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# Towards Harmonized Biobanking for Biomonitoring: A Comparison of Human Biomonitoring-Related and Clinical Biorepositories

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Human biomonitoring (HBM) depends on high-quality human samples to identify status and trends in exposure and ensure comparability of results. In this context, much effort has been put into the development of standardized processes and quality assurance for sampling and chemical analysis, while effects of sample storage and shipment on sample quality have been less thoroughly addressed. To characterize the currently applied storage and shipment procedures within the consortium of the European Human Biomonitoring Initiative (HBM4EU), which aims at harmonization of HBM in Europe, a requirement analysis based on data from an online survey was conducted. In addition, the online survey was addressed to professionals in clinical biobanking represented by members of the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB) to identify the current state-of-the-art in terms of sample storage and shipment. Results of this survey conducted in these two networks were compared to detect processes with potential for optimization and harmonization. In general, many similarities exist in sample storage and shipment procedures applied by ESBB members and HBM4EU partners and many requirements for ensuring sample quality are already met also by HBM4EU partners. Nevertheless, a need for improvement was identified for individual steps in sample storage, shipment, and related data management with potential impact on sample and data quality for HBM purposes. Based on these findings, recommendations for crucial first steps to further strengthen sample quality, and thus foster advancement in HBM on a pan-European level are given.

**Keywords:** biobanking, harmonization, sample quality, standardization, human biomonitoring, HBM4EU

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## Introduction

HUMAN BIOMONITORING, THE ANALYSIS of human samples for exposure to chemicals and/or their metabolites, provides a scientific basis for risk assessment and, if necessary, the derivation of mitigation measures. At a European scale, comparable and reliable data on human exposure from European Union countries are urgently needed. The European Initiative for Human Biomonitoring (HBM4EU) started work on January 1, 2017, to close data gaps on priority environmental pollutants in the European population and to provide sound scientific data as a basis for policy decisions. HBM4EU, co-funded under Horizon 2020, is a joint project of 30 mainly European countries, the European Environment Agency, and the European Commission. One of the aims of the initiative is the harmonization of preanalytical and analytical processes in human biomonitoring (HBM) across Europe and to increase knowledge transfer between scientists, politicians, stakeholders, and the general public.[1–3] Several European countries have been conducting HBM studies during the last decades, whereas such studies are still lacking in others. Since a full characterization of all substances humans are exposed to is not feasible, studies (e.g., from Germany, France, Spain, Czech Republic, Belgium, and Slovenia) have been covering only a selected number of environmental pollutants at the time.[4] Therefore, previous HBM studies differ largely between individual countries pertaining to the target population, questionnaires, matrices, and analytes. First, endeavors toward the harmonization of HBM research across Europe were made in the projects COPHES and DEMOCOPHES.[5,6] For the first time, samples from 120 mother-child pairs were collected in 17 European countries following a consensus protocol describing harmonized sampling and preparation, common questionnaires, and data analysis among others. Six biomarkers (mercury, creatinine, cotinine, cadmium, phthalate metabolites, and bisphenol A)[4] were analyzed according to standardized protocols and strong quality assurance (QA)/quality control (QC) measures. A quality assurance unit (QAU) was set up to guarantee the reliability and comparability of analytical results. The QAU implemented an Inter-laboratory Comparison Investigation and External Quality Assessment Schemes (ICI/EQUAS) program involving reference laboratories from all over the world[5,7]

Biobanking, the short- and long-term storage of human samples under cryogenic conditions, plays a critical role in the preanalytical phase of HBM studies. In contrast to what has long been happening in medical research, where biobanking and related preanalytical processes have been playing an important role for many years, in HBM, the relevance of using standardized biobanking procedures has only been recognized in the last 10 years. Therefore, a transfer of the well-established methods and standards, which are already in place in medical research, would be beneficial for the emerging field of HBM research.

Although several online surveys have been conducted to address missing knowledge on the extent of biobanking in Europe, HBM-specific biobanking activities have not been included so far.[8–10] The HBM4EU initiative comprises important HBM key players in Europe, and hence offers a unique opportunity to gather knowledge on harmonization and optimization needs to improve HBM-related biobanking. In this context, we conducted a requirement analysis regarding sample storage and sample shipment through an online questionnaire addressed to all HBM4EU partners. In addition, the current state-of-the-art methods for sample storage and shipment as applied by professionals in clinical biobanking were assessed by an online questionnaire addressed to members of the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB). ESBB provides a scientific network to advance *BIOSHARING* for a better world through mobilizing, inspiring, and educating the biobank community across Europe, Middle Eastern, and Africa. ESBB is open for everyone interested in all aspects of biobanking and biopreservation of biological resources (human, animal, plant, microbial, and environmental), including biobank management, QA and preanalytics, automation, IT solutions, research and innovation, education, ethical, legal, regulatory, and social issues. Members represent the full spectrum of individuals, academic institutions, and companies, whereas a substantial part of members represents clinical-related biorepositories (ESBB; www.esbb.org). Results of these surveys were used to develop a strategy document for human sample exchange between partners as a deliverable of the HBM4EU project. In this study, we present and discuss the main findings of this HBM4EU deliverable report D7.2 Strategy and Standard Operating Procedures (SOPs) for human sample exchange, including ethical demands.[11] To the best of our knowledge, a comparison of practices applied in HBM-related and clinical biorepositories was not reported so far. Besides offering insights into differences and similarities, our results may provide ideas and opportunities for harmonizing and optimizing processes in the emerging field of biobanking for HBM purposes.

## Materials and Methods

### *Survey design*

A cross-sectional online survey was developed on the web-based platform LimeSurvey. The survey was accessible through a link to the online platform for HBM4EU partners and ESBB members. The cover page of the survey stated the context of the study, asked for participant's consent to the use of the supplied responses, and confirmed anonymous treatment of participant's responses. A link to the HBM4EU survey website was disseminated by email to HBM4EU partners by the National Hub Contact Point (NHCP) with a short description of the purpose of the survey, instructions to forward the link to any HBM4EU repository contact not yet addressed, and a deadline for completing the survey within a period of 3 months. A link to the ESBB survey website was distributed through email to ESBB members by the ESBB office, with the same instructions as in the case of the HBM4EU survey. HBM4EU partners and ESBB members were asked to forward the email specifically to the person responsible for the operation of the respective biobank.

The survey consisted of 28 closed-form questions in either single-choice (SC) or multiple-response (MR) form, with most questions additionally allowing an open-form (OF) answer by choosing the option ''other'' and filling in free-form text. The survey was structured into six blocks representing the following topics: Biorepository Background, Legal and Ethical Considerations, Sample Types and Aspects of Sample Storage, Sample Shipment, Data Management, and Quality Management.

The survey addressed to HBM4EU partners was identical to the survey for ESBB members, except for the omission of the block on Biorepository Background, which had already been included in a previous survey (HBM4EU Task 7.1 survey) completed by 43 biobanks participating in HBM4EU.[12] The previous survey was carried out from March to the end of May 2017, the HBM4EU and ESBB surveys were open from September to the end of November 2017. As the study aimed to identify the status quo of HBM-related biobanks and to compare it with the current state-of-the-art in biobanking of ESBB members, the block on Sample Types and Aspects of Sample Storage focused on the five matrices most relevant in HBM research (whole blood, plasma, serum, 24-hour urine, and spot urine). Within this block, questions about storage conditions (temperature, containers, and duration) were asked once per individual matrix the participants had stated to store.

### *Data analysis*

Answers to the survey questions were exported in csv format and read into R (version 3.2.3) for further analysis. Survey results are presented in the results section in tabular form ordered by question blocks. For each question, the type of question (SC, MR, or OF) and the total number of survey participants the question was presented to are noted in the table header. The ratio and percentage (in brackets) of survey participants choosing a given answer are shown in the body of the table. The number of survey participants not providing an answer to a given question is noted under the answer option ''no answer.''

## Results

The following sections detail the results extracted from the survey responses. The first section describes completion rates of the survey and the subsequent sections detail the results of the individual question blocks the surveys were composed of.

### *Completion rate*

Forty-five responses of distinct biobanks were received from HBM4EU partners, out of which 36 were considered valid (seven responses contained answers to less than 30% of the survey questions and two responders did not agree to anonymize publication of their supplied data). The 36 valid responses answered at least 60% of the survey questions (mean completion rate: 83%). Thirty-two out of the 36 valid responses were supplied by biobanks that had already participated in the previous HBM4EU Task 7.1 survey.[12] The remaining four responses came from HBM4EU-partnered biobanks that had not been reached by the previous survey.

Twenty-nine responses of distinct biobanks were received from ESBB members, out of which 28 were valid (one responder did not agree to anonymize publication of their supplied data). The 28 valid responses answered at least 70% of the survey questions (mean completion rate: 92%) (Table 1).

### *Biorepository background*

Responses to the surveys indicate that the majority of both, biorepositories of HBM4EU and biorepositories of ESBB members who filled in the questionnaire, are hosted by public institutions (Table 2, Q1). HBM-related biorepositories identified by this survey are mostly operating within research institutes, whereas most biorepositories for clinical purposes are based in hospitals, universities, or research institutes (Table 2, Q2). The majority of HBM4EU repositories are operated as a single and individual repository, whereas ESBB members reported to operate mostly centralized biorepositories that store samples from multiple independent projects (Table 2, Q3). The host institution is most commonly offering not only biobanking services but also offers related processes and services ranging from sampling, sample processing, and biobanking to the analysis of samples (Table 2, Q4). A major difference between ESBB and HBM4EU biorepositories is the target population. Based on the aim to reveal the actual exposure and its effects on human health, HBM4EU responses clearly focus on the general population. In contrast, biorepositories of ESBB members participating in the survey mainly target samples from patients or clinical cohorts (Table 2, Q5). As a consequence, the design of their studies also revealed differences. While HBM studies mostly follow a cross-sectional or longitudinal study design, in clinical biorepositories case–control, case-only, and clinical trial studies are equally well represented (Table 2, Q6). Only a very small number of HBM4EU partner biorepositories were members of a biobanking society, for example, of the ESBB and the International Society for Biological and Environmental Repositories (ISBER), or participated in the Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium (BBMRI-ERIC). To gain insight in clinical biobanking, we addressed the questionnaire to ESBB members. In addition to ESBB, some of the biorepositories responded to also be a member of ISBER and/or BBMRI-ERIC (Table 2, Q7).

### *Legal and ethical considerations*

The use of human samples for research purposes postulates the prior informed consent of the sample donor. This can be

Table 1. Overview of Survey Participation

| | *HBM4EU Task 7.1 survey* | *HBM4EU survey* | *ESBB survey* |
|---|---|---|---|
| Number of responses | 43 | 45 | 29 |
| Insufficient answers (<30% of questions answered) | 0 | 7 | 0 |
| Agreement to publication of data lacking | 0 | 2 | 1 |
| Valid responses | 43 | 36 (32/36 biobanks also surveyed by Task 7.1) | 28 |

ESBB, European, Middle Eastern and African Society for Biopreservation and Biobanking; HBM4EU, European Human Biomonitoring Initiative.

Table 2. Biorepository Background

| | *Type of institution* | |
|---|---|---|
| *Q1—SC* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Public | 34/35 (97%) | 24/28 (86%) |
| Private | 1/35 (3%) | 4/28 (14%) |
| Other | 0/35 (0%) | 0/28 (0%) |
| No answer | 1 | 0 |
| | *Host institution of the biorepository* | |
| *Q2—MR* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Hospital | 5/36 (14%) | **13/28 (46%)** |
| University | 6/36 (17%) | 10/28 (36%) |
| Research institute | **20/36 (56%)** | **13/28 (46%)** |
| Patient's association | 0/36 (0%) | 0/28 (0%) |
| Company | 1/36 (3%) | 2/28 (7%) |
| Other | 8/36 (22%) | 1/28 (4%) |
| | *Organizational format* | |
| *Q3—SC* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Single individual biorepository | **23/33 (70%)** | 4/28 (14%) |
| Centralized biorepository (storing samples from multiple independent projects) | 8/33 (24%) | **21/28 (75%)** |
| Other | 2/33 (6%) | 3/28 (11%) |
| No answer | 3 | 0 |
| | *Carried out activities at the facility/biorepository* | |
| *Q4—MR* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Sample collection | 30/35 (86%) | 23/28 (82%) |
| Sample preparation | 26/35 (74%) | 25/28 (89%) |
| Storage | 34/35 (97%) | 28/28 (100%) |
| Sample shipment | 24/35 (69%) | 25/28 (89%) |
| Analysis | 25/35 (71%) | 18/28 (64%) |
| Other | 3/35 (9%) | 4/28 (14%) |
| No answer | 1 | 0 |
| | *Target population of studies from which samples are stored* | |
| *Q5—MR* | *HBM4EU (n = 43, previous survey)* | *ESBB (n = 28)* |
| General population | **42/43 (98%)** | 11/28 (39%) |
| Clinical population | 3/43 (7%) | **23/28 (82%)** |
| Other | 5/43 (12%) | 3/28 (11%) |
| | *Design of studies from which samples are stored* | |
| *Q6—MR* | *HBM4EU (n = 43, previous survey)* | *ESBB (n = 28)* |
| Cross-sectional | **17/42 (40%)** | 12/28 (43%) |
| Longitudinal | **24/42 (57%)** | 17/28 (61%) |
| Case–control | 5/42 (12%) | **10/28 (36%)** |
| Case-only | 0/42 (0%) | **13/28 (46%)** |
| Clinical trial | 0/42 (0%) | **9/28 (32%)** |
| Other | 5/42 (12%) | 6/28 (21%) |
| No answer | 1 | 0 |
| | *Is your institution a registered member of a biobanking society or infrastructure?* | |
| *Q7—MR* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| ESBB | 2/36 (6%) | **26/28 (93%)** |
| BBMRI-ERIC | 3/36 (8%) | **10/28 (36%)** |
| ISBER | 2/36 (6%) | **10/28 (36%)** |
| Other | 3/36 (8%) | 5/28 (18%) |
| None | **29/36 (81%)** | 0/28 (0%) |

Presented are the type of question (SC; MR), the total number of survey participants, as well as ratio and percentage (in brackets) of survey participants choosing a given answer. The number of survey participants not providing an answer is noted under ''no answer.''

The information marked in bold is the most relevant result.

BBMRI-ERIC, the Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium; ISBER, International Society for Biological and Environmental Repositories; MR, multiple response question; SC, single choice question.

Table 3. Legal and Ethical Considerations

| | *Type of broad consent* | |
|---|---|---|
| *Q1—MR* | *HBM4EU (n=43, previous survey)* | *ESBB (n=28)* |
| No broad consent | **17/43 (40%)** | 4/27 (15%) |
| Written informed consent | **25/43 (58%)** | **22/27 (81%)** |
| Parents' written consent | 17/43 (40%) | 10/27 (37%) |
| Oral consent | 1/43 (2%) | 2/27 (7%) |
| Other | 0/43 (0%) | 5/27 (19%) |
| No answer | 0 | 1 |
| | *Type of specific consent* | |
| *Q2—MR* | *HBM4EU (n=43, previous survey)* | *ESBB (n=28)* |
| No specific consent | 18/43 (42%) | 8/25 (32%) |
| Written informed consent | 24/43 (56%) | 15/25 (60%) |
| Parents' written consent | 15/43 (35%) | 5/25 (20%) |
| Oral consent | 0/43 (0%) | 1/25 (4%) |
| Other | 0/43 (0%) | 5/25 (20%) |
| No answer | 0 | 3 |
| | *Which of the following documents are available* | |
| *Q3—MR* | *HBM4EU (n=43, previous survey)* | *ESBB (n=28)* |
| Ethics approval | 42/43 (98%) | 24/28 (86%) |
| Informed consent | 42/43 (98%) | 24/28 (86%) |
| Data protection approval | **0/43 (0%)** | 16/28 (57%) |
| Biobank approval | **0/43 (0%)** | 19/28 (68%) |
| Material transfer agreement | 20/43 (47%) | **23/28 (82%)** |
| Other | 0/43 (0%) | 7/28 (25%) |
| | *Are terms and conditions for authorized sample usage defined in an MTA?* | |
| *Q4—SC* | *HBM4EU (n=36)* | *ESBB (n=28)* |
| No | 11/32 (34%) | 2/27 (7%) |
| Yes | **17/32 (53%)** | **22/27 (81%)** |
| Other | 4/32 (13%) | 3/27 (11%) |
| No answer | 4 | 1 |

Presented are the type of question (SC; MR), the total number of survey participants, as well as ratio and percentage (in brackets) of survey participants choosing a given answer. The number of survey participants not providing an answer is noted under "no answer."
The information marked in bold is the most relevant result.
MTA, Material Transfer Agreement.

either specific and allow only the use of samples for a well-defined set of analysis or can be broad to allow sample usage for a much wider range of analyses, even for such analysis not directly affiliated with the original research question. Results of our survey indicate specific and broad consents to be applied in HBM as well as in medical research. Currently, broad consents seem to be the preferred consent type used by ESBB-affiliated biorepositories (Table 3, Q1, Q2). We further asked which legal and ethical documents are available for the collections. Nearly all ESBB-registered biorepositories reported to have ethical approval forms (86%), informed consent forms (86%), and Material Transfer Agreements (MTAs, 82%), as well as data protection (57%) and biobank approvals (68%) available for the majority of collections. In medical research, MTAs are well-established tools to ensure legally approved sample exchange, as our results confirm (Table 3, Q4). However, only 47% of biorepositories of the HBM4EU consortium reported the use of MTAs. Data protection as well as biobank approvals were also lacking (Table 3, Q3).

### *Sample types and aspects of sample storage*

*Sample types.* Since whole blood, plasma, serum, 24-hour urine, and spot urine are often used sample types in HBM, the block on technical storage aspects focused on these sample types. Interestingly, besides collecting other sample types (like e.g., cell isolates, cell lines, and tissues), HBM-relevant sample types have also been collected by surveyed biorepositories in the ESBB community (Table 4, Q1). Furthermore, these samples are usually stored by ESBB biorepositories using similar supplements as HBM4EU biorepositories (EDTA or Na/Li-Heparin for whole blood and plasma samples, no supplement added to serum and urine samples, data not shown).

*Storage infrastructure.* Both surveyed groups still use a wide variety of sample containers (Table 4, Q3). However, not all containers are suited for cryopreservation of samples using liquid nitrogen (LIN) as the cooling agent. Therefore, the use of specific container types indicates widespread sample storage at temperatures above −130°C. In clinical

Table 4. Sample Types and Aspects of Sample Storage

| | *What type of biological samples/matrix do you store?* | |
|---|---|---|
| *Q1—MR* | *HBM4EU* (n = *36*) | *ESBB* (n = *28*) |
| Whole blood | 24/34 (71%) | 16/26 (62%) |
| Plasma | 24/34 (71%) | 21/26 (81%) |
| Serum | 21/34 (62%) | 19/26 (73%) |
| Urine (24 hours) | 8/34 (24%) | 11/26 (42%) |
| Urine (spot sample) | 23/34 (68%) | 9/26 (35%) |
| Other | 11/34 (32%) | 20/26 (77%) |
| No answer | 2 | 2 |
| | *How long are your samples stored?* | |
| *Q2—MR* | *HBM4EU* (n = *36*) | *ESBB* (n = *28*) |
| No storage | 0/35 (0%) | 1/27 (4%) |
| Short-term storage | 10/35 (29%) | 7/27 (26%) |
| Long-term storage | 33/35 (94%) | 26/27 (96%) |
| Other | 1/35 (3%) | 1/27 (4%) |
| No answer | 1 | 1 |
| | *What type(s) of sample container(s) do you use? (only shown to participants storing HBM-relevant samples)* | |
| *Q3—MR* | *HBM4EU* (n = *34*) | *ESBB* (n = *21*) |
| Cryo-vials | 13/32 (41%) | **15/20 (75%)** |
| Falcon/Corning tubes | 10/32 (31%) | 3/20 (15%) |
| Glass tubes/vials | 4/32 (13%) | 1/20 (5%) |
| Plates | 1/32 (3%) | 0/20 (0%) |
| Plastic bags/containers | 3/32 (9%) | 0/20 (0%) |
| Sterile containers | 6/32 (19%) | 5/20 (25%) |
| Straws | 0/32 (0%) | 2/20 (10%) |
| Tubes of type Eppendorf | 8/32 (25%) | 2/20 (10%) |
| Vacutainer | 8/32 (25%) | 5/20 (25%) |
| Other | 5/32 (16%) | 6/20 (30%) |
| No answer | 2 | 1 |
| | *At what temperature are samples stored for short-term storage? (only shown to participants short-term storing HBM-relevant samples)* | |
| *Q4—MR* | *HBM4EU* (n = *25*) | *ESBB* (n = *16*) |
| Not applicable | 4/25 (16%) | 1/16 (6%) |
| Room temperature | 1/25 (4%) | 2/16 (12%) |
| Refrigerator +4°C | **5/25 (20%)** | 3/16 (19%) |
| Freezer −20°C | **13/25 (52%)** | **5/16 (31%)** |
| Freezer −80°C | **9/25 (36%)** | **13/16 (81%)** |
| LIN, gas phase | 0/25 (0%) | **4/16 (25%)** |
| LIN, liquid phase | 1/25 (4%) | 1/16 (6%) |
| Other | 1/25 (4%) | 1/16 (6%) |
| | *At what temperature are samples stored for long-term storage? (only shown to participants long-term storing HBM-relevant samples)* | |
| *Q5—MR* | *HBM4EU* (n = *32*) | *ESBB* (n = *16*) |
| Not applicable | 0/32 (0%) | 1/16 (6%) |
| Room temperature | 0/32 (0%) | 0/16 (0%) |
| Refrigerator +4°C | 0/32 (0%) | 0/16 (0%) |
| Freezer −20°C | **12/32 (38%)** | 2/16 (12%) |
| Freezer −80°C | **23/32 (72%)** | **16/16 (100%)** |
| LIN, gas phase | **2/32 (6%)** | **5/16 (31%)** |
| LIN, liquid phase | 2/32 (6%) | 4/16 (25%) |
| Other | 2/32 (6%) | 0/16 (0%) |

(*continued*)

Table 4. (Continued)

| | *Design of the primarily used sample label* | |
|---|---|---|
| *Q6—SC* | *HBM4EU* (n = *36*) | *ESBB* (n = *28*) |
| Handwritten | **11/36 (31%)** | 2/28 (7%) |
| Registration number | **12/36 (33%)** | 5/28 (18%) |
| 1D barcode | 10/36 (28%) | **12/28 (43%)** |
| Data matrix | 2/36 (6%) | 6/28 (21%) |
| QR code | 1/36 (3%) | 2/28 (7%) |
| Other | 0/36 (0%) | 1/28 (4%) |
| | *Sample label ensures data protection/privacy through …* | |
| *Q7—SC* | *HBM4EU* (n = *36*) | *ESBB* (n = *28*) |
| Anonymization | 20/33 (61%) | 12/28 (43%) |
| Pseudonymization | 13/33 (39%) | 14/28 (50%) |
| Other | 0/33 (0%) | 2/28 (7%) |
| No answer | 3 | 0 |

Presented are the type of question (SC; MR), the total number of survey participants, as well as ratio and percentage (in brackets) of survey participants choosing a given answer. The number of survey participants not providing an answer is noted under ''no answer.''
The information marked in bold is the most relevant result.
1D, one dimensional; HBM, human biomonitoring; LIN, liquid nitrogen.

biobanking, the use of cryovials is much more common than in HBM-related biobanking. Long-term storage is of great importance for the HBM4EU consortium as well as for the ESBB community (Table 4, Q2). Within the HBM4EU initiative, most partners (72%) use electrical freezers for long-term storage at −80°C for at least one sample type (Table 4, Q5). Nevertheless, long-term storage at −20°C is also very prominent (38%). The latter is less common in ESBB biorepositories (12%), who all use electrical freezers at −80°C for storage of at least one sample type. Thirty-one percent of ESBB biorepositories additionally operate LIN-based infrastructures for long-term storage, which allow storage of samples at temperatures below −130°C, while the percentage of HBM4EU biorepositories capable of storage in LIN-based systems below −130°C is low (6%).

*Sample labeling.* Barcodes printed on cryo-compatible labels are widely applied in clinical as well as in HBM biobanking. However, handwritten labels are still used by almost a third of the surveyed HBM4EU-affiliated biorepositories (Table 4, Q6). Pseudonymization is a procedure by which the most identifying fields within a data record are replaced by one or more artificial identifiers, or pseudonyms. The purpose is to render the data record less identifying. The pseudonym allows tracking back of data to its origins, which distinguishes pseudonymization from anonymization where all person-related data that could allow backtracking have been purged. Survey responses indicate that sample labels are either anonymized or pseudonymized in both communities, HBM4EU and ESBB (Table 4, Q7).

### Sample shipment

HBM4EU partners and ESBB members have been shipping nonregulated and/or samples that are classified as category B samples (Diagnostic specimens, assigned to UN 3373) most frequently (Table 5, Q1). To inform the receiver before shipment is well established in both surveyed communities (Table 5, Q3). The sample transfer protocol (manifest) serves as a control sheet and gives a detailed summary of all samples to be shipped. In the ESBB community, 87.5% of surveyed biorepositories send a manifest to prospective sample recipients, whereas only 59% of HBM4EU-partnered biobanks use manifests (Table 5, Q4). Where manifests are used, HBM4EU partners and ESBB members do, however, include a comparable degree of detail (Table 5, Q5). An important parameter for assuring the sample quality is the recording (logging) of the temperature during sample shipment. Although some biorepositories of both communities log the temperature either at sending and reception or continuously, still 54% of responding ESBB members and 65% of HBM4EU partners do not log shipment temperature at all (Table 5, Q6).

### Data management

The majority of both interviewed communities already use a data management system—either by a homemade solution or a database with respective management software (Table 6, Q1). Most of the HBM4EU partners (54%) use homemade solutions (e.g., Excel sheets) for the documentation of sample-linked data, whereas the majority of ESBB members (75%) store these data in professional databases. Aside from the technical implementation of sample management systems, the degree of detail stored about a sample's history is an important parameter as well. Table 6, Q2, displays the percentage to which individual sample history items are collected and stored by surveyed HBM4EU and ESBB biorepositories. Currently, the sampling year, the date of sample receipt at the repository, the source of the sample, and the storage temperature are consistently stored by most surveyed biobanks. A very high proportion of surveyed ESBB biorepositories reported to record all of the items on sample history included in the survey question (for details see Table 6, Q2). A more differentiated picture emerges in HBM biobanking, where individual aspects with high relevance for QA (e.g., total storage duration, thaw and

Table 5. Sample Shipment

| | *What type of samples do you regularly exchange with other institutions?* | |
|---|---|---|
| *Q1—MR* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Nonregulated samples | 16/30 (53%) | 12/24 (50%) |
| Category B samples | 16/30 (53%) | 14/24 (58%) |
| Category A samples | 1/30 (3%) | 2/24 (8%) |
| Other | 1/30 (3%) | 1/24 (4%) |
| No answer | 6 | 4 |
| | *What packaging do you use?* | |
| *Q2—MR* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Compliant with PI 620 | 1/24 (4%) | 3/21 (14%) |
| Compliant with PI 650 | 12/24 (50%) | 14/21 (67%) |
| Compliant with PI 650 light | 1/24 (4%) | 4/21 (19%) |
| Compliant with PI 959 | 1/24 (4%) | 4/21 (19%) |
| Regular parcel | 8/24 (33%) | 7/21 (33%) |
| Other | 3/24 (13%) | 2/21 (10%) |
| No answer | 12 | 7 |
| | *Do you inform the recipient before sample shipment?* | |
| *Q3—SC* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Yes | 29/30 (97%) | 24/24 (100%) |
| No | 1/30 (3%) | 0/24 (0%) |
| No answer | 6 | 4 |
| | *Do you send an electronic manifest to the recipient before sample shipment?* | |
| *Q4—SC* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Yes | 16/27 (59%) | **21/24 (87.5%)** |
| No | 11/27 (41%) | 3/24 (12.5%) |
| No answer | 9 | 4 |
| | *What information does this manifest include? (only participants answering Q4 with yes)* | |
| *Q5—MR* | *HBM4EU (n = 16)* | *ESBB (n = 21)* |
| Name and contact details of shipper | 15/16 (94%) | 19/20 (95%) |
| Name and contact details of recipient | 13/16 (81%) | 17/20 (85%) |
| Shipping temperature | 10/16 (62%) | 15/20 (75%) |
| Date of sample shipment | 14/16 (88%) | 18/20 (90%) |
| Biological substance category | 9/16 (56%) | 11/20 (55%) |
| Sample type | 15/16 (94%) | 20/20 (100%) |
| Sample ID | 13/16 (81%) | 20/20 (100%) |
| Sample volume | 12/16 (75%) | 19/20 (95%) |
| Type of sample container | 5/16 (31%) | 10/20 (50%) |
| Number of samples and/or aliquots | 15/16 (94%) | 19/20 (95%) |
| Prior informed consent | 2/16 (12%) | 5/20 (25%) |
| Material transfer agreement | 6/16 (38%) | 11/20 (55%) |
| Other | 1/16 (6%) | 1/20 (5%) |
| No answer | 0 | 1 |
| | *How do you log sample temperature when shipping samples* | |
| *Q6—MR* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| No logging | 20/31 (65%) | 14/26 (54%) |
| Continuous logging | 7/31 (23%) | 9/26 (35%) |
| Logging at sending and reception | 6/31 (19%) | 6/26 (23%) |
| No answer | 5 | 2 |

Presented are the type of question (SC; MR), the total number of survey participants, as well as ratio and percentage (in brackets) of survey participants choosing a given answer. The number of survey participants not providing an answer is noted under ''no answer.''
The information marked in bold is the most relevant result.

Table 6. Data Management

| | *What data management system for documentation of withdrawal/adding of samples do you use?* | |
|---|---|---|
| *Q1—SC* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| Homemade solution (e.g., Excel sheets) | **19/35 (54%)** | 7/28 (25%) |
| Database and respective management software | 12/35 (34%) | **21/28 (75%)** |
| No data management system | 4/35 (11%) | 0/28 (0%) |
| No answer | 1 | 0 |
| | *What information about a stored samples history do you record?* | |
| *Q2—MR* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| No information | 1/35 (3%) | 0/28 (0%) |
| Source of the sample | 27/35 (77%) | 24/28 (86%) |
| Date of sample receipt at the repository | 29/35 (83%) | 28/28 (100%) |
| Date of sample shipment from the repository | 16/35 (46%) | 24/28 (86%) |
| Total storage duration | 18/35 (51%) | 22/28 (79%) |
| Sampling year/sampling period | 31/35 (89%) | 22/28 (79%) |
| Person in charge | 20/35 (57%) | 18/28 (64%) |
| Storage temperature | 25/35 (71%) | 26/28 (93%) |
| Thaw and refreezing cycles | 8/35 (23%) | 20/28 (71%) |
| Subaliquots | 15/35 (43%) | 21/28 (75%) |
| Deviations (e.g., interruption of cooling chain) | 11/35 (31%) | 18/28 (64%) |
| Other | 2/35 (6%) | 4/28 (14%) |
| No answer | 1 | 0 |

Presented are the type of question (SC; MR), the total number of survey participants, as well as ratio and percentage (in brackets) of survey participants choosing a given answer. The number of survey participants not providing an answer is noted under ''no answer.''
The information marked in bold is the most relevant result.

Table 7. Quality Management

| | *Is your institution certified, accredited, or otherwise qualified in a quality management system?* | |
|---|---|---|
| *Q1—SC* | *HBM4EU (n = 36)* | *ESBB (n = 28)* |
| No | 18/34 (53%) | 12/28 (43%) |
| Yes | 16/34 (47%) | 16/28 (57%) |
| No answer | 2 | 0 |
| | *Please specify according to which norm(s)/systems your institution is certified/accredited or otherwise qualified (only shown to participants answering Q1 with yes)* | |
| *Q1A—OF* | *HBM4EU (n = 16)* | *ESBB (n = 16)* |
| ISO 9001 | 8/16 (50%) | 12/16 (75%) |
| ISO 17025 | 9/16 (56%) | 2/16 (13%) |
| GCP/GLP | 0/16 (0%) | 5/16 (31%) |
| ISO 15189 | 1/16 (6%) | 2/16 (13%) |
| NFS 96–900 | 1/16 (6%) | 1/16 (6%) |
| ISO 15025 | 1/16 (6%) | 0/16 (0%) |
| ISO 14001 | 0/16 (0%) | 1/16 (6%) |
| ISO 18001 | 0/16 (0%) | 1/16 (6%) |
| | *For which activities has a quality management system been established (only shown to participants answering Q1 with yes)* | |
| *Q2—MR* | *HBM4EU (n = 16)* | *ESBB (n = 16)* |
| Sampling | 8/14 (57%) | 13/16 (81%) |
| Distribution | 4/14 (29%) | 11/16 (69%) |
| Shipment | 4/14 (29%) | 12/16 (75%) |
| Data management/IT | 6/14 (43%) | 12/16 (75%) |
| Processing | 11/14 (79%) | 15/16 (94%) |
| Infrastructure | 6/14 (43%) | 13/16 (81%) |
| Storage | 13/14 (93%) | 16/16 (100%) |
| No answer | 2 | 0 |

Presented are the type of question (SC; OF; MR), the total number of survey participants, as well as ratio and percentage (in brackets) of survey participants choosing a given answer. The number of survey participants not providing an answer is noted under ''no answer.''
OF, open-form question.

refreeze cycles, and deviations) are recorded by 51% or less of the surveyed biorepositories (Table 6, Q2).

### *Aspects of quality management*

Only 16 out of the 34 HBM4EU-partnered biorepositories providing an answer (47%) have already established a quality management system. Furthermore, out of those 16, only 4 (25%) established a quality management system for sample distribution and sample shipment. Fifty-seven percent of surveyed ESBB members responded that they have established quality management systems (Table 7, Q1). The norms applied most commonly by HBM-related repositories are DIN EN ISO 9001 and DIN EN ISO/IEC 17025. Clinical repositories additionally apply GCP-/GLP-based QMS (Table 7, Q1A). Table 7, Q2, details the survey regarding establishment of quality management for different biobanking-related activities. In general, quality management and control measures appear to be implemented to a greater extent at ESBB biorepositories.

## Discussion

HBM-related biorepositories differ from repositories for clinical research in many aspects. as confirmed by our results. The most prominent differences are highlighted in bold in Tables 1 to 7. Briefly, HBM-related biorepositories in most cases are based at public research institutes, organized as single/individual biorepository with samples only for the purpose of revealing the exposure to environmental pollutants, and hence, focus on cross-sectional or longitudinal studies with samples from the general population. In contrast, ESBB members report clinical-related biorepositories to be mostly based in hospitals or public research institutes, organized as centralized facilities with samples from multiple independent projects. Due to the clinical approach, case–control, case-only, and clinical trial studies are equally well represented and samples from patients or clinical cohorts are in focus. This implies differences in technical and operational details (e.g., differences in storage temperature, sample container, sample labeling, and data management). Although the purpose of clinical biorepositories differs from HBM-related biorepositories, there are overlaps in quality requirements and biobanking processes, and thus, harmonization and standardization are crucial in both areas of application. Large efforts have already been undertaken to harmonize biobanking-related processes and procedures, including ethical and legal aspects in biobanking for medical research across Europe as well as globally.[13–15] General guidelines are provided by ISBER in the ISBER Best Practices[16] and the Organisation for Economic Co-operation and Development (OECD) guidelines on human biobanks and genetic research databases.[17] In Europe, the planning phase of BBMRI was already initiated in 2008,[18,19] and evolved into an European Research Infrastructure Consortium (ERIC) in the following years. BBMRI-ERIC aims at providing access to biobanks of different formats, harmonizing standards, establishing operational procedures, including ethical, legal, and societal aspects, and securing sustainable funding for European biobanks.[19,20] Since 2011, ESBB has been providing a scientific platform for knowledge exchange in the biobanking field and as scientific society has been vitally supporting biosharing on a European scale through mobilizing, inspiring, and educating. Interestingly, the majority of HBM4EU partners are not registered as member of a biobanking society (e.g., ESBB and ISBER) or research infrastructure (BBMRI-ERIC). Knowledge exchange between these communities, however, is vital and participation in such societies provides access to standards and best practices in biobanking, promoting harmonization in this area. Despite controversial discussions on harmonization in health-related biobanking and the many aspects in biobanking that have to be considered,[14,15,21,22] harmonization has, in many cases, been achieved or substantial efforts are in progress. Although many requirements are already met by HBM4EU partners, there is still a need for improvement regarding some legal and technical issues. Ethical and legal aspects build the basic framework for the usage of human samples. The consent given by the sample donor sets the scene in research and defines boundaries or opens doors. In HBM research, a specific consent limiting use of samples to the analysis of the addressed environmental pollutants has been considered sufficient for decades. In medical research, consent forms allowing a broader use of samples are discussed intensively, especially since interoperability between biobanks and researchers requires exchange and sharing of high-quality samples and data to manage the various challenges in today's biomedical research.[23,24] A key point for elevating HBM in Europe to the next level will be the combination of health and HBM surveys to share expertise, transfer knowledge, and jointly use available samples and associated data, while aiming at a better understanding of the impact of environmental stressors on human health. How beneficial such a combination can be is demonstrated by the various outcomes of the National Health and Nutrition Examination Survey (NHANES) conducted regularly by the U.S. Centers for Disease Control and Prevention (CDC).[25] Combining both survey types on a European scale will generate valuable data that are urgently needed as the scientific basis for a political regulation pertaining to the use of harmful chemicals in Europe. Recently, two internal feasibility studies were started in HBM4EU, with the aim to test the possibility of integrating HMB modules in health surveys (LIFE, Germany; KuoBio, Finland) and to investigate if already collected samples might be suitable for HBM research. Interestingly, our survey results revealed that relevant sample types required for HBM analysis are also stored in clinical repositories of ESBB members. Samples might be stored in different sample containers, in different volumes, and at different temperatures. Whether theses samples are suitable to support HBM activities in Europe and their exchange between both communities is legally acceptable need further investigation. In any case, particularly for sample exchange and interdisciplinary sample usage, the donor has to consent accordingly. HBM4EU hence can benefit from experience and knowledge already gained by clinical biobanks with regard to the handling and implementation of broad consents. Often, the required legal framework, for example, sample exchange between a study owner (biobank) and third parties (e.g., researches and laboratories), is not clear, since different regulation mechanisms might apply, especially between different countries. The implementation of the General Data Protection Regulation (GDPR) in May 2018 even increased complexity, since the exchange of samples in most cases is accompanied

by personal data as defined in Article 4 of GDPR. A valuable tool to guarantee legally approved exchange of samples is MTAs or Material and Data Transfer Agreements (MDTAs). They define the terms and conditions under which samples and associated data can be transferred and used.[26–29] However, terms and conditions defined in an MTA have to comply with the consent given by the sample donor. Minimum requirements on MTAs/MDTAs are defined in the ISBER Best Practices. Since our survey revealed a limited use of MTAs among HBM4EU partners, an MDTA has been developed jointly with a strategy document for harmonized sample exchange within HBM4EU. This MDTA is publicly available for download in the online library of the official HBM4EU homepage (https://www.hbm4eu.eu/). Briefly, general terms and conditions are defined in a HBM4EU master MDTA. As pseudonymized data will be exchanged with any material transfer within HBM4EU, the HBM4EU MDTA also includes a data controller/data processor agreement to comply with the requirements on data exchange and usage of the GDPR. This integrated agreement governs the transfer and processing of the material-associated pseudonymized data. A second document, the HBM4EU Material and associated Data Transfer Record Form (HBM4EU MDTRF), is used to specify the general terms and conditions of the HBM4EU master MDTA and to document each individual transfer of material between material and data provider and recipient. With the signing of this form by both parties, the terms and conditions defined in the HBM4EU master MDTA and specified in the HBM4EU MDTRF, including the data controller/data processor agreement, are accepted.

Besides these ethical and legal aspects, biomedical research as well as HBM demand a certain level of sample quality. Experiences in medical research revealed the significant impact of variations in preanalytical steps, including sample storage and shipment on various sample components.[30–35] With regard to HBM-relevant chemicals, single studies confirm that preanalytical steps may alter sample components of interest too.[36–38] Within HBM4EU, standardized protocols are already available for sampling and sample preparation. In addition, several ISO norms are available for a standardized sample preparation. High-quality genomic DNA, RNA, proteins, and related state-of-the-art methods (e.g., whole-genome sequencing and single-cell sequencing) are becoming more and more important for the development of new biomarkers of effect and to identify methylation patterns and epigenetic alterations related to chemical exposure.[39–42] In consequence, adopting the ISO 20186 and ISO 20184 series for a standardized isolation of RNA, DNA, and proteins from fresh and frozen samples would be most valuable for the HBM4EU community. Standards for tissues uncommon for use in HBM are additionally available, for example, formalin-fixed tissues (ISO 20166 series), which may be relevant in the future. Differences in sample handling, preparation, and storage between both communities can be explained by the different aims. Currently, HBM focuses on the analysis of chemicals in human samples, while clinical research deals with the analysis of highly labile molecules, for example, DNA, RNAs, proteins, metabolites, and hormones.

Pertaining to sample exchange, important aspects have been condensed into a strategy document and an accompanying HBM4EU SOP facilitating sample exchanges between HBM4EU partners (https://www.hbm4eu.eu/deliverables/, Deliverable 7.2). However, not much focus was put on the harmonization of storage conditions in HBM studies across Europe yet. Results indicate a wide variety of storage temperatures are used predominantly by the HBM4EU partners. In the context of medical research, it has been proven that different storage temperatures and temperature fluctuations during storage impact sample integrity with regard to biomarkers of interest.[30,43–46] The impact of storage conditions has also been demonstrated in cases of individual HBM-relevant substances, for example, polychlorinated biphenyls, brominated flame retardants, some pesticides, or arsenic species.[36,47] It is therefore reasonable to assume that other environmental pollutants might be equally affected by different storage conditions. To provide high-quality samples, especially pertaining to DNA, RNA, or cell lines, long-term storage requires temperatures below the glass transition temperature.[48] To consistently support reproducibility, compliance, and robustness of HBM sample storage, harmonization and standardization and related biobanking processes on a European level are a prerequisite. Only the availability of high-quality and comparable samples will guarantee the generation of reliable and comparable analytical results. Due to the relatively high investment needed to install LIN-based storage technologies, not every partner within HBM4EU might be able to realize storage conditions to protect samples from alteration as far as possible. Since compatibility of the samples has to be guaranteed, it is recommended to document and harmonize storage conditions between HBM4EU partners for long-term storage to at least −80°C or lower. Besides storage temperature, the shipping of the samples should also be harmonized. To secure high quality of samples through maintaining low temperatures during shipment, it is recommended to ship all frozen samples on dry ice within HBM4EU and to continuously record the shipping temperature with either a temperature logger or alternatively to measure the temperature of the sample before shipment, and on receipt, to confirm temperature maintenance. Moreover, to increase comparability of newly collected samples in HBM4EU, centralized national storage facilities as national hubs of a European Biobank for HBM samples (HBM4EU Biobank) could be established at HBM4EU partner or third linked party sites at which a required LIN-based infrastructure is already available and which could be expanded with reasonable expenditure. This certainly includes many ethical and legal challenges, which still have to be identified and targeted, especially with regard to data protection. National hubs could act as quality-controlled centralized backup facilities at which samples can be stored and distributed when defined standards of HBM4EU are not met by single institutions. Similar European and global biobanks are already established for other research purposes.[49,50] In addition, such facilities could provide training and capacity building for regional institutions and technology transfer to the HBM4EU consortium. In this context, QA and quality management could doubtlessly improve sample quality and effectiveness of collaborations between researchers in biomedical research and HBM.[23,51] QA is an effort to continuously improve processes to generate high-quality samples with comparable and reliable data. Key components of QA are management structures, clearly defined workflows described in SOPs or operation instructions, a transparent documentation of processes and deviations, and a regular evaluation of the

established QA measures. QA should already start at the first, preanalytical steps, including sample collection. In this context, the Biospecimen Reporting for Improved Study Quality guidelines (BRISQ) as a tool for documenting and reporting preanalytical factors might be beneficial for HBM research.[52] In addition, the ISBER Biospecimen Science Working Group has developed the standard preanalytical code (SPREC) to facilitate documentation and communication of the most important preanalytical quality parameters of different types of biospecimens used in biomedical research.[53–55] This code system was specifically developed for the use in biomedical research, and is therefore rarely applied in HBM studies. To document the quality of a human sample in terms of viability, functionality, structural integrity, and stability, documentation of sample-associated data as well as data related to sample exchanges is essential. In particular, the sample annotation by unique identifier and labels as well as the history tracking of sample-associated events, such as, for example, shipments or processing steps, play a central role in data management and transfer. Adaptation of tools like BRISQ and SPREC to HBM needs, and their integration into HBM-related biobanking processes thus have the potential to foster harmonization of HBM efforts. Considering QM systems and related norms, our results revealed that the norms applied most commonly are DIN EN ISO 9001, DIN EN ISO/IEC 17025, DIN EN ISO 15189, and GCP/GLP. These norms are not focused on biobanking in particular, but rather focus on management structures in general (ISO 9001), testing and calibration laboratories (ISO 17025), medical laboratories (ISO 15189), and clinical, respectively, laboratory practice. Since 2017, general requirements on biobanking are defined in the ISO 20387 norm.[56,57] Most institutions that operate a biorepository for HBM purposes are not medical or testing and calibration laboratories, but environmental medical, occupational medical, or toxicological institutes, which operate their repository mainly to support their main occupation. To standardize and harmonize QA/QC activities pertaining to biobanking within HBM4EU, HBM4EU institutions that collect, store, and distribute samples should implement the requirements of ISO 20387. This will allow a certification of a QA/QC system specifically and solely for biobanking processes without interfering with other processes operated by the institution, e.g., environmental analysis, which might require a different level of QA/QC.

Although valuable information is gained, the conducted survey shows some limitations. As the survey is aimed at HBM4EU partners, it was carried out, in part, to identify biorepositories within the initiative that collect and store samples for the purpose of HBM; therefore, the link to the questionnaire was spread through the HBM4EU community, resulting in an unknown number of recipients. In the case of the survey addressed to ESBB members, the instructions in the email sent out also included a request for forwarding the mail to contacts responsible for the operation of biorepositories. In addition, while we sent out the survey to all ESBB members, not all ESBB members represent a clinical biobank. Hence, in both cases, the total number of biorepositories addressed is unknown and so the response rate is lacking. Nevertheless, with the reasonable number of received responses, the intention of this survey, gaining general insights into biobanking processes at the two surveyed types of repositories, should be fulfilled.

## Conclusion

Besides analytics, biobanking is a valuable component of HBM research, since more and more samples are needed to compare exposure levels between European countries over time. The term biobanking, however, does not only describe sample storage but also includes a variety of processes, for example, sample reception, handling, and shipment. Taken together, these biobanking-related preanalytical processes play an important role with regard to sample quality, and hence, in the particular case of HBM with regard to the comparability and reliability of chemical analytical results. In these preanalytical processes, the conducted survey identified many similarities between ESBB-affiliated and HBM4EU-partnered biorepositories. Nevertheless, a need for harmonization was identified for some processes in sample storage, shipment, and related data management. The full harmonization of biobanking activities between European countries for HBM purposes is a challenging task. However, to reach a reasonable minimum in harmonization, some important aspects, for example, pertaining to sample and associated data exchange, have been addressed within the HBM4EU initiative. In the context of standardizing sample storage for HBM purposes, although, some questions still remain unanswered. Empirical data, especially on long-term stability of exposure biomarkers and the impact of different storage temperatures on sample integrity, would be helpful. An engagement of the HBM4EU initiative with key organizations in biobanking, such as ESBB, ISBER, and BBMRI-ERIC, can further enhance harmonization of activities and create higher visibility for both biobanking and HBM in Europe.

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