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Coordination of chemical analyses under the European Human Biomonitoring Initiative (HBM4EU): Concepts, procedures and lessons learnt

Katrin Vorkamp [a,*], Marta Esteban López [b], Liese Gilles [c], Thomas Göen [d], Eva Govarts [c], Parvaneh Hajeb [a], Andromachi Katsonouri [e], Lisbeth E. Knudsen [f], Marike Kolossa-Gehring [g], Christian Lindh [h], Stefanie Nübler [d], Susana Pedraza-Díaz [b], Tiina Santonen [i], Argelia Castaño [b]

[a] Aarhus University, Department of Environmental Science, Roskilde, Denmark
[b] Instituto de Salud Carlos III, National Centre for Environmental Health, Majadahonda, Spain
[c] VITO Health, Flemish Institute for Technological Research, Mol, Belgium
[d] Friedrich-Alexander Universität Erlangen-Nürnberg, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Erlangen, Germany
[e] State General Laboratory, Ministry of Health, Nicosia, Cyprus
[f] University of Copenhagen, Institute of Public Health, Copenhagen, Denmark
[g] German Environment Agency (UBA), Berlin, Germany
[h] Lund University, Division of Occupational and Environmental Medicine, Lund, Sweden
[i] Finnish Institute of Occupational Health, Helsinki, Finland

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ABSTRACT

The European Human Biomonitoring Initiative (HBM4EU) ran from 2017 to 2022 with the aim of advancing and harmonizing human biomonitoring in Europe. More than 40,000 analyses were performed on human samples in different human biomonitoring studies in HBM4EU, addressing the chemical exposure of the general population, temporal developments, occupational exposure and a public health intervention on mercury in populations with high fish consumption. The analyses covered 15 priority groups of organic chemicals and metals and were carried out by a network of laboratories meeting the requirements of a comprehensive quality assurance and control system. The coordination of the chemical analyses included establishing contacts between sample owners and qualified laboratories and monitoring the progress of the chemical analyses during the analytical phase, also addressing status and consequences of Covid-19 measures. Other challenges were related to the novelty and complexity of HBM4EU, including administrative and financial matters and implementation of standardized procedures. Many individual contacts were necessary in the initial phase of HBM4EU. However, there is a potential to develop more streamlined and standardized communication and coordination in the analytical phase of a consolidated European HBM programme.

1. Introduction

The European Human Biomonitoring Initiative (HBM4EU) was launched in 2017 to develop and establish a coordinated and harmonized approach to human biomonitoring (HBM) across Europe. It built on the previous European projects *Expert Team to Support Biomonitoring in Europe (ESBIO)*, *European Coordination Action on Human Biomonitoring (COPHES)* and its demonstration project *DEMOCOPHES*, and on national or regional HBM programmes of some European countries (Kolossa-Gehring et al., 2012; Schindler et al., 2014; Den Hond et al., 2015; Joas et al., 2015). One of the characteristics of HBM4EU was a high degree of diversity, as it encompassed partners from 30 countries with different levels of HBM experience. Furthermore, it supported national as well as European authorities in chemical risk assessment, and it addressed a variety of chemicals, exposure scenarios and health outcomes (Ganzleben et al., 2017; Kolossa-Gehring et al., 2023). Consequently, coordination points had a vital role in HBM4EU in advancing the initiative from distinct activities to a coherent programme.

The chemical analyses in HBM4EU included human samples from four complementary approaches: Aligned national and regional HBM

* Corresponding author.
E-mail address: kvo@envs.au.dk (K. Vorkamp).

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studies, connections to previous analyses in *DEMOCOPHES*, occupational exposure monitoring and an intervention study focussing on mercury (Table 1). These studies addressed two groups of priority substances. The first group had been selected in the preparation of HBM4EU according to policy-relevant questions defined by HBM4EU partner countries and European authorities, and the second group was defined in a prioritization process developed in HBM4EU (Ougier et al., 2021) (Table 1). An additional study on pesticide exposure using non-target and suspect screening, abbreviated SPECIMEn, was conducted in HBM4EU as well (Vitale et al., 2022), but not included in the coordination of analyses of the priority compounds. Except for some existing data from *DEMOCOPHES* or national and regional HBM programmes, new chemical analyses of the priority compounds were conducted in HBM4EU, based on the prerequisite of coordinated and harmonized approaches (Ganzleben et al., 2017).

For that purpose, a comprehensive quality assurance and control (QA/QC) programme was designed in HBM4EU, open to all European laboratories with an interest in performing HBM analyses of exposure biomarkers of the priority substances (Esteban López et al., 2021). It was organized and coordinated by the Quality Assurance Unit (QAU) established in HBM4EU and involved different HBM4EU partners taking responsibility for interlaboratory comparison investigations (ICIs) and/or external quality assurance schemes (EQUAS) in their field of expertise. This approach ensured greatest scientific expertise for the priority chemicals, substance-tailored ICI and EQUAS approaches with a common design and optimized timelines in parallel ICIs/EQUAS. The programme specified the criterion of at least two successful rounds of ICI/EQUAS participation to qualify for the analysis of specific biomarkers in HBM4EU.

The QA/QC programme resulted in the qualification of 75 laboratories from 25 countries for HBM analyses of different biomarkers related to the priority substances in Table 1. It was up to the sample owner, providing the samples to HBM4EU, to select a laboratory for the chemical analysis, on an informed basis. Collecting and conveying this information was part of the coordination of the analytical phase in HBM4EU, under the responsibility of Aarhus University (AU). The coordination also included progress monitoring of the chemical analyses. The Covid-19 pandemic required communication efforts beyond regular updates as well as adjustments of work plans that affected the overall HBM4EU timelines.

The objective of this article is to present and discuss the coordination of the chemical analyses in HBM4EU, starting from the conceptual approach and subsequently detailing the main activities. The article also includes the challenges encountered in the process and possible solutions for future projects.

2. Conceptual approach

The first step in the coordination of the analytical phase was to connect the qualified laboratories, i.e. laboratories with successful participation in the HBM4EU QA/QC programme, and the sample owners, with the purpose of providing the sample owners with the necessary information to select laboratories for the planned analyses (Fig. 1). In addition, this connection should give the laboratories the possibility to prepare for potential analytical tasks in their work plans. This first step required inputs from other tasks and work packages (WPs) in HBM4EU, including lists of qualified laboratories (Esteban López et al., 2021) and of the sample owners with their specific analytical interests (Gilles et al., 2021).

Once the sample owners had selected a laboratory, AU assisted with potential questions about administrative and technical issues. When the samples had been shipped to the selected laboratory, the monitoring phase began, i.e. the second part of the coordination work (Fig. 1). It involved regular contacts to each laboratory to enquire about progress and potential difficulties, which was intensified during the Covid-19 pandemic when work conditions became unpredictable as laboratories were affected by lockdowns and/or reduction of activities. AU regularly summarized the status of the analytical work in internal progress reports for the attention of task and WP leaders.

Although consecutive in the conceptual approach, the connecting efforts and the progress monitoring proceeded in parallel and overlapped in their timing. As the chemical analyses in HBM4EU included two groups of prioritized substances (Table 1) and both were covered by the QA/QC programme, the process in Fig. 1 was applied twice. However, fewer laboratories were involved in the second round of analyses than in the first one. In addition, the chemical analyses included a comparison of concentrations at different time points and samples from occupational studies, although the number of analyses was considerably lower than in the HBM4EU Aligned Studies (Table 1).

In the HBM4EU-MOM study and the HBM4EU occupational study on exposure in e-waste management, the coordination requirements were reduced to the progress monitoring. In both studies, one central laboratory was pre-selected for each type of analysis. The occupational studies on diisocyanates further included analyses of hemoglobin adducts and urine lysine adducts, which were of exploratory nature and thus not included in the HBM4EU QA/QC programme or the coordination of the analytical phase (Jones et al., 2022).

The outputs of the analytical phase were HBM data on the priority substances in the individual studies in Table 1, accompanied by contextual QA/QC information. These data were further processed and analysed in other WPs in HBM4EU and not part of the coordination of the analytical phase (Fig. 1). However, it meant that the analytical phase

Table 1
Summary of chemical analyses in studies on priority substances under HBM4EU.

Study	First group of priority substances	Second group of priority substances	Number of analyses	Reference
HBM4EU Aligned Studies: Alignment of national and regional HBM studies	Phthalates and 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH), bisphenols, per- and polyfluoroalkyl substances (PFAS), organophosphorous flame retardants (OPFRs), halogenated flame retardants (HFRs), polycyclic aromatic hydrocarbons (PAHs), cadmium	Acrylamide, mycotoxins, pesticides, UV filters, arsenic	29,074	Gilles et al. (2021); Gilles et al. (2022); Govarts et al. (2023)
Comparisons of different time points, including *DEMOCOPHES* samples	Phthalates and DINCH, bisphenols, OPFRs, PAHs, cadmium	–	4863	Vogel et al. (2023)
Occupational exposure studies	Chromium[a], PFAS[a], OPFRs[b], HFRs[b], phthalates[b] and DINCH[b], cadmium[b]	Diisocyanates[b], mercury[b], lead[b]	8574	Galea et al. (2021); Jones et al. (2022); Santonen et al. (2019, 2022); Scheepers et al. (2021)
HBM4EU-MOM[c]: Intervention study on mercury	–	Mercury	1305	Namorado et al. (2021); Katsonouri et al. (2023)

[a] First occupational study: Exposure to chromium.
[b] Second occupational studies: Exposure to diisocyanates and exposure in e-waste management, respectively.
[c] Methylmercury-control in expectant mothers through suitable dietary advice for pregnancy.

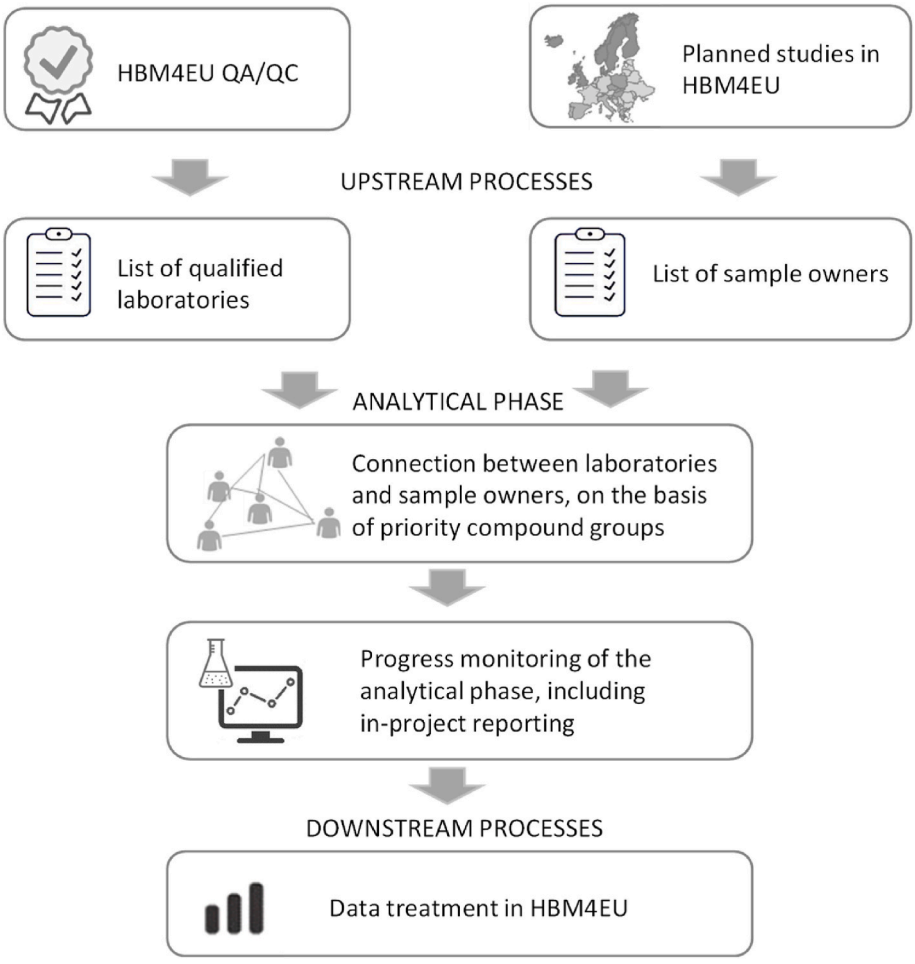


Fig. 1. Concept of coordination of the chemical analyses in HBM4EU.

had to be closely connected to upstream processes (lists of qualified laboratories, planned studies) and downstream processes (data processing and interpretation).

3. Connecting qualified laboratories and sample owners

Fig. 2 lists the activities included in the first step of the coordination work, i.e. the establishment of connections between qualified laboratories and sample owners. In order to collect information on analyses,

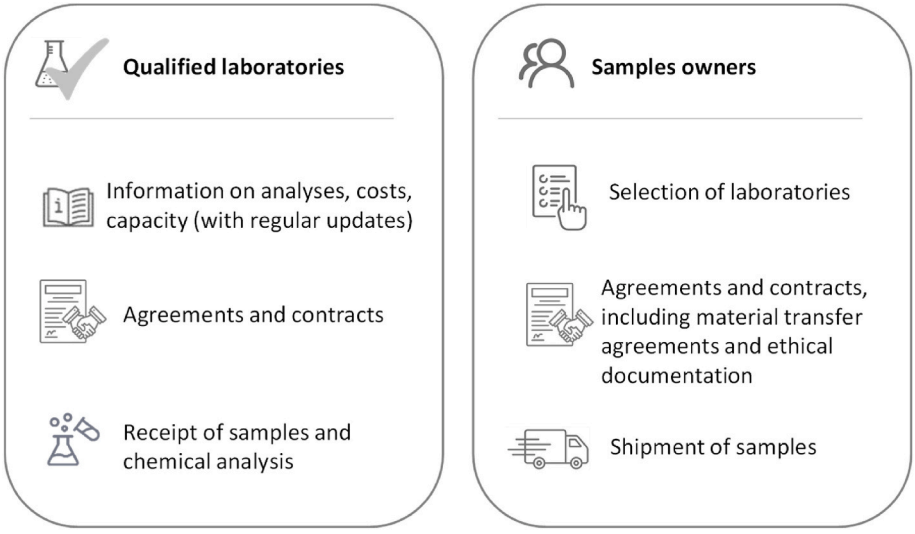


Fig. 2. Topics covered in the first step of the coordination of the chemical analyses in HBM4EU, i.e. the establishment of contacts between qualified laboratories and sample owners.

costs and capacity, a questionnaire was prepared for the qualified laboratories, including questions on the laboratory itself (e.g. use of a quality management system, involvement in HBM4EU and contact details), the specific biomarkers that the laboratory offered to analyze, the analytical methods (e.g. sample volume required, limit of quantification (LOQ), extraction, clean-up and instrumental techniques), the price and time frames for the specific analysis and whether or not the laboratory required any information from the sample owner. The questionnaire for bisphenols is shown as an example in Fig. 3. Questionnaires for the other priority substances are available in the Supporting Information (Fig. S1 - Fig. S13). The questionnaires were adapted to each group of substances to account for different biomarkers, matrices (urine, serum) and analytical methods.

Membership in the HBM4EU consortium was not a prerequisite to be selected for analysis. However, whether or not a laboratory was a partner in HBM4EU had administrative implications for the invoicing, as further discussed in Section 5. The only criterion for conducting analyses in HBM4EU was the successful participation in the QA/QC programme. The candidate list for the QA/QC programme was open for non-HBM4EU as well as HBM4EU laboratories (Esteban López et al., 2021). All laboratories were informed, as part of the questionnaire, that the analytical method had to be identical with that applied in the ICIs and EQUASs. Potential changes had to be disclosed in the questionnaire and would lead to an expert assessment of eligibility. However, no laboratory reported any changes.

Price for analyzing bisphenol biomarkers in urine

HBM4EU will investigate the human exposure to a list of prioritized substances in the European population. We kindly request your offer for analyses of bisphenol biomarkers in urine samples, to be performed in the HBM4EU project. The information in this form will be used in subsequent deliberations and negotiations between sample owners and laboratories.

Please fill in the requested information, sign the form and return it to hbm4eu@envs.au.dk.

Laboratory information	
Laboratory name	
Head of the laboratory	
Number of staff and qualifications	
Address	
Contact person	
Phone	
E-mail	
Is the laboratory member of the HBM4EU consortium?	
Is the laboratory ISO/IEC 17025 accredited?	
If not, does it work under a quality management system?	
Biomarkers	
Please indicate which biomarkers are included in the analytical method	
Bisphenol A (BPA)	
Bisphenol F (BPF)	
Bisphenol S (BPS)	
Analytical method	
Sample volume required (ml)	
LOQ (ng/ml)	
Will the analytical method be identical with that used in the HBM4EU ICI/EQUAS?	
If not, please specify any deviations, subject to evaluation by the HBM4EU Quality Assurance Unit. Please note that inconsistencies with the HBM4EU ICI/EQUAS might affect the eligibility of the laboratory for analyses in HBM4EU.	
In-house quality assurance/quality control	
Internal standards used for analysis	
Calibration method	
Extraction and clean-up	
Sample pre-treatment	
Type of deconjugation	
Enzyme used (ref number)	
SPE offline including type of column	
SPE online including type of column	
Other extraction and clean-up methods	
Derivatization (reagent)	
Instrumental analysis	
GC-MS (model, brand, column, ionisation)	
GC-MS/MS (model, brand, column, ionisation)	
LC-MS/MS (model, brand, column, ionisation)	
Other (please specify)	
Price	
Price, in Euro, for 300 samples	
Please specify person months (PM) for the analysis of 300 samples, costs of PM for different categories of staff involved in the analyses, and direct costs (consumables).	
Does the price include the determination of creatinine?	
If not, what is the price for creatinine determination in 300 samples? If possible, please specify PM and direct costs.	
Capacity and timeframe for analysis	
Time frame for 300 samples (assuming that they will be available in approximately one month).	
How much time does the laboratory need in advance to plan and prepare the analysis of 300 samples?	
Are there variations in the laboratory's capacity (due to holidays etc.)? If so, please specify.	
Does the laboratory have the capacity to analyse several sets of 300 samples in parallel?	
If yes, what is the maximum capacity?	
If no, what would be the time frame for several sets of 300 samples?	
Information required from the sample owners	
What information does the laboratory need from the sample owner for a potential contract for analyses?	
Other comments	
Validity of this document until	
Please note any additional comments.	

Date and signature

Fig. 3. Example of a questionnaire sent to laboratories qualified in HBM4EU, here for the analysis of bisphenols.

It should be noted that the design of the QA/QC programme, including the criterion of two successful rounds of participation, meant that the laboratories qualified for specific biomarker analyses at different points in time. Consequently, the collection of information from the laboratories was a rolling process, repeated after each update of the list of qualified laboratories in relation to completed rounds of ICIs and EQUAS. Furthermore, as the laboratories indicated in the questionnaires for how long this information was valid (Fig. 3), updates were requested from the laboratories when this time had passed. The information received from the laboratories was compiled in a table, with updates marked, and circulated to the sample owners on a weekly basis. The qualified laboratories, but no details on prices, capacities or methods, were also published on the HBM4EU website.

Parallel to the regular contacts with the qualified laboratories, inventories of all planned analyses were established and kept up-to-date, mainly based on information provided by the task leaders responsible for the studies in Table 1. This overview is shown in Table S1 of the Supporting Information, details are also given by Gilles et al. (2021, 2022), Govarts et al. (2023) and Santonen et al. (2019, 2022). In collaboration with the task leaders responsible for the studies in Table 1, questions were prepared for the sample owners, including information on the status of the sampling campaign, preparatory steps, such as ethical approval (Knudsen et al., 2023), and availability of auxiliary data. The selected laboratories were regularly added to the inventory, for internal use in HBM4EU. If a lack of progress was noted, the sample owners were contacted and asked if a decision had been reached on the choice of laboratory.

The sample owners were encouraged to contact AU as coordinators for the analytical phase to request information and updates according to their work plans. In some cases, sample owners had pre-selected a qualified laboratory or chosen to analyze the samples in-house, which they were also asked to communicate to AU's coordinating team. It is also worth noting that in this process of establishing contacts and exchanging information of relevance to the analytical work, including analytical costs, AU as the coordinator of the analytical phase was not involved in any deliberations of financial matters between the sample owners and the laboratories. AU and others assisted with guidance on the technicalities of budget transfer, as further specified in Section 5, but price negotiations between sample owners and laboratories or any involvement in the actual selection process were not part of the coordinating activities in the analytical phase.

Shipment of samples to the laboratories followed Standard Operating Procedures (SOPs) developed in HBM4EU (Pack et al., 2023). It was accompanied by Material and Data Transfer Agreements, which were also filed in a central HBM4EU database under the auspices of the HBM4EU ethics coordinator (Lermen et al., 2020; Knudsen et al., 2023). Thus, AU as coordinator for the chemical analyses was in close contact with the ethics coordinator to ensure correct documentation in accordance with rules for ethics and data protection. The HBM4EU coordinator, holding the main responsibility for ethics and data management in HBM4EU, was also copied on correspondence in this field.

4. Progress monitoring of the chemical analyses

In order to know the status of the HBM analyses and to assist with

potential difficulties on a one-on-one basis, close contacts to the sample owners and the selected laboratories were established. As discussed in Section 3, agreements between the sample owners and the selected laboratories were reached at different time points in HBM4EU. Consequently, sample shipment and the analyses in each laboratory had their own timelines. At a given point in time, the individual analyses in the studies of Table 1 had progressed very differently. The status was described in progress reports for internal use in HBM4EU, providing leaders and colleagues in other WPs with regular updates relevant for their work in HBM4EU. The first laboratories had passed the qualification criteria in July 2019, whereas the last analyses were completed with the end of the project in June 2022.

Monitoring the progress of the chemical analyses proceeded via e-mail communication, mainly with the responsible project leaders as the first contacts, but also, with their agreement and information, directly with the selected laboratories or sample owners. This communication was not standardized in any way, beyond carbon copying to the institutions involved in the respective study. In hindsight, standardized progress forms could have been circulated at regular intervals, but a more informal and individualized approach was chosen in HBM4EU, reflective of the close collaboration amongst most partners as well as the wish to create possibilities for open discussion and solution-oriented dialogue in case of problems or delays. Thus, a small team formed around each study, which proved efficient in finding solutions and conveying relevant information to other groups in HBM4EU.

Table 2 summarizes the analyses in HBM4EU according to the prioritized substance group, also including the number of laboratories qualified and eventually selected for the chemical analyses. As mentioned in Section 1, the total number of qualified laboratories was 75, but as one laboratory could be qualified for multiple biomarkers, the total number in Table 2 is higher. Of the 75 qualified laboratories, 34 laboratories (45%) were selected for analysis in HBM4EU, some of them for multiple analyses. Their geographical distribution is summarized in Fig. 4. A corresponding figure, stratified by priority group, is shown in the Supporting Information (Fig. S14).

The number of qualified laboratories is highest in the larger European countries as well as in those with existing HBM programmes (Fig. 4). The differences are smaller for the number of selected laboratories. However, while a large number of laboratories was selected for the chemical analyses, the number of samples analysed per laboratory varied considerably, ranging between 60 and 5198. About 30% of all analyses were conducted by three of the 34 selected laboratories, located in Germany, the Czech Republic and Denmark.

Fig. 5 shows how many samples in percentage of the total number were analysed in their country of origin. A corresponding figure with absolute numbers is presented in the Supporting Information (Fig. S15). The high percentage of cadmium analyses conducted at the national level suggests that this analysis is well-established in many European countries. Cadmium was also the biomarker with the highest number of laboratories qualified for analyses in HBM4EU (Fig. S14). However, other factors may also influence how many samples are analysed in the same country: Samples might have been chosen for HBM4EU analyses because analytical capacities were available in the country. Likewise, participation in the HBM4EU QA/QC programme might have been prioritized because samples were to be analysed from the same country. For the second group of priority substances (Table 1), only few invited expert laboratories had qualified for HBM4EU analyses, limiting the possibility for national-based analyses.

5. Challenges

5.1. Standardization

One of the central objectives of HBM4EU was the standardization and harmonization of procedures, taking into account that a large number of European countries and institutions participated in HBM4EU. While some of them had no prior experience with HBM and had to establish new routines, others with some HBM experience had to adjust their procedures to meet the standards developed in HBM4EU (Pack et al., 2023). This transition towards standardized procedures covered

Table 2
Substance groups and qualified laboratories performing chemical analyses.

Priority substance (group)	Individual biomarkers[a]	Matrix	Qualified laboratories	Selected laboratories	Analyses	QA/QC programme
Acrylamide	2	Urine	5	2	1795	Esteban López et al. (2021)
Arsenic	6	Urine	2	1	900	Esteban López et al. (2021)
Bisphenols	3	Urine	25	8	3613	Vaccher et al. (2022)
Cadmium	1[b]	Urine, blood[c]	38	11	3967	Nübler et al. (2021)
Chromium	1[b]	Urine, plasma, blood[d]	28	11	2758	Nübler et al. (2022a)
Diisocyanates	3	Urine	3	3	356	Jones et al. (2022)
DINCH	2	Urine	8	8	6160	Mol et al. (2022)
Halogenated flame retardants	10	Serum	15	5	1178	Dvorakova et al. (2021)
Mercury[e]	1	Hair	–	1	1305	-[e]
Mycotoxins	1	Urine	4	3	1304	Esteban López et al. (2021)
Organophosphorous flame retardants	4	Urine	5	5	2856	Dvorakova et al. (2021)
Per- and polyfluoroalkyl substances (PFAS)	12	Serum	21	6	1663	Nübler et al. (2022b)
Pesticides	9	Urine	2	2	2188	Esteban López et al. (2021)
Phthalates	15	Urine	20	9	5949	Mol et al. (2022)
Polycyclic aromatic hydrocarbons (PAHs)	13	Urine	5	5	2856	Nübler et al. (2023)
UV filters	2	Urine	2	1	1975	Esteban López et al. (2021)

[a] For a full list of biomarkers, see Esteban López et al. (2021).
[b] One parameter, but several matrices.
[c] Blood analyses were included in the HBM4EU QA/QC programme, while the final HBM4EU studies only included urine samples.
[d] The HBM4EU studies analysed Cr in red blood cells and plasma. Blood was used as a surrogate in the QA/QC programme, see details in Nübler et al. (2022a).
[e] Not included in the QA/QC programme because of a pre-selected laboratory accredited for these analyses and with prior experience from *DEMOCOPHES*.

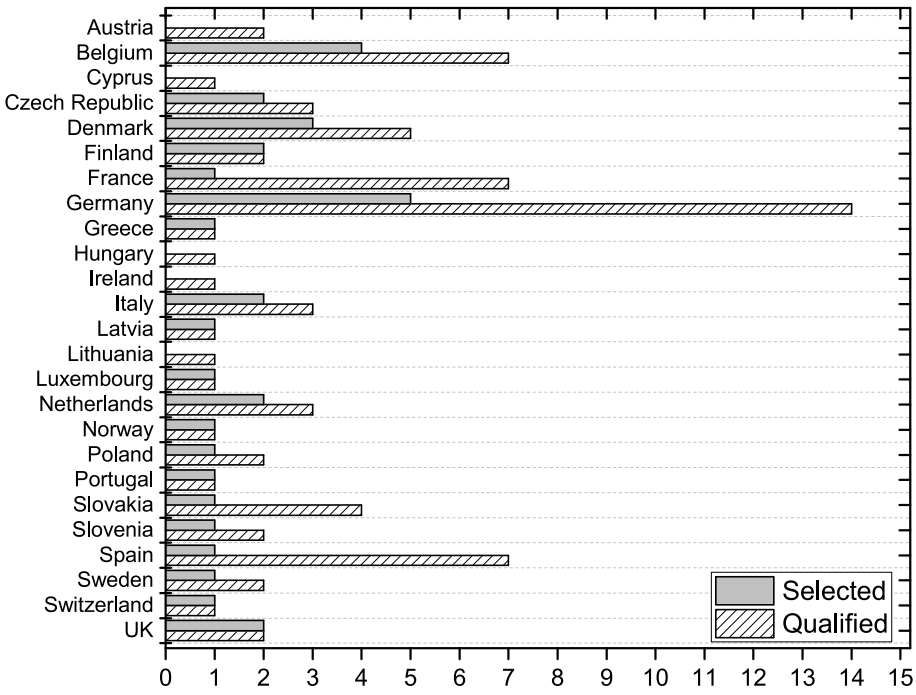


Fig. 4. Number of laboratories from different countries qualified and selected for the chemical analyses in HBM4EU.

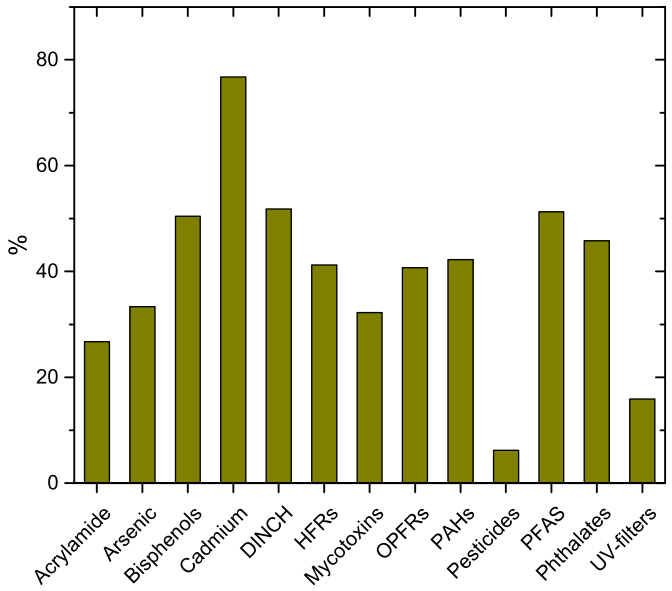


Fig. 5. Percentage of samples for different priority substances analysed by a laboratory of the same country as the sample owner, for the Aligned Studies and the time trend analyses. HFRs: Halogenated flame retardants. OPFRs: Organophosphorous flame retardants. PAHs: Polycyclic aromatic hydrocarbons. PFAS: Per- and polyfluoroalkyl substances.

many aspects of HBM4EU, including the material and data transfer. "Data" in this sense refers to (personal) data associated with the sample material, in contrast to (chemical) data as a result of the chemical analysis.

A detailed guidance document was developed in HBM4EU to ensure that procedures were in compliance with the General Data Protection Regulation (GDPR) of the European Union, also detailing terms and conditions for material transfer. This document contained a Material and Data Transfer Agreement form (Fig. S16 of the Supporting Information), to be completed by providers (sample owners) and recipients (qualified laboratories) and submitted to the ethics coordinator and HBM4EU coordinator (Knudsen et al., 2023). Establishing smooth workflows in this field proved challenging, probably reflective of an adaptation process, also including the translation of documents from national languages to English and vice versa, for example for the occupational exposure studies. An example of the difficulties encountered was the correct, standardized file naming, to ensure systematic entries in the database. Challenges related to ethics and GDPR were further discussed by Knudsen et al. (2023).

The extent of standardization in analytical chemistry is not a new question. As summarized in Table 3 and further discussed in Section 7,

Table 3
Details of analytical methods used by the qualified laboratories in HBM4EU.

Priority substance (group)	Matrix	Sample volume (mL)	LOQ (ng/mL)	Instrumental analysis
Acrylamide	Urine	0.1–2	1–5	LC-MS/MS
Arsenic	Urine	0.7–1	0.1–0.6	ICP-MS
Bisphenols	Urine	0.2–5	0.01–0.7	LC-MS/MS, GC-MS/MS
Cadmium	Urine	0.2–10	0.001–0.5	AAS, ICP-MS
Chromium	Blood, Urine	0.2–5	0.028–2.5	AAS, ICP-MS
DINCH	Urine	0.2–2	0.05–0.7	LC-MS/MS
Halogenated flame retardants	Serum	0.2–5	0.0001–2	GC-MS, GC-MS/MS, GC-HRMS
Mycotoxins	Urine	1–3	0.05–0.5	LC-MS/MS, LC-HRMS/MS
Organophosphorous flame retardants	Urine	0.3–5	0.02–0.5	LC-MS/MS, GC-MS/MS
Per- and polyfluoroalkyl substances (PFAS)	Serum	0.05–5	0.01–0.5	LC-MS/MS, LC-HRMS/MS
Pesticides	Urine	0.05–5	0.1–0.6	LC-MS/MS, GC-MS/MS
Phthalates	Urine	0.2–5	0.1–3.5	LC-MS/MS
Polycyclic aromatic hydrocarbons (PAHs)	Urine	0.5–11	0.001–6	LC-MS/MS, GC-MS, GC-MS/MS
UV filters	Urine	0.1–1	0.01–0.2	LC-MS/MS

LC: Liquid chromatography. MS: Mass spectrometry. ICP: Inductively coupled plasma. AAS: Atomic absorption spectroscopy. GC: Gas chromatography. HRMS: High resolution mass spectrometry.

different analytical methods were applied in HBM4EU. It is common practice in chemical monitoring programmes that laboratories follow general guidelines (e.g. OSPAR, 2016; EFSA, 2022), but keep some flexibility with regard to specific methods, as long as the quality of the data is ensured. Typically, laboratories document satisfactory performance in their chemical analyses by participation in externally organised proficiency testing schemes, in the same way as the ICIs and EQUAS organised in HBM4EU, and/or the analysis of certified reference materials (Arnaud et al., 2020; Göen et al., 2012a). This approach aims at the harmonization rather than the standardization of analytical methods and was the preferred approach in a multicentre HBM study like HBM4EU.

However, details in the analytical methods might require a higher degree of standardization to ensure comparability, for example the calculation of limits of detection (LODs) and LOQs, the use of either LODs or LOQs as well as the handling of concentrations below LOQs. For many chemicals, exposure levels of the general population are low or cover a relatively large range from low to higher concentrations (Göen et al., 2012b). How LOQs are defined and whether values below LOQs are considered as lower, medium or upper bound concentrations (EU, 2014; 2017), or assigned a different value, can therefore have an impact on the overall exposure level that is reported and assessed.

In addition, variability in LOQs can cause challenges in the comparability and aggregation of results (Table 3). This was experienced in the HBM4EU chromate study, where differences in LOQs in blood analyses of Cr led to considerable differences in detection frequencies between samples analysed in different laboratories (Galea et al., 2021; Ndaw et al., 2022). The variability was mainly a result of differences in the sensitivity of the analytical method, although differences in calculation methods also contributed to it.

5.2. Financial procedures

Since the chemical analyses were conducted in the framework of HBM4EU, an EU Horizon 2020 project, their invoicing followed the overall financial rules of HBM4EU. These were perceived as complex by many of the sample owners and qualified laboratories, especially the rules related to the difference in reimbursement rates between chemical analyses (50%) and other work in HBM4EU (70%). In addition, many laboratories were used to providing a total price for a service, but were now expected to differentiate person months and direct costs for the different chemical analyses. AU and other task leaders received many questions requesting clarifications on these matters. In response, the HBM4EU coordinator took the initiative, in collaboration with the relevant WP and task leaders, to prepare a guidance document that explained the administrative procedures of correct invoicing (Fig. S17 in the Supporting Information). It distinguishes three main cases:

- The sample owner and qualified laboratory are identical (i.e. in-house analysis)
- The qualified laboratory is a partner in HBM4EU
- The qualified laboratory is outside of HBM4EU (i.e subcontracting)

The second case occurred most frequently and was addressed by a budget transfer from the sample owner to the qualified laboratory, as approved by AU as part of the coordination process. However, this held the challenges that a) co-financing was necessary to cover the qualified laboratory's expenses, by either of the two partners, i.e. sample owner or laboratory, or another source, and b) a budget had to be allocated to the sample owner before the actual costs of analyses were known, as this information was collected as part of the analytical phase (Fig. 3). In order to work with realistic estimates, a survey was conducted in the first year of HBM4EU, to collect preliminary information on prices for chemical analyses. This led to a situation where some qualified laboratories felt that they were providing the same type of information repeatedly during the course of HBM4EU.

Clarifying the situation about invoicing and co-financing resulted in some delays in starting the chemical analyses, due to a combination of factors. The problems had to be understood in detail, several partners with leading functions in HBM4EU had to be involved, and a specific guidance document had to be prepared. Given the importance of this document, it passed several rounds of comments and adjustments, prior to broader communication to the sample owners and qualified laboratories.

5.3. Non-qualified laboratories

Although the prerequisite of passing the QA/QC programme to be eligible for analyses in HBM4EU and the associated criteria were clearly communicated at all levels of HBM4EU, a few analyses during HBM4EU were conducted by non-qualified laboratories (Table 4). These were usually laboratories that were qualified for other analyses in HBM4EU, possibly analysing the same samples for other priority substances, and adding more biomarkers from a cost-benefit perspective. Thus, these analyses were usually an "add-on" and did not result in a loss of information. As documented in Table 4, this was limited to very few analyses in the overall project, accounting for 2.4% of all analyses. Therefore, the main challenge was related to noticing this issue and communicating it efficiently to the downstream process (Fig. 1). These data were flagged as not quality assured through the HBM4EU QA/QC programme and disregarded in the calculations of European exposure values and geographical comparisons, as detailed by Govarts et al. (2023). This is different from the case of pre-HBM4EU data, for example for the time trend analyses, which were included if evaluated as being of acceptable quality. This was the case if the laboratory qualified in the HBM4EU QA/QC programme using the same method and documented continuous internal QA/QC measures (Govarts et al., 2023).

Furthermore, some biomarkers were novel and/or used on a more exploratory basis. In these cases, they were not covered by the full QA/QC programme and some pragmatic approaches had to be chosen to ensure analytical quality and comparability. This was the case for chromium analyses in exhaled breath condensate in the occupational studies, for which a small interlaboratory comparison was performed among the laboratories involved in these analyses (Leese et al., 2023).

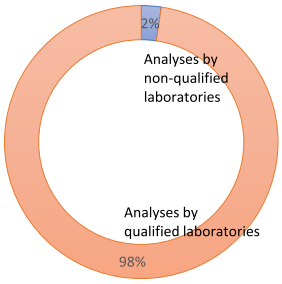
5.4. Capacity loss during the Covid-19 pandemic

The Covid-19 pandemic affected all partners in HBM4EU and caused delays in all project-related activities, in particular in sampling campaigns and laboratory work. Most research institutions and laboratories were shut down in spring 2020 and resumed work with varying capacity at different time points. However, as only few laboratories returned to full capacity immediately and all had to catch up with analyses that had been postponed in spring 2020, delays expanded. This situation required frequent contacts to sample owners and laboratories, to stay up-to-date with developments in each country and each laboratory and institution and to assess the implications for the overall work plan in HBM4EU. As Covid-19 countermeasures varied for each country and over time, these contacts and regular updates resulted in substantial additional work, which had not been foreseen in the planning of the analytical phase.

In addition to the regular progress reports, AU prepared "corona crises analysis" tables for the information of leaders in HBM4EU as well as the HBM4EU Management and Governing Boards. It soon became apparent that the Covid-19 related delays would have effects on the completion of the overall projects, as analytical results would be available later than anticipated. Based on updated information on the progress of the analytical phase, and on developments in the Covid-19 related effects on laboratory capacity, the HBM4EU Governing Board opted for a six months' extension of HBM4EU.

Table 4
Summary of analyses conducted by non-qualified laboratories during HBM4EU.

Study	Study group	Priority substances	Matrix	Analyses
HBM4EU Aligned Studies	Teenagers	PFAS[a]	Serum	300
	Teenagers	Arsenic	Urine	300
	Adults	Mycotoxins	Urine	200
Comparison of different time points, including *DEMOCOPHES* samples	Adults	OPFRs[b]	Urine	94
	Children	OPFRs[b]	Urine	99



[a] PFAS: Per- and polyfluoroalkyl substances
[b] OPFRs: Organophosphorous flame retardants

6. Lessons learnt

In general, the lessons learnt are connected to the fact that HBM4EU was a very large and ambitious project whose partners had different points of departures, in terms of previous experience. Reaching the stage of a harmonized and standardized HBM initiative across Europe was an ambitious goal and an achievement in itself.

6.1. Time buffers

Despite many years of experience in the field, a risk remains of underestimating the time required to implement certain steps in a new project. The size and diversity of HBM4EU amplified these usual time requirements. Changing established routines or building up new workflows in standardization attempts was more difficult and time-consuming than expected. It is an obvious and slightly banal lesson that time estimates should be conservative, including buffers that also allow newcomers in the field to catch up with experienced partners. However, it remains challenging to implement more generous timelines while keeping up with the rapid international development in research and monitoring, including ambitions of leading the development in some fields, as well as responding to urgent data needs for risk assessment and regulatory purposes.

6.2. Administrative guidance

The administrative and financial side of the analytical phase in HBM4EU was generally considered complex. To avoid confusions and delays, guidance should be developed and provided a priori. A help desk function was included in the WP for QA/QC and chemical analyses, which would probably benefit from an administrative counterpart, preferably staffed with administrative and financial experts rather than scientists. In general, the categorization of activities with different internal funding rates should be avoided. A uniform funding rate would have precluded the substantial additional administrative effort experienced in HBM4EU (Kolossa-Gehring et al., 2023).

6.3. Standardization

In addition to the standardized procedures around ethics and the standardization of technical elements such as LOQs, the coordination of the analytical phase could also be developed towards more standardization, provided that the HBM programme has a more permanent structure. While the same forms were used for regular updates in the phase connecting the sample owners and qualified laboratories (Fig. 3), also providing recognizability for the recipients, the monitoring of the chemical analyses was still mainly based on one-to-one correspondence. This was useful in the establishment of HBM4EU, but could be replaced by more standardized forms in a long-term perspective. Similarly, while progress reports had a recognizable format, they were prepared at varying intervals and would benefit from more regularity, perhaps aligned with HBM4EU Management Board meetings. Flexibility in the communication will still be important, to allow discussions of partner-specific questions and concerns, but developments towards SOPs in the coordination of the chemical analyses could be an option.

6.4. Connection to ethics

Although not included in the original concept (Fig. 1), it proved useful and efficient to collaborate with the ethics coordinator and to assist with the filing of Material and Data Transfer Agreements. As coordinator of the analytical phase, AU was in regular contact with sample owners and qualified laboratories and could use these communication channels to follow up on information required elsewhere in HBM4EU. In general, it is worth considering how to focus the communication, so partners do not feel that they receive uncoordinated and potentially duplicate requests. Shared sites for document exchange and communication could be an improvement to e-mail-based communication. It will be important to optimize communication both between different parts of the project and over time.

6.5. Capacity building

During HBM4EU, an increasing number of laboratories participated in the HBM4EU QA/QC scheme and obtained satisfactory results, documenting an increase in the HBM analytical capacity in Europe (Esteban López et al., 2021). However, approximately one third of the chemical analyses were conducted by only three European laboratories, leaving room for a wider implementation of high-quality HBM analyses. This extension may require a first analysis of existing obstacles. Training activities were included in HBM4EU (Kolossa-Gehring et al., 2023), but would benefit from more continuous and focused initiatives to improve technical capabilities and overcome potential obstacles. Capacity building could be linked to a set of minimum performance criteria for an HBM programme, including satisfactory results in regular proficiency testing and sufficiently low LOQs to avoid discrepancies in detection frequencies.

7. A network of laboratories – discussion of the HBM4EU experience

Different strategies exist for chemical analyses in HBM programmes around the world. In the US National Health and Nutrition Examination Survey (NHANES), for example, the analyses are centralised at the Environmental Health Laboratory of the Centers for Disease Control and Prevention (CDC) (CDC, 2022). HBM4EU has chosen a decentralized approach in its analytical phase, reflecting the European diversity as well as the wish to build transnational capacity in the field of HBM

analyses. In addition, an unprecedented high number of analyses had to be completed in a relatively short time frame, which was not possible for a single laboratory. Obviously, this strategy required a higher degree of coordination, in addition to the QA/QC programme, to ensure high-quality and comparable results as well as administrative clarity. However, many of the coordination efforts were related to the fact that HBM4EU was new and to the unexpected challenges of Covid-19 during the analytical phase. As discussed in Section 6, communication between partners could be more streamlined in an established and more permanent programme. This would reduce the correspondence that was necessary in coordinating the chemical analyses in HBM4EU.

Regarding efficiency, the network of laboratories carrying out the chemical analyses in HBM4EU has advantages and disadvantages. Laboratories that had successfully participated in the HBM4EU QA/QC programme could start the chemical analyses immediately without further method development. Distributing the work amongst several expert laboratories, according to their reported capacities, increased efficiency. On the other hand, the data analysis in HBM4EU was dependent on complete datasets, meaning that potential delays in one single laboratory carried the risk of delaying the whole downstream data analysis process. The interlinkages and inter-dependencies might need stronger emphasis in the communication with the participating laboratories. However, the different timelines between laboratories were also related to the upstream processes, which provided samples from the HBM4EU Aligned Studies at different points in the HBM4EU project.

The fact that HBM4EU only needed a six months' extension to complete its work plan, including the chemical analyses, indicates a robust design and an efficient steering that was not severely affected by Covid-19 restrictions. After the first wave in spring 2020, Covid-19 countermeasures began to vary between countries and over time, ranging from temporary lockdowns to near-normal work routines. This diversity made the decentralized analytical strategy more robust than the concentration on few expert laboratories would have been. Some progress was always possible with the chemical analyses, and the close contact between laboratories, sample owners and the coordinators for the analytical phase ensured regular updates and individually optimized solutions.

For some of the priority substances, a variety of methods was applied by the 75 laboratories qualified for the chemical analyses in HBM4EU (Table 3). Most suitable analytical methods had been discussed and recommended in HBM4EU (Vorkamp et al., 2021), but the laboratories were free to use a method of their choice provided it had generated satisfactory results in the HBM4EU QA/QC programme (Esteban López et al., 2021). This diversity of methods increased robustness and might also favour methodological developments as different methods are tested and optimized. In addition, it has a strong capacity building component since laboratories can learn from each-other and implement procedures needed for chemical monitoring. Laboratories with less experience in HBM analyses were given the opportunity to establish and improve their analytical capabilities. However, some method standardization may be advisable, for example in terms of minimum performance criteria, as discussed in Section 5. Furthermore, the harmonization of different methods requires external QC, in terms of regular proficiency testing exercises and certified reference materials. Given the large number of compounds and laboratories, this is a considerable effort, but with the obvious benefit of creating long-term structures for coordinated and harmonized HBM chemical analyses in Europe.

8. Conclusions and outlook

The analytical phase in HBM4EU included a large number of participants in terms of sample owners (providing samples to the HBM4EU Aligned Studies from national and regional cohorts and collections) and laboratories having passed a comprehensive QA/QC scheme to qualify for chemical analyses in HBM4EU. This required a high degree of coordination, also ensuring connections to upstream and downstream processes in HBM4EU, i.e. the preparation of the analytical phase and the data treatment, respectively. A central coordination point was essential in HBM4EU, also regarding the unexpected challenge of managing consequences of Covid-19 measures. Given the novelty and complexity of the HBM4EU project, it initially operated largely on an individualized communication basis. There is potential to further develop streamlining and standardization of the coordination process in a long-term and consolidated programme, in close collaboration with experts in administrative, financial, ethical as well as data-related questions.

The decentralized approach of chemical analyses involving a network of laboratories appears to be the best solution for a European HBM programme, generating high-quality and comparable data in a harmonized, efficient and robust framework. It has the potential to be consolidated in a group of national and European reference laboratories in the HBM field. Certain aspects of the chemical analyses, for example LOD and LOQ calculations, would benefit from more standardization, and a set of minimum performance criteria will ensure better comparability between laboratories. Thus, the coordination of the chemical analyses should be linked to general QA/QC questions, as addressed in the HBM4EU QAU. Regular proficiency testing and certified reference materials for HBM are points where more discussion has been initiated to overcome current lacks.

Combining and formalizing the chemistry-related structural elements of HBM4EU, such as the laboratory network, the QA/QC programme, the QAU and the coordination of the chemical analyses, would create a cornerstone of a European HBM programme. These structures should be sufficiently flexible to include possibilities of extensions, towards other chemical substances, novel biomarkers and emerging scientific questions. An obvious extension could be the connection to chemical analyses in exposure media and the environment, as envisaged in the Horizon Europe Partnership for the Assessment of Risks from Chemicals (PARC).

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Appendix A. Supplementary data

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