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A step towards harmonising human biomonitoring study setup on European level: Materials provided and lessons learnt in HBM4EU

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ABSTRACT

Internal exposure of the human body to potentially harmful chemical substances can be assessed by Human Biomonitoring (HBM). HBM can be used to generate conclusive data that may provide an overview of exposure levels in entire or specific population groups. This knowledge can promote the understanding of potential risks of the substances of interest or help monitoring the success of regulatory measures taken on the political level. Study planning and design are key elements of any epidemiologic study to generate reliable data. In the field of HBM, this has been done using differing approaches on various levels of population coverage so far. Comparison and combined usage of the resulting data would contribute to understanding exposure and its factors on a larger scale, however, the differences between studies make this a challenging and somewhat limited endeavour.

This article presents templates for documents that are required to set up an HBM study, thus facilitating the generation of harmonised HBM data as a step towards standardisation of HBM in Europe. They are designed to be modular and adaptable to the specific needs of a single study while emphasising minimum requirements to ensure comparability. It further elaborates on the challenges encountered during the process of creating these documents during the runtime of the European Joint Programme HBM4EU in a multi-national expert team and draws up lessons learnt in the context of knowledge management.

1. Introduction

Human Biomonitoring can be used as an effective tool to measure the body burden of substances in an individual and, if applied in an appropriate study design, provide an overview of the exposure distribution of a population (Angerer et al., 2007). Depending on the set-up,

Abbreviations: CC, Coordinating Centre; COPHES, Consortium to Perform Human Biomonitoring on a European Scale; DEMOCOPHES, Demonstration of a study to Coordinate and Perform Human Biomonitoring on a European Scale; EHES, European Health Examination Survey; ESBIO, Expert Team to Support Biomonitoring in Europe; EU, European Union; GDPR, General Data Protection Regulation; GEP, Good Epidemiological Practise; ISCED, International Standard Classification of Education; HBM, Human Biomonitoring; HBM4EU, European Human Biomonitoring Initiative; PI, Principal Investigator; Q, Questionnaire; SOP, Standard Operating Procedure.

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this can provide policy makers with baseline information to check if existing regulations are effective or if new measures need to be taken as well as to identify new needs related to emerging exposures.

Some European countries already have established national or regional HBM programs, for example Belgium (Schoeters et al., 2012) for the region of Flanders, the Czech Republic (Černá et al., 2017), France (Dereumeaux et al., 2017), Germany (Kolossa-Gehring et al., 2012; Schulz et al., 2007), Spain (Pérez-Gómez et al., 2013), and Italy (Bocca et al., 2010). For a European view on the exposure of humans to harmful chemicals, a fully standardised approach pertaining study design, fieldwork including pre-analytical steps e.g., sampling of human body fluids (e.g. urine, whole blood, plasma), processing of biological samples, storage and transportation as well as data recording and data processing would be ideal. Steps into this direction have already been taken in the past by bringing together European expertise in the field of HBM and advancing a harmonised European HBM approach, e.g. in the projects ESBIO and COPHES/DEMOCOPHES (Den Hond et al., 2015; Joas et al., 2012). So far though, a cohesive regulation to ensure standardised data collection still needs to be developed. That a standardised collection of health-related data in Europe is generally possible can be considered proven by the existence of the European Health Interview Survey (European Commission, Eurostat, 2018).

As previously elaborated (Fiddicke et al., 2021b), developing and performing an HBM study is a complex and challenging task and requires the consideration of a diversity of aspects concerning resources, financial and personnel, as well as time. Even more aspects need to be considered if applied in a European context (Fiddicke et al., 2015), which ultimately requires more resources as well.

This article now presents materials developed in the European Human Biomonitoring Initiative (HBM4EU, www.hbm4eu.eu) to support the harmonisation process of HBM studies concerning basic aspects of study design.

HBM4EU is a joint effort of 30 countries and the European Environment Agency, co-funded by the European Commission. It is aimed at harmonizing procedures and establishing data platforms in the field of HBM by building upon programs carried out or to be carried out in the participating countries with the final goal of supporting policy making (Ganzleben et al., 2017; Kolossa-Gehring et al., 2023, in this issue). Within the initiative, the HBM4EU Aligned Studies are a survey aimed at collecting biological samples and data as harmonised as possible from (national) studies to derive current internal exposure data representative for the European population/citizens across a geographic spread (Gilles et al., 2022). One of the final goals of the initiative is to generate European exposure values (Gilles et al., 2021) and HBM guidance values (Apel et al., 2020). Not to solely rely on post-harmonisation procedures for data harmonisation of the HBM4EU Aligned Studies, HBM4EU made great efforts to provide templates, guidelines and personal support to enable a harmonised approach for new studies initiated. These materials are designed to not just be used during the lifetime of this project, but also to promote the sustainability of the network of national expertise set up through HBM4EU. As such, they may aid the further development of subsequent Europe-wide as well as national studies and through this, continue to contribute to the harmonisation efforts HBM4EU is striving for even after project runtime. The materials aim to strike a balance between being adaptable to the needs of single studies in different (national) settings and meeting minimum requirements for harmonisation. They may further support other studies worldwide that include human participants and aim at producing data comparable to those from HBM4EU as a first step towards standardisation. Detailed aspects of data collection and management, as recommended by Good Epidemiological Practice (GEP) (Hoffmann et al., 2019), are to be discussed elsewhere. This article also reflects on the use of these documents by countries participating in HBM studies and provides lessons learnt from the creation process.

2. Methods

Within the HBM4EU project, one work package was dedicated to provide participating countries with documents to support a harmonised study design and personal assistance regarding aspects of participant recruitment, fieldwork, the collection of biological samples and their preservation, and even ethical issues for the approval of the studies by the corresponding ethics committee. Partners with longstanding experiences in the area of epidemiological studies (Dereumeaux et al., 2017; Kolossa-Gehring et al., 2012; Pérez-Gómez et al., 2013; Schoeters et al., 2012) from several European countries contributed to this work package and supported the development of a broad variety of documents necessary for study conduct. Different working clusters were set up to develop the necessary documents for all steps of an HBM study: Strategies for recruitment and sampling as well as for exchange of human samples, the development of questionnaires and communication with participants comprised the main involved groups. The members of these groups jointly elaborated and reviewed results before feeding the outcome into overall project reports. This process was overseen by the group leaders and an overall lead position coordinating all groups to ensure a joint approach.

To promote capacity building and distribute the outcome, training was offered to interested parties during the first and second HBM4EU Training Schools in 2018. The elaborated documents have also been distributed within the HBM4EU consortium and are freely available in the project's Online Library (https://www.hbm4eu.eu/online-library/).

Due to the high number of different materials, it was considered likely that Principal Investigators (PIs) of the studies involved in the HBM4EU Aligned Studies (Gilles et al., 2021), might require support concerning their usage or application. Therefore, a work plan was set up to offer personal assistance to the studies if requested. The concept was specifically developed to target new studies that were still planning to take biological samples as they would be most likely to use the materials and may require assistance in their application.

It was assumed that any requests coming from the study PI would first have to reach someone capable of providing an answer in that field. Therefore, a flowchart was created (Fig. 1) that involved the respective contact persons in the project for the study PIs as well as the responsible Work Package Leaders to distribute the request. Two different types of requests were identified: a) distinct requests, e.g. a question that could be solved quickly or b) more complex requests that require e.g. an in-depth analysis of the respective study and its characteristics. A distinct request would be responded to directly by the experts involved in document creation on a case-by-case basis. In case of a complex request, a person familiar with the development of the documents would have been proposed as a mentor to accompany the study PI or the respective study more closely, thus offering continuous support.

The eight experts available as "mentors" were from various countries with different native tongues which may facilitate the contact and analysis of study documents which are likely to be provided in the national language.

An assessment of the usage and applicability of the baseline materials HBM4EU developed to support the conduct of HBM studies has been prepared. For this assessment, an online questionnaire was sent electronically to the Principal Investigators of the study (study PIs) of the HBM4EU Aligned Studies in April 2021 to gain insight into the use of the available materials. All responses received were collected and considered for the assessment. The key results are presented later in this article.

3. Results and discussion

This section is split up into three categories: A) Materials developed under HBM4EU to support study setup and conduct, B) the conclusions drawn from a usage survey concerning the developed materials, and C) lessons learnt from the process are drawn to support future endeavours with similar aims.

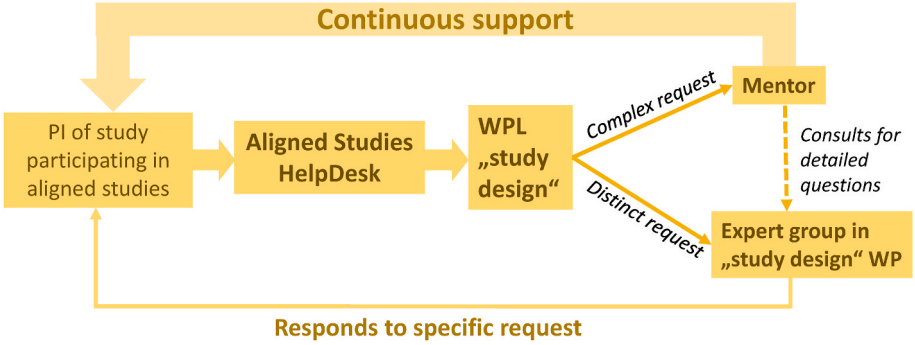

Fig. 1. Workflow of actions for mentorship concerning implementation of harmonised documents.

Table 1
Four classes of developed documents to serve the quality of HBM surveys.

	Class	Description	Related documents available in HBM4EU
1.	**Overarching** documents	Collection of all essential information about the study	Study Protocol; Fieldwork/Operational Manual
2.	**Questionnaires (Q)** and related background documents	Materials aiming to collect individual characteristics of study participants tailored to the study objectives	Basic and specific Q; Non-responder Q; Satisfaction Q; Optional: Risk perception Q; Interviewer Manual
3.	Standard Operating Procedures (**SOPs**)	Instructions that allow for a standardised approach concerning the study design	Selection of participants; Quality Assurance and Quality Control for Recruitment and Fieldwork; Procedure for obtaining human samples; Procedure for the exchange of biological samples
4.	**Communication** material	Material for participants required during recruitment, sampling and for the communication of personal results	Invitation; Information leaflet; Informed consent; Communication of personal results; SOPs for participants

A) Materials developed under HBM4EU to support study setup and conduct

Like any other thoroughly planned epidemiological study (Hoffmann et al., 2019; Swaen et al., 2018), each HBM study requires the replicability of the results and the necessary quality assurance built on a detailed, step-wise and well-documented approach to deliver conclusive results. Furthermore, such multicentre studies including multiple fieldwork teams require a high level of coordination with regard to data record and sampling. Describing all relevant processes in standard operating procedures and making these documents available for use in respective studies is an essential step. The use of standardised documents also supports resource efficiency by providing templates for the often resource-intensive written elements required for HBM studies.

The developed documents in the frame of HBM4EU can be divided into the four categories shown in Table 1. For convenient access, all direct links to the available documents are collected within this paper.

These documents can be adapted to specific needs of a study while maintaining the minimum requirements to ensure comparability. Further elements to conform to the guidelines of Good Epidemiological Practice (GEP) (Hoffmann et al., 2019), national legislation and regulation, as well as ethical and cultural practices may easily be added.

3.1. Overarching documents

Study Protocol and Fieldwork manual collect essential information about the study. Table 2 provides a brief description and the relevant references to the documents developed.

3.1.1. Study protocol

Describing the study characteristics in written format (e.g. hypothesis, objectives, target population, biomarkers, sampling time, recruitment strategy) offers guidance for studies of other research groups (Swaen et al., 2018). For HBM studies, the core elements are participant recruitment and fieldwork, including exposure assessment through questionnaires and sampling, similar to what Hoffmann et al. (2019) described already for epidemiological studies in general.

A systematic approach including the topics described above has already been developed in COPHES (Becker et al., 2014). It demonstrates the striking importance of a study protocol and a common, yet flexible approach in a multi-country setting (Fiddicke et al., 2015).

The concept for a Study Protocol developed under HBM4EU focusses directly on the key characteristics to be considered during the study setup and specifically addresses the different phases of a study. The underlying concept of phases has been described by Fiddicke et al. (2021b).

3.1.2. Fieldwork Manual

Whereas the study protocol gives an outline or overview on the planned study, the Fieldwork Manual (or operational manual) is essentially a very detailed compilation of materials necessary for the execution of the study including all specifically elaborated paper works or information on the devices and procedures that will be implemented (Hoffmann et al., 2019). The HBM4EU Fieldwork Manual template recommends to first provide information on the study and therefore suggests to begin with the Study Protocol.

The aim of this Fieldwork Manual template is to encourage the user to create a complete collection of all information and procedures relevant for the planned study, e.g. the ones described more in detail in the following sections. It can serve both the training of fieldworkers and standardisation of the fieldwork as well as provide a written reference of what exactly was done and how the data were collected, after the

Table 2
Overview of the overarching study design materials developed under HBM4EU to support study setup and conduct.

Type of material	Short description	Direct link
Study Protocol	Basic information on all the aspects related to the study	https://doi.org/10.5281/zenodo.6355476
Fieldwork/ Operational Manual	Detailed information on the study, central compilation of all materials necessary for study conduct	https://doi.org/10.5281/zenodo.6394411

completion of the study. As a compilation of all materials for study conduct, it is also relevant to receive ethical approval depending on the responsible Ethical Committee's requirements.

3.2. Questionnaires

Alongside the chemical analysis of biological samples, well-designed questionnaires are core instruments in an HBM study. The information they deliver are used to adequately characterise the exposure to substances of interest, e.g. exposure factors, the duration, frequency, and pattern of exposure. For the comparison of results between studies the use of reliable, validated and harmonised and, ideally, standardised questionnaires are generally recommended. As the participants are volunteers, the relation between benefit of the study results and burden to the participating individual is a limiting factor (Swaen et al., 2018). In an HBM study, burdens may be connected to the sampling process, but also to questionnaire length and complexity. If new questionnaires are used in a study or new questions are additionally taken up a pilot study to test this new data acquisition should be conducted (Cui et al., 2021; Nieuwenhuijsen, 2005).

The questionnaires' administration format (e.g. self-administered vs. interview, or paper vs. web-based) has great influence on their design and response rate (Van Gelder et al., 2010). In the frame of HBM4EU, questionnaires with different foci have been developed. Those questionnaires designed to gather extensive information about sources of exposure or the sampling process have been designed based on the assumption that they will be administered to a participant in an interview with a trained fieldworker in a pen-and-paper format. Questionnaires to ask the participants for their satisfaction or their risk perception are intended to be self-administered. Table 3 provides an overview of the questionnaires and the supporting Interviewer Manuals developed in HBM4EU that may be used as templates or guidance when setting up standardised HBM studies.

In HBM4EU, prioritised substances (Ougier et al., 2021) have been determined and, due to financial limitations, a selected number of biomarkers of these substances would be investigated in the three age groups defined for the HBM4EU Aligned Studies (6–11 years; 12–19 years and 20–39 years) (Gilles et al., 2021). In line with this, the *HBM4EU basic and substance-specific questionnaires* ask for the participants' basic information in the domains of sociodemographic characteristics, residential environment and home exposures, dietary habits, lifestyles, occupational exposures, and health status. Questions are elaborated to cover specific areas of interest concerning the selected substances and have been adjusted to fit the needs of the different age groups.

Documenting details about the biological sample itself, e.g. the time of collection, is an important aspect of quality assurance in epidemiological studies in general (Holland et al., 2003). In the context of HBM, it can also be useful to gather information on behavioural aspects of the sample-donating individual around the time of sampling that may influence the information content of the sample. For this purpose, specific questionnaires to accompany the sampling process have been developed. As they differ depending on the type of biological sample taken, these have been titled *matrix-specific questionnaires*.

The inclusion of questions into questionnaires such as the ones named above is generally accompanied by a scientific justification, e.g. it serves to reveal the exposure sources and exposure-related factors. In case questionnaires are applied in an interview, additional instructions can be given regarding the way a question needs to be answered or explanations for answer categories could be provided. This information can be gathered in an *Interviewer Manual* as has been done for the questionnaires mentioned above.

In the setting of HBM, the aim is often to gather data representative for a population. To be able to extrapolate the results of the study to the target population, it is important to know if there are systematic differences between those randomly selected individuals who agree to

Table 3
Overview of the template questionnaires and supporting materials developed under HBM4EU to support study setup and conduct.

Type of material	Short description	Direct link
Basic and specific Questionnaire	Information on sources of exposure to prioritised substances. Prepared for administration in an interview in pen-and-paper-format	• 1st priority substances: https://doi.org/10.5281/zenodo.6414615 • 1st priority substances for children (6–11 years): https://doi.org/10.5281/zenodo.6534565 • 1st priority substances for adolescents (12–15 years): https://doi.org/10.5281/zenodo.6534668 • 1st priority substances for adolescents (16–19 years): https://doi.org/10.5281/zenodo.6535128 • 1st priority substances for adolescents (16–19 years) with support from legal guardians: https://doi.org/10.5281/zenodo.6536151 • 2nd priority substances: https://doi.org/10.5281/zenodo.6532526 • 2nd priority substances for children (6–11 years): https://doi.org/10.5281/zenodo.6538050 • 2nd priority substances for adolescents (12–15 years): https://doi.org/10.5281/zenodo.6539341 • 2nd priority substances for adolescents (16–19 years): https://doi.org/10.5281/zenodo.6539362 • 2nd priority substances for adolescents (16–19 years) with support from legal guardians: https://doi.org/10.5281/zenodo.6539388
Matrix-specific (sampling) Questionnaire	Information on the biological samples and sample collection issues. Prepared for administration in an interview in pen-and-paper-format	• 1st priority substances: https://doi.org/10.5281/zenodo.6557231 • 2nd priority substances: https://doi.org/10.5281/zenodo.6557320
Non-responder Questionnaire	Information on those who disagreed to participate (non-responders). Relevant especially for a population representative study	https://doi.org/10.5281/zenodo.6394444
Satisfaction Questionnaire	Information on the satisfaction of the participant with single aspects/instruments of the study. Relevant especially if further studies are likely to be planned	https://doi.org/10.5281/zenodo.6397536
Interviewer Manual	Background, justification and general instructions to all questions (e.g. food gallery, International Standard Classification of Education (ISCED)-Code). To inform participants and support interviewers	• 1st priority substances: https://doi.org/10.5281/zenodo.6557060 • 2nd priority substances: https://doi.org/10.5281/zenodo.6557181 • Matrix-specific questionnaire: https://doi.org/10.5281/zenodo.6557279
Optional: Risk perception Questionnaire	In case the matter of risk perception is intended to be explored alongside an HBM	https://doi.org/10.5281/zenodo.6532464

(*continued on next page*)

Table 3 (*continued*)

Type of material	Short description	Direct link
	study: Information on how participants perceive risks of man-made chemicals in the human body by enquiring the individual's personal views and behaviour concerning chemicals	

participate and those who disagree or refuse (non-responders or non-respondents). For this purpose, a *concept for a non-responder questionnaire in the frame of HBM4EU* has been developed which delivers key points for the setup of a non-responder questionnaire that aims to gather information on potential systematic differences between these groups.

A study that consists of several modules or uses different instruments with the participants, and that might be repeated in following years, is well guided if it also includes a *satisfaction questionnaire*. The HBM4EU template collects information on the satisfaction of the participants with single aspects and instruments of the study, ideally when study results are received, and can contribute to the further improvement of the study concept.

González-Alzaga et al. (2022) describe the process of questionnaire development in HBM4EU and elaborate on the content and purpose of the materials mentioned in this section so far in detail.

In the frame of HBM4EU, also the possibility to combine HBM and health surveys was explored (Tolonen et al., 2022). For health surveys, more extensive health information is needed about the health status and determinants of health. This can be obtained through questionnaires, objective health measurements and/or through record linkage to administrative health records.

In addition to the questionnaires listed above that primarily contribute towards the goal of gathering data for the interpretation of the results coming in from sample analysis in HBM studies, the *Risk Perception questionnaire* offers a different approach: it aims to collect information about the study participants' perception of risks originating from man-made chemicals in the human body. This type of questionnaire has rarely been used in HBM studies. So far, risk perception questionnaires in literature have primarily addressed the public's perceptions of environmental chemicals, but were not focused on perception of chemicals in the human body, as measured through HBM (Keune et al., 2008). Risk communication strategies and risk management strategies increasingly depend on understanding of the public's perceptions. Exploring risk perception of chemicals in the body in the future in a multi-country setting, e.g. in the context of a follow-up HBM initiative or the Eurobarometer, could deliver additional information useful for communication activities.

3.3. Standard operating procedures (SOPs)

Standard Operating Procedures (SOPs) are necessary to ensure a standardised execution of repeated procedures, whether by the same people or different ones (Boogaard and Money, 2008) and are the basis for a solid quality management. In this context, SOPs are necessary for all relevant procedures. In HBM4EU, SOPs are publicly available concerning four topics in the area of fieldwork and recruitment. These are summarised in Table 4 and described in more detail below.

3.3.1. Selection of participants and recruitment

This SOP provides a first overview of aspects to consider when selecting and recruiting potential participants for a study. It includes a description of the general study design and the participants to be involved (age, sample size, target population, etc.), but allows for the flexibility required for recruitment in multi-country HBM settings (Fiddicke et al., 2015). Following recommendations 3.2 and 3.8 (sample size) of GEP (Hoffmann et al., 2019), the SOP informs on possibilities for selecting sampling locations, invitees and how to conduct the recruitment. More detailed considerations for the HBM4EU Aligned Studies concerning this aspect which could also be of general interest in this context were elaborated in detail in one of the project reports (Govarts et al., 2018) and have recently been reported on (Gilles et al., 2021, 2022).

Table 4
Overview of the Standard Operating Procedures (SOPs) developed under HBM4EU to support study setup and conduct.

Type of material	Short description	Direct link
Standard Operating Procedure (SOP): Selection of participants	Description how to select participants and communication with authorities	https://doi.org/10.5281/zenodo.6394043
SOP: Quality Assurance and Quality Control for Recruitment and Fieldwork	Information on procedures for internal (or external) quality assurance measures and checklists	https://doi.org/10.5281/zenodo.6394078
SOP: Procedure for obtaining human samples	Description of all (non-invasive and invasive) procedures for human sampling. This includes general aspects and specific instructions for sampling concerning substances and substance groups from the first round of prioritisation). Also, issues related to the samples' traceability, conservation, transport, reception, etc.	https://doi.org/10.5281/zenodo.6394202
SOP: Procedure for the exchange of biological samples	If biological samples shall be transported or exchanged. Material (and Data) Transfer Agreements (to be signed)	https://doi.org/10.5281/zenodo.6417740

3.3.2. Quality assurance for recruitment and fieldwork

The necessity for quality assurance and control is common for laboratory procedures (Esteban López et al., 2021). Recruitment and fieldwork procedures also require to be quality assured. Information on the planned procedures for internal and/or external quality assurance measures need to be laid down. Checklists provided for the field staff and e.g. for interviewers facilitate the routine check of all procedures. Main documents for quality assurance are the already described Fieldwork Manual and the Interviewer Manual (the latter specifically to train interviewers for face-to-face interviews). A third aim of this SOP is to describe quality control measures – internal (with own staff not engaged in the study itself) and/or external (by a hired organisation or from a different part of the own organisation familiar with quality control) to avoid mistakes as well as to ensure that given standards are followed correctly. External quality control measures are recommended for larger studies.

3.3.3. Obtaining human samples

The collection of human samples is the most crucial procedure for high quality data on exposure levels according to guideline 6 of GEP (Hoffmann et al., 2019). It is part of the pre-analytical phase. Besides the sample collection, this phase involves the handling, aliquoting and conservation, transport and storage of samples until the analysis. This process of collecting human samples needs to be described in detail, including all other procedures of the pre-analytical phase, e.g. the selection of the sampling materials, the storage temperature, additives and pre-treatment as well as quality assurance methods to avoid interfering factors such as sample contamination. A survey among the HBM4EU partners showed that many different approaches have been used in European HBM research with regard to these aspects, particularly the storage temperatures, which can impact the sample integrity, require optimisation and harmonisation (Lermen et al., 2020). Continuous training of the field staff to apply the SOP correctly is necessary to guarantee a high quality of biological sample and data. If samples will be

collected by the participants, respective procedures need to be clearly described (see communication material for participants). Important aspects of the pre-analytical phase for the substance groups of the first HBM4EU prioritisation round (Phthalates, Hexamoll®DINCH, Bisphenols, Flame retardants, PFAS, PAHs, Anilines, and Cadmium & Chromium) have been described in the HBM4EU SOP on the procedure for obtaining human samples.

3.3.4. Procedure for sample exchange/transport

After human samples have been collected and further processed (e.g. aliquoted, cryopreserved), the analysis of the substances of interest takes place. Usually, the analysis will be done by expert laboratories not in close geographical proximity to the collection site. Therefore, a transport and within project consortia an exchange of biological samples is likely. In general, liquid specimens from humans are considered potentially infectious and respective packaging guidelines have to be applied. If the collection of samples is part of a European or international study, an exchange of the samples across country borders might be necessary and customs requirements have to be considered. A high priority is on the ethical and legal aspects as an exchange of samples is always accompanied with an exchange of data that have to meet the objectives of the General Data Protection Regulation (GDPR). Many aspects of sample exchange are in need for a harmonised approach (Lermen et al., 2020). For this reason, HBM4EU provided an SOP for Sample Exchange and ready to use templates for all associated documents (e.g. Material and Data transfer Agreement, Sample Transfer Protocol, Sample Data Transfer Template, Pro Forma Invoice).

3.4. Communication material for participants

Participants are a crucial category of stakeholders in HBM studies, since their willingness to volunteer their time, biological samples, and related personal information ultimately determines the success of the project. For this reason, the engagement of citizens and workers as participants in HBM studies was taken into account in HBM4EU.

Building on valuable experiences from previous European and national projects (Exley et al., 2015; Tolonen et al., 2018) as well as on personal communications with HBM4EU national contact points, guidelines and template materials were prepared. The guidelines support interested parties with the preparation of effective communication materials for participants, with the foremost objective of building trust through transparency and explaining the frame and value of their participation. The template materials were prepared to support recruitment of participants, obtaining their informed consent according to ethical and personal data protection requirements, arranging for quality-assured sampling, and communicating personal results back to each participant at the end of the project. Template materials for children and adolescent participations were also prepared. Table 5 provides a short description of the different types of material and Appendix A Supplementary data (Supplementary Table 1) provides the direct links to the relevant documents.

Table 5
Overview of the groups of communication materials developed under HBM4EU to support study setup and conduct.

Type of material	Short description
Invitation	Personal invitation to participate in the study and materials to support scheduling of appointments
Information leaflet	Short description of main aspects of the study (aims, frame of participant's involvement, data protection issues)
Informed consent	Written documentation that the participant is adequately informed about the frame of her/his participation; Signed proof of unforced consent to participate (ethics and data protection issues)
Communication of personal results	Personalised report of the participant's results and their interpretation to the extent possible
Standard Operating Procedures (SOPs) for participants	Explaining collection of biological samples from participants (e.g. for urine sample)

The template materials were implemented in parallel in different European countries and their use was shown to be effective (Katsonouri et al., in preparation).

B) **Use of provided documents**

All countries contributing to the HBM4EU Aligned Studies were encouraged to adopt and apply the tailored HBM4EU materials, thus following a centrally developed protocol. As the HBM4EU Aligned Studies also include completed studies conducted after 2014 with available biobanked samples and studies that were ongoing, it was not possible for all the participating studies to adopt and apply the HBM4EU materials. Only a few new studies that were in the planning phase could adapt their own materials to HBM4EU materials. The survey launched among the study PIs of the HBM4EU Aligned Studies yielded responses from 16 study PIs from 15 different European countries. According to the responses to the four main questions of the survey (see Table 6), first insights on the use of the provided documents were identified.

The responses received firstly provide hints that all materials were consulted by the respondents, however, not all materials appear to have been used to the same degree. For example, materials on communication with participants and materials on the exchange of human samples were consulted more frequently than the informed consent forms or manuals. Secondly, the respondents appear to have indeed taken the materials into account, but have not adopted their content into their own materials. An explanation for these first indications could be the fact that some of the studies under the HBM4EU Aligned Studies contributed with biobanked samples or were ongoing and thus it was not possible to adapt those materials that are needed early on in a study, e.g. informed consent forms or questionnaires.

When asked to rate the available materials, the overall feedback was very positive. The most common responses were that the document was complete and very useful or that the document was well developed, but some points remain open for improvement. With respect to questionnaires, the respondents indicated sometimes that the complete questionnaire(s) was/were too long.

Additionally, some suggestions were provided for improvement regarding the developed materials. For example, more information was needed concerning the materials on the exchange of human samples such as to who the document should be distributed or on the safety of

Table 6
Questions and answer options of the survey for study PIs regarding usage of HBM4EU study materials (Q = Question; AO = Answer option).

Q 1	Did you consult the [title of the document] for your own study?
Q 2	How was the [title of the document] used?
AO 2a	*The material was integrally adopted for our own study.*
AO 2b	*Our own materials were adapted based on HBM4EU materials.*
AO 2c	*We only consulted the document but did not adopt the content of the materials into our own materials.*
AO 2d	*Others: [free text]*
Q 3	How would you rate the [title of the document]?
AO 3a	*The document was incomplete.*
AO 3b	*The document was well developed but some points remain open for improvement.*
AO 3c	*The document was complete and very useful.*
AO 3d	*Others: [free text]*
Q 4	Do you have suggestions how to complete and/or improve the [title of the document]?

sending associated personal data or that a simplification would be necessary for the Material and associated Data Transfer Agreement. With respect to the communication materials, more infographics were suggested for the chemical factsheets and recommendations on harmonised actions based on levels found in the report of personal results would be appreciated.

These results, although based on a small number of responses, may offer a first round of suggestions that could feed into a further improvement of the developed materials in a follow-up initiative. A detailed analysis of these results can be found in (Fiddicke et al., 2021a).

HBM4EU demonstrated the usefulness of the materials for all kind of HBM related studies, such as occupational surveys (Galea et al., 2021; Santonen et al., 2019), studies on mixtures (Ottenbros et al., 2023, in this issue), feasibility studies on environment and health (Elonheimo et al., 2023) and intervention studies HBM4EU materials served as a blueprint for study specific material and most are also available at https://www.hbm4eu.eu/online-library/.

C) **Overarching considerations and lessons learnt**

Though some countries in Europe already have HBM programs established, and joint European actions have been taken in the past, fully regulated, standardised and sustainable procedures at European level for the planning and conduct of HBM studies that provide comparable data are still missing. This leads to differences between the gathered datasets which can have a negative effect on the possibility of comparing existing data. This might limit their reliability for use as a basis for policy decisions and European Union (EU)-wide regulation of chemicals. Though post-harmonisation may partly be possible, through data clearing and statistical analysis, larger differences in fieldwork and sampling may still have tremendous impact on comparability and can hardly be corrected (Reineke et al., 2019). The national priorities, available resources and legislations currently make it difficult to find a common approach to follow in all countries. The definition of Europe-wide provisions related to human biomonitoring would facilitate the implementation of harmonised HBM studies.

One of the aims of the European Human Biomonitoring Initiative is the establishment of a sustainable foundation for a long-term European Human Biomonitoring that produces comparable data as a basis for legally binding regulatory decisions and the information of citizens. The materials presented in this paper and on the project website have been developed to take the first step towards a more standardised approach at the baseline of HBM data generation: the design of a study. As the materials are provided publicly, they may also be useful also for future studies for any interested party.

The materials introduced above were elaborated by a group of experts whose multi-national knowledge exchange allowed to draw some conclusions regarding the creation and use of these materials in form of the lessons learnt listed below.

Lesson 1 - Meta-level of harmonised materials: not just the content matters, but also the presentation

To keep the threshold of using guidance materials as low as possible, their accessibility and applicability should always be considered when guidelines and templates are set up. They need to be user-friendly, accessible with standard applications and ideally be tested for their usability before publication.

Large documents set up to encompass the harmonisation needs of many different studies should allow the selection of specific criteria depending on the study's requirements (e.g. national needs, specific biomarkers/substances). The setup of questionnaires and generation of variables within data management for the later assessment of results should ideally be a parallel, collaborative process.

Updates of the developed documents with new, relevant findings should be foreseen.

Lesson 2 - Materials and information should match requirements and be available as early as possible

A priori harmonisation is only possible as long as none of the participating parties has started (ideal scenario) or concluded (acceptable scenario) the planning of their study. It also requires the study owners to commit to a joint endeavour. As the studies are often nationally funded, they have to cover national priorities and might have to keep their procedures to discover trends in comparison to previous cycles.

Identifying the correct recipient, their specific needs and the most opportune point in time for establishing contact can prove challenging, especially in a multi-country setting. Determining Principal Investigators (PIs) for relevant studies takes time and effort. At the same time, studies foreseen to be harmonised might already be passing the planning phase or be finished altogether in the participating countries.

A Global Reference Framework for HBM studies as envisioned by Zare Jeddi et al. (2021) could be explored as a central reference point for PIs from different countries and for organisers of overarching, multi-national approaches. As templates and guidelines to be used by all studies should be made available before the studies' planning phase even begins, so they can be adapted according to each study's specific requirements. Such a reference framework for HBM that includes these materials studies could contribute greatly to timely availability while at the same time serve as a platform to announce any necessary updates.

Lesson 3 - Available materials need to be broadly advertised and incentives for creating harmonised or even standardised datasets should be provided

Knowledge about the availability of support and supporting documents in the participating countries is key. At the same time, experts in the field of knowledge management stipulate that mere creation and distribution of knowledge in documents is usually not enough for their good reception in the desired target group and shared knowledge should rather be applied (Choi et al., 2010).

A first step into this direction was taken with a workshop directed at study PIs. In the frame of the HBM4EU training schools, this offered the chance to discuss the documents more in-depth. Ideally, this exercise should have been intensified as it functioned not just as a platform for sharing documents, but also helped to identify and underline a common goal which Leinonen and Bluemink (2008) highlighted as an important aspect for successful knowledge management.

This identification of a common goal ties into another point: A positive effect should be connected to the implementation (or perhaps even a negative effect in case of refusal) of harmonised documents.

Large studies in the field of HBM outside of Europe appear to usually be organised under national governance (Kawamoto et al., 2014; NCHS, 2017; Statistics Canada et al., 2020). In Europe, cross-national initiatives organised and co-funded by the European Commission as a multi-national authority have already taken place (Den Hond et al., 2015; Ganzleben et al., 2017). It could be concluded that this overarching approach in the field of HBM has a dual function: setting the focus on a common goal by setting political frameworks and directions while also offering an incentive by providing co-funding for the additional effort required from each participating country.

Siakas et al. (2010) bring up yet another point in support of the added value of cross-national projects: That diverse cultural values in a team can provide a competitive advantage. However, a project-based approach is usually not a sustainable one and may not provide equal opportunities for all countries to participate. A long-term perspective is needed: The European Health Examination Survey (EHES) was a pilot project that laid the foundation by preparing materials, setting up networks and offering trainings in 2010–2012 already. More than five years later, Tolonen et al. (2018) report that countries conducting a Health Examination Survey quite systematically still make use of the

foundation laid by the pilot project and continuously supported by a Coordination Centre (CC).

In a similar vein, the materials developed in HBM4EU could become a stepping stone to a sustainable and more inclusive cross-border HBM as well. Implementing a continuous coordinating activity, like the EHES CCs, in the frame of e.g. a follow-up program aimed at sustainability could facilitate the approach. This could mark the beginning point of standardisation in the field of HBM, similar to how health-related data is already being collected based on a regulation to ensure standardisation set in place for the European Health Interview Survey (European Commission, Eurostat, 2018) for example.

Outside of the area of fieldwork and general planning, there are other study phases such as the chemical analysis, data analysis as well as storage and biobanking that require a common approach, ideally, standardised procedures. The documents and guidelines presented here comprise just one piece of the overall bouquet of materials and networks developed during the project runtime. More can be found in the project's Online Library (https://www.hbm4eu.eu/online-library/).

4. Conclusions

Of course, it is not possible to answer all questions on different exposures, health risk, and effects in the time frame of a project and there is more to achieving standardised (and even harmonised) studies than mere usage of the same documents. Knowledge management underlines the importance of a common goal as a basis for working together (Leinonen and Bluemink, 2008) while also stressing that knowledge transfer processes need to take place not just horizontally, but also vertically, between different generations (Kalkan, 2006). Both of these aspects can be interpreted as support that a more sustainable approach to the harmonisation and then, ideally, standardisation of HBM study material is necessary in Europe than a single project with a defined end date.

In a potential follow-up program, the above mentioned should be considered for the maintenance, further development and dissemination of the presented documents. The upcoming Partnership for the Assessment of Risks from Chemicals (PARC), briefly introduced by Zare Jeddi et al. (2021), is currently gearing up to take on this challenge.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijheh.2023.114118.

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