, A., 2012. Harmonised human biomonitoring in Europe: activities towards an EU HBM framework. *Int. J. Hyg Environ. Health* 215, 172–175.
- Knetsch, G., Ruether, M., 2016. The European Information Platform for Chemical Monitoring (IPCHEM)—How Can You Realize Interoperability?.
- Kromerová, K., Bencko, V., 2019. Added value of human biomonitoring in assessment of general population exposure to xenobiotics. *Cent. Eur. J. Publ. Health* 27, 68–72.
- 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.
- 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.
- Mustieles, V., d'Crúz, S.C., Couderq, S., Rodríguez-Carrillo, A., Fini, J.-B., Hofer, T., Steffensen, I.-L., Dirven, H., Barouki, R., Olea, N., 2020. Bisphenol A and its analogues: a comprehensive review to identify and prioritize effect biomarkers for human biomonitoring. *Environ. Int.* 144, 105811.
- Mustieles, V., Fernández, M.F., 2020. Bisphenol A shapes children's brain and behavior: towards an integrated neurotoxicity assessment including human data. *Environ. Health* 19, 1–8.
- OECD, 2018. Consideration for Assessing the Risk of Combined Exposure to Multiple Chemicals, Series on Testing and Assessment, No. 296. Environment, Health and Safety Division, Environment Directorate.
- 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.
- Romano, M.E., Gallagher, L.G., Eliot, M.N., Calafat, A.M., Chen, A., Yoltou, K., Lanphear, B., Braun, J.M., 2020. Per- and polyfluoroalkyl substance mixtures and gestational weight gain among mothers in the Health Outcomes and Measures of the Environment study. *Int. J. Hyg Environ. Health* 231, 113660.
- SAICM, 2013. Strategic Approach to International Chemical Management.
- Santonen, T., Alimonti, A., Bocca, B., Duca, R.C., Galea, K.S., Godderis, L., Göen, T., Gomes, B., Hanser, O., Iavicoli, I., 2019. Setting up a collaborative European human biological monitoring study on occupational exposure to hexavalent chromium. *Environ. Res.* 177, 108583.
- Sexton, K.L., Needham, L.L., Pirkle, J., 2004. Human Biomonitoring of Environmental Chemicals: measuring chemicals in human tissues is the "gold standard" for assessing people's exposure to pollution. *Am. Sci.* 92, 38–45.
- St-Amand, A., Werry, K., Aylward, L.L., Hays, S.M., Nong, A., 2014. Screening of population level biomonitoring data from the Canadian Health Measures Survey in a risk-based context. *Toxicol. Lett.* 231, 126–134.
- Who, 2015a. Human Biomonitoring: Facts and Figures. WHO Regional Office for Europe, Copenhagen.
- Who, 2015b. Human Biomonitoring: Facts and Figures. WHO Regional Office for Europe Copenhagen.
- Wikoff, D., Lewis, R.J., Erraguntla, N., Franzen, A., Foreman, J., 2020. Facilitation of risk assessment with evidence-based methods—A framework for use of systematic mapping and systematic reviews in determining hazard, developing toxicity values, and characterizing uncertainty. *Regul. Toxicol. Pharmacol.* 118, 104790.
- Wilhelm, M., 2020. Human biomonitoring: its importance in toxicological regulation. *Regulatory Toxicology* 1–20.
- Wilkinson, M.D., Dumontier, M., Aalbersberg, I.J., Appleton, G., Axton, M., Baak, A., Blomberg, N., Boiten, J.-W., da Silva Santos, L.B., Bourne, P.E., 2016. The FAIR Guiding Principles for scientific data management and stewardship. *Scientific data* 3, 1–9.
- Williams, A.J., Yerin, A., 2013. Automated systematic nomenclature generation for organic compounds. *Wiley Interdisciplinary Reviews: Computational Molecular Science* 3, 150–160.
- Wolfe, T.A., Whaley, P., Halsall, C., Rooney, A.A., Walker, V.R., 2019. Systematic evidence maps as a novel tool to support evidence-based decision-making in chemicals policy and risk management. *Environ. Int.* 130, 104871.
- 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., 2020. Towards a systematic use of effect biomarkers in population and occupational biomonitoring. *Environ. Int.* 146, 106257.