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Chemical prioritisation strategy in the European Human Biomonitoring Initiative (HBM4EU) – Development and results

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ABSTRACT

The European Human Biomonitoring Initiative (HBM4EU¹) has established a European Union-wide human biomonitoring (HBM) programme to generate knowledge on human internal exposure to chemical pollutants and their potential health impacts in Europe, in order to support policy makers' efforts to ensure chemical safety and improve health in Europe.

A prioritisation strategy was necessary to determine and meet the most important needs of both policy makers and risk assessors, as well as common national needs of participating countries and a broad range of stakeholders. This strategy consisted of three main steps: 1) mapping of knowledge gaps identified by policy makers, 2) prioritisation of substances using a scoring system, and 3) generation of a list of priority substances reflective of the scoring, as well as of public policy priorities and available resources.

For the first step, relevant ministries and agencies at EU and national levels, as well as members of the Stakeholder Forum each nominated up to 5 substances/substance groups of concern for policy-makers. These nominations were collated into a preliminary list of 48 substances/substance groups, which was subsequently shortened to a list of 23 after considering the total number of nominations each substance/substance group received and the nature of the nominating entities.

For the second step, a panel of 11 experts in epidemiology, toxicology, exposure sciences, and occupational and environmental health scored each of the substances/substance groups using prioritisation criteria including hazardous properties, exposure characteristics, and societal concern. The scores were used to rank the 23 substances/substance groups. In addition, substances were categorised according to the level of current knowledge about their hazards, extent of human exposure (through the availability of HBM data), regulatory status and availability of analytical methods for biomarker measurement.

Finally, in addition to the ranking and categorisation of the substances, the resources available for the project and the alignment with the policy priorities at European level were considered to produce a final priority list of 9 substances/substance groups for research activities and surveys within the framework of the HBM4EU project.

1. Introduction

Human biomonitoring (HBM) measures levels of chemicals directly in human biological samples (e.g. blood, urine, hair). This type of measurement aggregates exposure from all relevant routes and sources

and, as such, is a powerful tool for tracing the uptake of chemicals in the human body (Angerer et al., 2007). Assessment of human exposure provides important information for health risk assessments, but it requires considerable coordination efforts, harmonised and comparable methods and financial investment. Therefore, the selection of substances

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¹ www.HBM4EU.eu.

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for inclusion in HBM surveys needs to be well thought out. The identification of policy-relevant chemicals to be included in the Human Biomonitoring Initiative in Europe (HBM4EU) is a crucial step towards achieving these goals (Apel et al., 2020; Buekers et al., 2018; David et al., 2020; Louro et al., 2019).

HBM4EU is a joint effort of 30 countries, the European Environment Agency (EEA) and the European Commission (EC), which takes part in the project through the European Union (EU) Policy Board. The initiative aims to generate knowledge on human exposure to specific chemicals and chemical groups in Europe and on the human health impacts of this exposure. Running from 2017 to 2021, HBM4EU is co-funded by participating partners and the EC's Horizon 2020 research programme. It is organised to answer policy-relevant questions for priority chemicals, as identified by the partner countries' National Hubs (i.e. bodies set up at national level representing the national network of HBM activities), the EU Policy Board (representatives of EC services and EU agencies dealing with chemicals) and a Stakeholder Forum (comprised of non-governmental organisations (NGOs), industry and trade unions). The generated knowledge will support the efforts of policy makers to enhance chemical safety in Europe, as well as to set research priorities at the European level.

The selection of the first list of high-priority substances for action in HBM4EU was undertaken in 2016, at the stage of developing the proposal for this H2020 initiative. This step involved consortium partners and representatives from EU institutions (General Directorates and EU agencies in charge of chemical policy, monitoring and regulation), and took into account both national and EU level policy needs to better understand chemical exposure and health outcomes. This first prioritisation exercise resulted in 9 substances or substance groups: phthalates and Hexamoll® DINCH, bisphenols, per-/polyfluoroalkyl substances (PFAS), flame retardants, cadmium and chromium VI, polycyclic aromatic hydrocarbons (PAHs), anilines, chemical mixtures and emerging substances.

Because two additional rounds of chemical prioritisation were planned during the course of the project, a prioritisation strategy was developed to make the process more accountable, transparent, legitimate and useful for the next two rounds. This strategy consisted in a multi-step approach involving the consultation of the EU Policy Board, the National Hubs, and members of the HBM4EU Stakeholder Forum, which we present here. Its actual use for the first time and its results, namely the second list of HBM4EU priority substances, are also described. In addition, we offer recommendations for further

improvement, emerging from the feedback of the various entities that participated in this second HBM4EU prioritisation round.

2. Chemical prioritisation strategy developed and applied in HBM4EU

In the first instance, a review of the literature was performed to collect criteria used for chemical prioritisation in HBM programmes worldwide. Prioritisation criteria used in the following HBM programmes were identified: the United States (US) National Health and Nutrition Examination Survey (NHANES), the Canadian Health Measures Survey (CHMS), the German Environmental Survey (GerES), the French Longitudinal Study of Children (ELFE), the French cross-sectional health survey (Esteban) and the Flemish Environment and Health Study (FLEHS) (Casteleyn et al., 2015; CDC 2002; 2003; 2006; Fillol et al., 2014; Fréry et al., 2012; Haines et al., 2017; Health Canada 2010; 2013; 2015; Kolossa-Gehring et al., 2012a; Schoeters et al., 2017). The prioritisation criteria were assessed in relation to their relevance to the objectives and specificities of the HBM4EU project (Ganzleben et al., 2017). The selected criteria related to hazardous properties, exposure characteristics, regulatory status, public concern and technical feasibility for HBM (HBM4EU 2017).

In brief, the strategy consisted of the implementation of three successive main steps, as described in Fig. 1. The first step was to *map knowledge needs* (nomination of substances along with their policy and knowledge needs; holding of a stakeholder workshop) and *initiate the prioritisation* (based on relatively simple frequency weightings to produce a short list of substances). The second step was to *rank nominated substances/substance groups* from the short list according to a priority score reflective of their level of concern and thus the relevancy to have them prioritised. In addition, a category (from A to D) was allocated to each substance to inform on the current level of knowledge on the substance, mainly from the perspective of HBM research. These substance categories aimed to support the prioritisation process by indicating the information gaps that research activities in HBM4EU could target. The third step consisted of consulting with the EU Policy Board and the HBM4EU Management Board to agree on a list of proposed priority substances, based on the ranked list of substances but also according to resources and policy considerations. Each of these steps is described in more detail below. The second priority list of substances, proposed according to this methodology, was finally approved by the HBM4EU Governing Board.

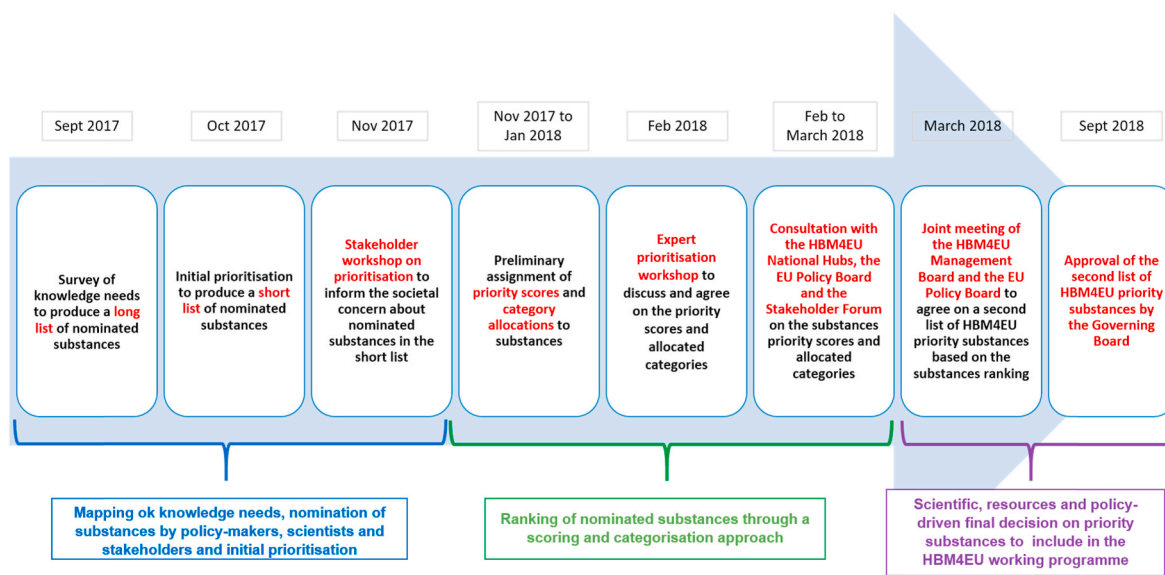


Fig. 1. Overview of the chemical prioritisation strategy under HBM4EU.

2.1. Mapping of knowledge needs for substances and initial prioritisation

The objective of the *mapping of knowledge needs* was to identify the activities and research needed on specific substances, as expressed by the EU Policy Board, the National Hubs and the HBM4EU Stakeholder Forum. These three groups of participants ensured an overarching knowledge input that would benefit the results generated under HBM4EU. It was therefore necessary to gain a comprehensive understanding of the specific needs of these groups of participants.

The key steps for determining the knowledge needs were to: 1) run an online survey for the nomination of substances; 2) produce a short list of nominated substances and 3) organise a stakeholder workshop to collect more input.

2.1.1. Online survey for the nomination of substances: polling European chemical research needs under HBM4EU

The online survey was structured around the selected set of prioritisation criteria consisting of the hazardous properties, exposure characteristics, regulatory status, public concern, and technical feasibility for HBM measurement. The complete online survey with questions is included in Supplementary Material - Annex 1. It ran from July to September 2017 and was opened to the following key entities: members of the EU Policy Board, the participating countries represented by their National Hubs and members of the HBM4EU Stakeholder Forum (Fig. 2).

Each entity could nominate up to 5 substances (or groups of substances) by completing the full online survey for each nominated substance/substance groups, as well as by defining the policy-related questions they thought HBM4EU research activities should address for each substance and how new knowledge generated under the project could benefit society. They were required to submit any available information and evidence on the nominated substance/substance groups involving questions related to the prioritisation criteria. Respondents could re-nominate substances that were already on the first list of HBM4EU prioritised substances, to emphasise their high priority and the fact that HBM-related research is still needed. These substances were communicated directly to the respective chemical group leaders (CGL) of the HBM4EU first priority list of substances (CGLs are tasked with developing scoping documents on current policy questions and proposals for relevant monitoring and research activities for the substances under their remit) and were not considered further in the process for obtaining the second HBM4EU priority list.

The survey participants nominating groups of substances were asked to provide a rationale for grouping these substances together. This included common analytical methods for measuring a panel of substances in a single biological sample, substances with similar use with possibility of substitution within the group or substances with similar toxicological profiles.

The survey results were collated to produce a long list of nominated substances and substance groups. This involved consolidating multiple nominations for individual substances and for groups of substances, where there was an overlap.

2.1.2. Producing a short list of substances and drafting background documents

Because the developed methodology for prioritising chemicals requires assessing information on the substances' hazards, exposures, regulations and HBM analytical feasibility, it was necessary to have a manageable number of substances to assess within the established timeframe. Therefore, the next step consisted in shortening the long list of all nominated substances down to a shorter list of approximately 25 substances/substance groups. The initial criterion for including a substance in the short list was to consider the number of nominations, on the basis of having been nominated by at least one member of the EU Policy Board and/or 9 National Hubs (representing just over one-third of the participating countries). In practice, there was less commonality across the nominations than expected, which meant the above criteria

had to be adapted by including:

- all substances and groups prioritised by the EU Policy Board (with the objective of meeting EU knowledge needs for policy support), as well as
- substances nominated by two or more National Hubs, or by at least one National Hub and one member of the Stakeholder Forum.

For each substance/substance group on the short list, informative so-called draft background documents were produced with the information provided in the online survey, including details on toxicological information, effects on human health and exposure characteristics required in the later stages of the prioritisation process, as also knowledge gaps and proposed research efforts.

2.1.3. Stakeholder workshop on chemical prioritisation: including stakeholder needs in the process

A stakeholder workshop on prioritisation was held in November 2017 to apprehend stakeholders' perspectives on the societal relevance of new HBM4EU-generated knowledge on the substances from the short list, and to better understand stakeholders' substance priorities and the reasoning behind these priorities. Stakeholders were asked to vote for the three substances/substance groups from the short list that they considered as most important to include in the HBM4EU project activities. The number of votes obtained for each substance was converted into a score, which was later used for scoring the substances in light of the public concern criterion (one of the selected prioritisation criteria).

2.2. Ranking of nominated substances through a scoring and categorisation approach

The second main step of the strategy consisted of *ranking the substances* from the short list based on their priority score, which was calculated against a set of prioritisation criteria according to the methodology described in more detail below. The category allocated to the substances (reflective of the availability of HBM data in Europe, current analytical capacity to measure them in HBM studies, their current EU regulatory status and the level of knowledge about their hazards) was also used to propose an alternative ranking, i.e. according to the substance's priority score but this time among the substances in the different categories (A to D).

This step involved a panel of 11 experts, from a wide variety of fields such as epidemiology, toxicology, exposure sciences, and occupational and environmental health (details available in Supplementary Material - Annex 2). As the data and information provided in the online nomination survey (and gathered in draft background documents) formed the basis for the substance's scoring and categorisation, these experts were first tasked with reviewing and, if necessary, supplementing these documents with any missing important information. Each draft background document was reviewed by two experts, who were also asked to propose a priority score (according to a previously defined methodology) and a category to the substance(s) covered by the document they had to review. In order to reach consensus priority scores and categories among the 11 experts, these were then presented and discussed by the expert panel during a two-day scoring workshop held in February 2018, especially in case of divergent proposals from the two experts. Agreed priority score and category were included in the revised background document for each substance/substance groups.

2.2.1. Scoring the substances or substance groups included in the short list of nominations

The scoring of the substances involved a three-step process, which included: 1) setting a consensus weighting value to be applied to each prioritisation criterion; 2) scoring the substances against each chosen prioritisation criterion and 3) calculating the substance's overall score. The process is further described below.

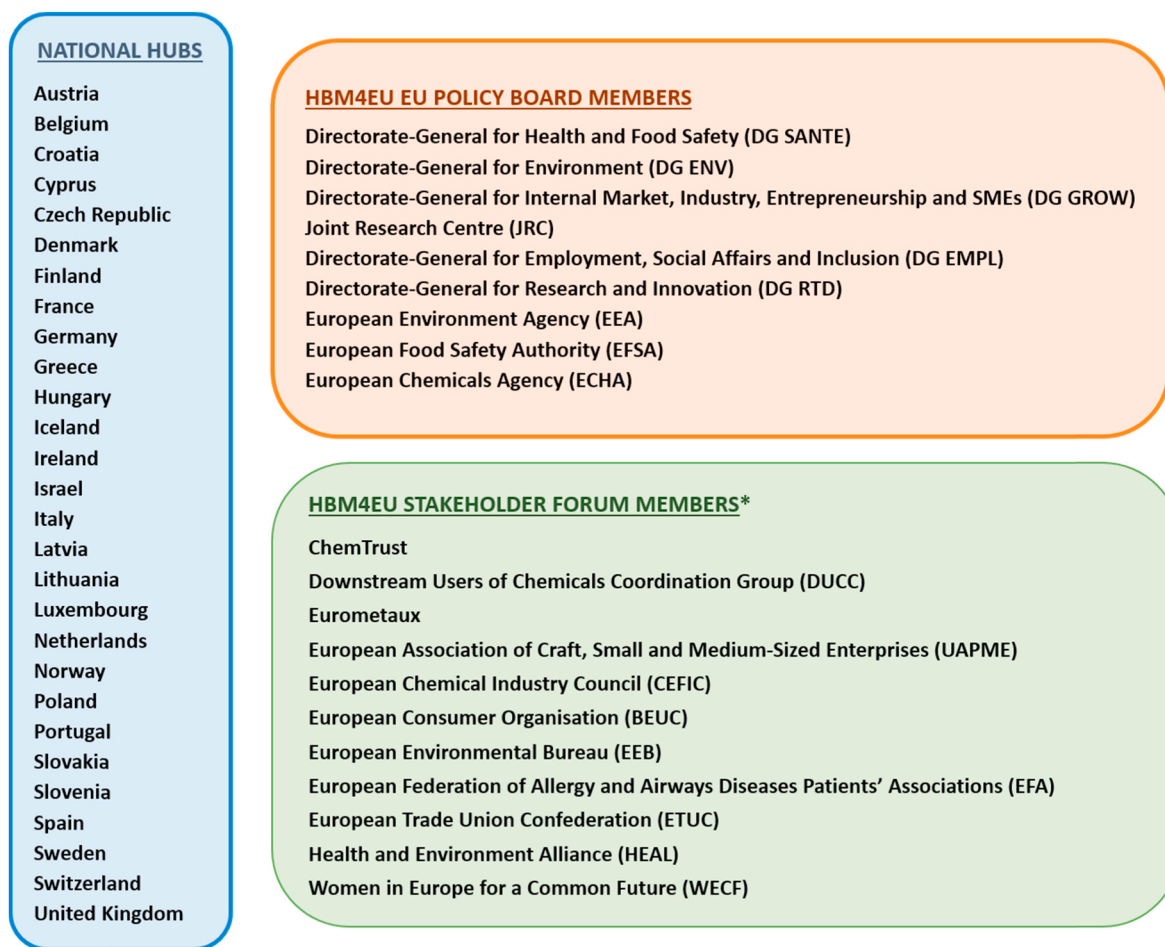


Fig. 2. Entities invited to nominate substances for prioritisation under HBM4EU.

* In 2019, two new stakeholders joined the Stakeholder Forum: Pesticide Action Network (PAN) and Plastics Europe. They did not take part in the 2017 round of chemical prioritisation.

2.2.1.1. Setting a consensus weighting value to be applied to each prioritisation criterion. An adapted Delphi method was adopted to weight the prioritisation criteria (hazards, exposure characteristics, regulatory status, public concern and technical feasibility for HBM measurement) according to their relative importance in the prioritisation process. The adapted Delphi method involved two rounds of consultation:

- 1) During the first round, a questionnaire was sent to the 11 experts, asking them to assign a percentage to each criterion to reflect its relative weight for the scoring step (i.e., their estimated importance for the priority setting). The sum of the weighting value assigned to each prioritisation criterion had to reach 100%. Experts had the possibility of justifying the given weighting values. Considering all expert responses, the median and boundary (minimum and maximum) values were calculated for each prioritisation criterion and were shared with all experts.
- 2) A conference call was organised to discuss the weighting values given during the first consultation round. Experts could explain the rationale for giving their values. Following these discussions, a second consultation round was organised during which each expert had the opportunity to modify the weighting values that he had given in the first round.

For each prioritisation criterion, the median of the weighing value given by the experts during the second consultation round was finally retained.

2.2.1.2. Scoring the substances against each selected prioritisation criterion. In order to score the substances against the criteria “hazardous properties” and “exposure characteristics”, a systematic approach was implemented through the scoring rules that are summarised in [Table 1](#) (scoring rules for different hazard endpoints) and [Table 2](#) (scoring rules for different exposure characteristics). As informed by the information included in the substance’s revised background documents, scores of 6, 3 or 1 were given, corresponding to, respectively, a High, Moderate or Low category of severity (towards hazard endpoints) or level (towards exposure characteristics). This approach is based on the GreenScreen® for Safer Chemicals method,² which has been designed to identify chemicals of high concern and safer alternatives using criteria to classify the human health and environmental hazard level for a chemical.

If no information was available to score a hazard endpoint/exposure parameter or if the available data was considered inadequate, a Data Gap score of 2 was given. If available toxicological data did not suggest any related effect or mode of action toward an endpoint, a Low severity score of 1 was assigned for that endpoint instead of a Null score. This conservative approach is justified by the fact that toxicological tests may not currently be sensitive enough to detect effects.

Scores could deviate from the rules only if justified and accepted by the expert group involved in the scoring.

The scoring of the “public concern” criterion was informed in particular by the results of the vote held during the stakeholder

² <https://www.greenscreenchemicals.org/learn/full-greenscreen-method>.

Table 1
Scoring rules for endpoints of the *hazardous properties* criterion.

Hazardous properties		Severity level				Highest score by endpoint
Endpoint	Source of information	High (score of 6)	Moderate (score of 3)	Low (score of 1)	Data gap (score of 2)	
Carcinogenicity	EU – CLP regulation (H-Statements)	Carc. 1A or 1B (H350 or H350i)	Carc. 2 (H351)			
	EU – SVHC List IARC classification	Candidate List Group 1 or 2A	Group 2B	Group 4 (or Group 3 in specific cases)	Group 3	
Mutagenicity	Peer-reviewed literature EU – CLP regulation (H-Statements)	Muta. 1A or 1B (H340)	Muta. 2 (H341)			
	EU – SVHC List Peer-reviewed literature	Candidate List				
Reproductive toxicity	EU – CLP regulation (H-Statements)	Repr. 1A or 1B (H360F, H360FD, H360Fd)	Repr. 2 (H360Df, H361f, H361fd)			
	Peer-reviewed literature EU – CLP regulation (H-Statements)	Repr. 1A or 1B (H360D, H360FD, H360Df, H362)	Repr. 2 (H360Fd, H361d, H361fd)			
Endocrine activity	Peer-reviewed literature EU – SVHC List (article 57f)	Candidate List				
	EU - BKH List US - TEDX List		Cat. 1 or cat. 2 Inclusion in the list	Cat. 3		
STOT RE (Systemic toxicity after repeated exposure)	Peer-reviewed literature EU – CLP regulation (H-Statements)	STOT -RE 1 (H373)	STOT-RE 2 (H373)			
	Adverse effects (e.g. on liver, kidneys, cardiovascular function) after chronic exposure to the substance, indicated from peer-reviewed literature	Yes	Suspected	Not identified		
Neurotoxicity ^a	Chemical Scorecard ^b Peer-reviewed literature	Strong evidence	Suspected	Not identified		
Immunotoxicity ^a	Chemical Scorecard ^b Peer-reviewed literature	Strong evidence	Suspected	Not identified		
Respiratory sensitiser ^a	EU – CLP regulation (H-Statements)	Resp. Sens. 1A or 1B (H334)				
	EU – SVHC List (article 57f) Peer-reviewed literature	Candidate List				
Skin sensitiser ^a	EU – CLP regulation (H-Statements)	Skin. Sens. 1A or 1B (H317)				
	Peer-reviewed literature					
Total score ^c						x
Adjusted total score for the hazardous properties criterion ^d						x/60 = X

CLP: Classification, Labelling and Packaging; EU: European Union; IARC: International Agency for Research on Cancer; STOT-RE: Specific target organ toxicity - repeated exposure; SVHC: Substances of Very High Concern; US: United States.

^a Considered only if not yet addressed in another entry (to avoid double counting).

^b Chemical Scorecard is an information service provided by the US Environmental Defense Fund that uses data from the US Environmental Protection Agency's Toxic Release Inventory plus other governmental and scientific agencies. Health effects are provided for more than 5000 chemicals.

^c For each endpoint, the highest score was used to calculate the total score, which constitutes a conservative approach.

^d The adjusted total score for the hazardous properties criterion was obtained by dividing the calculated total score by the highest possible score of 60 (10 endpoints of high severity category).

workshop on prioritisation. The number of stakeholder votes for each substance/substance group on the short list was translated into a corresponding score (e.g. a score of 4 for 4 votes). In addition, information on whether the substance is included in the SIN list³ and/or in the Trade Union List for REACH authorisation⁴ and whether NGO campaigns have been conducted regarding the substance were also considered (Table 3).

2.2.1.3. Calculating the overall score for each substance. The adjusted total score for each selected criterion (hazardous properties, exposure characteristics and the public concern) was multiplied by its respective median weighting value. Finally, the sum of the products resulted in the overall priority score for each substance (Table 4).

2.2.2. Categorising the substances or substance groups included in the short list of nominations

The categorisation step aimed to assign a category to each substance to reflect the level of knowledge on the availability of HBM data in

³ <http://sinlist.chemsec.org/>.

⁴ <https://www.etuc.org/IMG/pdf/TUListREACH.pdf>.

Table 2
Scoring rules for the parameters of the *substance exposure characteristics* criterion.

Exposure characteristics		Source or information	Severity level High (score of 6)	Moderate (score of 3)	Low (score of 1)	Data gap (score of 2)	Highest score per parameter
Persistence and/or bioaccumulation potential		EU – SVHC List (articles 57d and 57e for PBT and vPvB) Peer-reviewed literature/ Institutional report	Candidate List Persistent and evidence of bioaccumulation or significant biological half-life in mammals	Persistent (without evidence of bioaccumulation) or significant biological half-life in mammals			
Tonnages		ECHA	>1000 tpa	10-1000 tpa	<10 tpa		
Extent of exposure		ECHA	EU wide	Country/regional	Hotspot		
Routes of exposure		Peer-reviewed literature/ Institutional report	Multipathway exposure (oral, inhalation, dermal)	Multipathway (two routes of exposure only)	One route of exposure		
Passage of placental barrier		Peer-reviewed literature/ Institutional report	Strong evidence	Limited evidence	No		
Exposed populations	Workers	ECHA/Peer-reviewed literature/ Institutional report	Widespread (professional use and use in different industrial sectors)	Some professional/industrial use	Intermediate use only		
	General population		Evidence of wide exposure (multiple media) - dispersive use	Limited evidence of exposure through external media	No significant exposure		
	Vulnerable groups exposed		Neonates, children, pregnant women				
Level of concern of the exposure	HBM data	ECHA/EFSA/Peer-reviewed literature/ Institutional report	Recent HBM data above or close to an established health-based HBM guidance value		Recent HBM data well below an established health-based HBM guidance value		
	External exposure data		Recent external exposure data above or close to a regulatory reference value		Recent external exposure data well below a regulatory reference value		
Total score ^a							y
Adjusted total score for the exposure characteristics criterion ^b							y/60 = Y

ECHA: European Chemicals Agency; EFSA: European Food Safety Authority; EU: European Union; PBT: Persistent, Bioaccumulative and Toxic; SVHC: Substances of Very High Concern; tpa: tonnes per annum; vPvB: very Persistent and very Bioaccumulative.

^a For all parameters, the highest score was used to calculate the total score, which constitutes a conservative approach.

^b The adjusted total score for the exposure characteristics criterion was obtained by dividing the calculated total score by the highest possible score of 60 (10 parameters of high severity category).

Table 3
Scoring rules for the *public concern* criterion.

Level of public concern	Related score
Stakeholder votes reflecting their interest in certain substances (or groups) from the short list of nominated substances during the stakeholder workshop on prioritisation	Number of votes translated into scores (maximum score = 9)
Inclusion in the SIN List and/or the Trade Union Priority List for REACH Authorisation	No = 0; Yes = 1
Recent NGO campaigns/media coverage	No = 0; Yes = 1
Total score	z
Adjusted total score for the public concern criterion ^a	z/11 = Z

^a The adjusted total score was obtained by dividing the total score by the highest possible score.

particular and, to a lesser extent, on the hazards, regulatory status or analytical capabilities for implementing HBM. Five substance categories (A to E) were defined in the HBM4EU project, as informed in [Table 5](#).

Because category E substances are not yet constitutively identified substances, none of the substances nominated during the prioritisation

Table 4
Calculation method of the overall priority score for substances included in the short list of nominations.

Prioritisation criterion	Criterion adjusted total score	Weighting value (W _i)	Product of the criterion adjusted total score by W _i
Hazardous properties	X	W ₁	X*W ₁
Exposure characteristics	Y	W ₂	Y*W ₂
Public concern	Z	W ₃	Z*W ₃
Overall priority score of the substance			Σ[X*W ₁ + Y*W ₂ + Z*W ₃]

process would belong to this category. Hence, substances were classified into the categories A to D, based on the information contained in the revised background document. For substance groups, categorisation was performed either for several substances included in the group or at least for an identified representative substance of the group.

The aim of allocating the substances to these categories was to ensure a balanced workload across the different areas of activity of the HBM4EU project by including substances from categories A to D in the

Table 5
Definition of category A to E substances under HBM4EU.

Substance's category within HBM4EU	Definition
Category A	Substances for which HBM data are sufficient to provide an overall picture of exposure levels across Europe, and interpretation of biomonitoring results in terms of health risks is possible. Risk management measures have been implemented at national or European level. Improvement of knowledge for these substances will therefore focus on policy-related research questions and evaluation of the effectiveness of existing regulatory measures.
Category B	Substances for which HBM data exists, but not sufficiently to have a clear picture across Europe. Also, knowledge on the extend of exposure, levels and impact on the human health should be improved, in order to give policy makers relevant and strategic data to establish appropriate regulations and improve chemical risk management. Analytical method and capacities to monitor the substances across Europe might have to be improved.
Category C	Substances for which HBM data scarcely or does not exist. Efforts to develop an analytical method to obtain relevant HBM results need to be done. Hazardous properties of the substances are identified, yet greater knowledge on toxicological characteristics and effects on the human health is needed. Interpretation of HBM data is not possible, due to the lack of HBM guidance values.
Category D	Substances for which a toxicological concern exists but HBM data are not available. HBM4EU research may be focused on the development of suspect screening approaches permitting to generate a first level of data enabling to document the reality of human exposure and better justify further investment in a full quantitative and validated method development.
Category E	Substances not yet identified as of toxicological concern and for which no HBM data are available. A bottom-up strategy will be applied, consisting to non-targeted screening approaches coupled to identification of unknowns capabilities for revealing, and further identifying, new (i.e. not yet known) markers of exposure related to chemicals of concern for HBM (parent compound or metabolite).

final list of priority substances. Indeed, according to the definitions of the substance categories, substances classified as A or B would require more public policy-oriented work, whereas C or D substances would require more research efforts such as developing HBM analytical methods or identifying biomarkers of effect.

2.3. Scientific, resources and policy driven final decision on the second HBM4EU priority list

The ranked list of substances was sent to the HBM4EU Management Board and the EU Policy Board, allowing them to weigh the scientific and policy merit of conducting research on each substance. Both boards met separately to discuss their priorities for action. Finally, a joint discussion with members of each of the two boards took place to agree on the final list of HBM4EU priority substances, considering also the resources available to conduct research activities during the 2019–2021 period.

2.4. After chemical prioritisation: feedback survey and suggestions for improvement

A survey was sent out in June 2019 to obtain feedback from the different participants who contributed to the second round of HBM4EU chemical prioritisation. This survey was designed to garner suggestions on how to further refine and streamline the overall strategy, including the scientific aspects of the elaborated method. The feedback received

was taken into account to improve the overall process ahead of the third round of HBM4EU chemical prioritisation, which will take place in 2020–21.

3. Results

3.1. Mapping of knowledge needs for substances and initial prioritisation

3.1.1. Results of the online survey for the nomination of substances for research under HBM4EU

One hundred and thirty-two substances with policy needs were nominated in the online survey (this initial list is available [here](#)). Respondents were from 24 National Hubs, 4 members of the Stakeholder Forum and 6 members of the EU Policy Board.

As mentioned in section 2.1.1, re-nominations of substances that were part of the first list of HBM4EU priority substances were communicated to the respective CGLs and consequently removed to produce a 92-nomination list (cf. Annex 3 - Supplementary Material). This list was further refined by looking for overlaps across nominations:

- Single substances were grouped when they were associated to each other. For example, “mercury” was combined with “mercury and its compounds”.
- Substance groups were used when consolidating some of the nominated single substances or smaller groups into larger groups of substances.

Finally, 23 single substances and 25 substance groups were obtained in the so-called “long list” of nominated substances, which is available [here](#).

3.1.2. Results from the initial prioritisation to produce a short list of substances

Following application of the established criteria to reduce the long list of nominations (see section 2.1.2), a “short list” of 23 substances/substance groups was produced. This was a manageable number of substances in order to apply the further steps of the prioritisation strategy (i.e. the scoring and categorisation) in the allotted time. This short list is available in Annex 4 of the Supplementary Material.

Fig. 3 summarizes the overall process starting from all the nominations received up to the short list of nominated substances.

3.2. Ranking of nominated substances included in the short list through the scoring and categorisation approach

3.2.1. Consensual weighting values for the prioritisation criteria

When implementing the adapted Delphi approach, the 11 experts agreed that two of the five prioritisation criteria (i.e. regulatory status, and technical feasibility for HBM measurement) were not of highest relevance for the scoring step. Indeed, scoring the substances according to their current regulatory status was not considered appropriate, because this would produce a bias towards already regulated substances for which more follow-up activities are needed instead of gaining new knowledge. Likewise, as the HBM4EU project entails activities aiming to develop analytical methods for measuring biomarkers, it was not considered informative to de-prioritise lesser-known substances for which no analytical biomonitoring methods currently exist (C or D category substances). While finally not used for the scoring step, these two prioritisation criteria were nonetheless useful for the categorisation step, as this defines the type of work to be performed in HBM4EU.

Table 6 indicates the weighting values assigned to each of the three selected prioritisation criteria (hazardous properties, exposure characteristics and the public concern) during the second round of consultation with the 11 involved experts. The median values were considered thereafter as the consensus weighting value to be applied to the adjusted score of each prioritisation criterion.

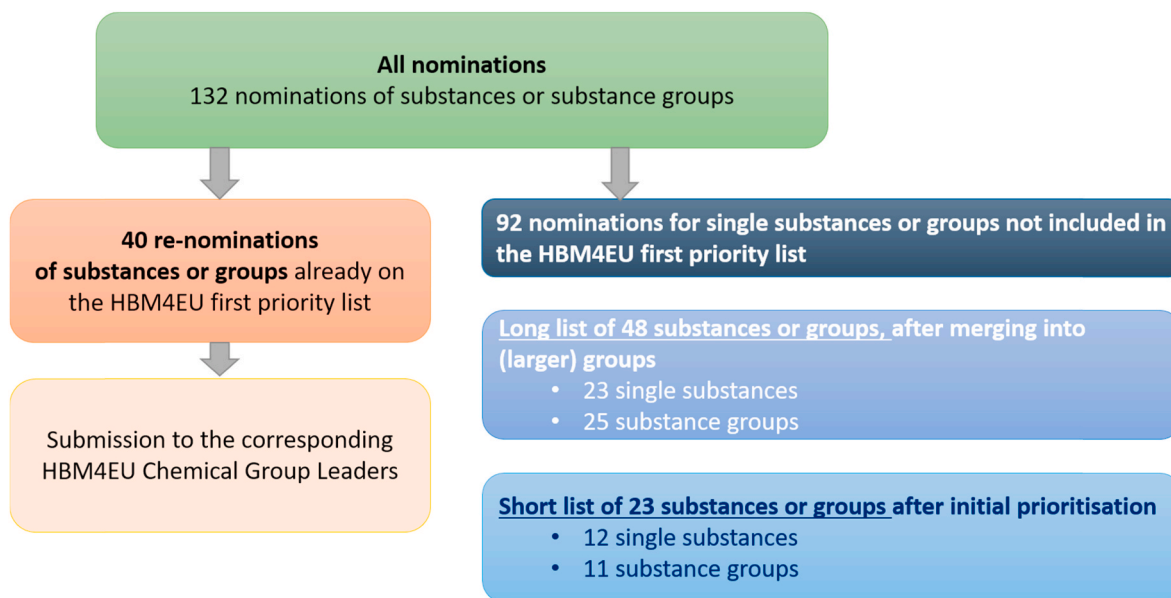


Fig. 3. Overview of the process to obtain the short list of substances/substance groups in the second HBM4EU prioritisation round.

Table 6

Weighting values assigned to the prioritisation criteria by experts during a second round of consultation as part of an adapted Delphi method and resulting consensus weighting values.

Prioritisation criterion	Weighting values (%) assigned by the experts											Resulting consensus weighting value (median)
	Expert number											
	1	2	3	4	5	6	7	8	9	10	11	
Hazardous properties	30	35	50	40	40	40	30	40	40	50	25	40%
Exposure characteristics	50	45	40	40	40	40	50	40	40	30	50	40%
Public concern	20	20	10	20	20	20	20	20	20	20	25	20%

3.2.2. Ranking the substances/substance groups according to their priority score (and category)

The substance's/substance group's scores against the hazard, exposure and public concern criteria that were discussed and approved by the expert panel involved in the scoring and categorisation steps, have been used to calculate the substance's/substance group's overall priority score following the approach described in section 2.2.1. These scores (individual score against each prioritisation criterion and overall priority score) and the category assigned by the experts to each substance/substance groups are available in the substance's revised background documents under <https://www.hbm4eu.eu/prioritisation-step-5/>. As an example, the scoring and categorisation of acrylamide is also provided in Supplementary Material - Annex 5.

The substances (or selected "lead" substances representing a nominated substance group) from the short list were then ranked according to their overall priority score (Table 7). As several single "lead" substances belonging to wide groups of substances have been scored (e.g. nano titanium dioxide, nano silver and carbon nanotubes were scored within the nominated nanomaterials group), 29 substances were ranked although only 23 substances/substance groups were included in the short list of substances' nominations. The substance's category, as indicator of the type of activity to be undertaken in the project for each substance (either policy-oriented activities as for example derivation of HBM guidance values or rather research activities as development of analytical methods) was specified next to the priority score. An alternative way of ranking the substances consisted in considering the priority score but this time among the substances from a certain category (ranking not shown).

3.3. Finalisation and approval of the second HBM4EU prioritisation list

The EU Policy board and the HBM4EU Management Board agreed on a final substances priority list after having engaged discussions on the substance's ranking and on the priorities for action from a policy perspective. The resources available for the project were considered in order to calibrate the number of substances to be included in the final list. This consideration also explains why few substances that had been ranked highly were not included in the final list. As an example, nanomaterials were not included due to the complexity to characterize them and the considerable resources that would be required for the development of analytical methods to measure them in biological matrices.

The second HBM4EU substance priority list, later approved by the HBM4EU Governing Board, is presented in Table 8.

3.4. Results of the feedback survey and recommendations for improvement of the chemical prioritisation strategy

In June 2019, a survey for the refinement of the prioritisation strategy was sent in anticipation of the third round of prioritisation under HBM4EU. Detailed information on this survey is available in the Annex 6 of the Supplementary Material. Main suggestions and improvements made are described below and will be taken into account for future rounds of prioritisation.

First, considering the nomination of groups of substances, the question was raised if it had to remain an option, considering the methodological difficulties that have been encountered to score such groups. The majority of respondents were still in favour of keeping this possibility. However, the nomination of a group should be manageable with regard to the resources of the programme. Substances of a given group

Table 7

Ranking of nominated substances or representative substance(s) for a substance group based on their overall priority score, along with the allocated knowledge-level representing category (A to D).

Rank	Substance (substance group)	Hazard score	Exposure score	Public concern score	Overall score ^a	Substance category (A to D) ^b
1	Arsenic (and its inorganic compounds)	27.2	38.0	9.0	74.2	B
2	Lead	25.3	36.0	9.0	70.3	A
3	Acrylamide	27.2	36.8	5.4	69.4	B
4	Aflatoxin B1 (<i>Mycotoxins</i>)	30.8	27.2	5.4	63.4	B
5	Chlorpyrifos (<i>Pesticides</i>)	13.3	29.2	20.0	62.5	B
6	Dimethoate (<i>Pesticides</i>)	12.4	31.2	18.0	61.6	C
7	Pyrethroids (<i>Pesticides</i>)	16.0	27.2	18.0	61.2	B
8	Permethrin (<i>Pesticides</i>)	14.0	28.0	18.0	60.0	B
9	Mercury (<i>Mercury & its organic compounds</i>)	17.2	28.0	10.8	56.0	A
10	DDAC (<i>Quaternary ammonium salts</i>)	9.2	32.8	12.8	54.8	C
11	Methylmercury (<i>Mercury & its organic compounds</i>)	22.0	23.2	9.0	54.2	B
12	Nano titanium dioxide (<i>Nanomaterials</i>)	16.0	26.8	10.8	53.6	D
13	4,4-MDI, 2,4-TDI & 2,6-TDI (<i>Diisocyanates</i>)	18.0	28.0	7.2	53.2	C
14	Glyphosate (<i>Pesticide</i>)	7.2	32.0	12.8	52.0	B
15	Deoxynivalenol (DON) (<i>Mycotoxins</i>)	18.0	28.0	5.4	51.4	C
16	BP-3 (<i>UV filters-Benzophenones</i>)	12.8	29.2	9.0	51.0	B
17	D4 (<i>Cyclic Siloxanes</i>)	5.6	33.2	11.0	49.8	C
18	N,N-dimethylformamide (DMF) (<i>Reprotoxic aprotic solvents</i>)	16.0	30.0	3.6	49.6	B
19	Nano silver (<i>Nanomaterials</i>)	14.0	26.0	9.0	49.0	D
20	BHT (2,6-di-tert-butyl-p-cresol)	14.0	32.8	1.8	48.6	C
21	Fumonisin B1 (<i>Mycotoxins</i>)	18.0	24.0	5.4	47.4	C
22	Fipronil (<i>Pesticide</i>)	16.8	25.2	3.6	45.6	C
23	Perchlorate	13.2	30.0	1.8	45.0	C
24	1-methyl-2-pyrrolidone (NMP) (<i>Reprotoxic aprotic solvents</i>)	12.0	27.2	3.6	42.8	B
25	UV-328 (<i>Phenolic benzotriazoles</i>)	12.0	27.2	3.6	41.0	C
26	Carbon nanotube (<i>Nanomaterials</i>)	12.8	18.8	9.0	40.6	D
27	BENPAT (<i>Substituted phenylenediamines</i>)	15.2	24.8	0	40.0	D
28	POE-tallow amine	12.0	20.0	3.6	35.6	C
29	N,N-diethyl-m-toluamide (<i>Pesticides</i>)	7.2	25.2	0.0	32.4	C

^a The overall priority score was obtained by adding the weighted prioritisation criteria scores.

^b An A to D category was allocated to the substance considering its knowledge level as informed in the revised background document and according to the definitions of the categories.

Table 8

Approved second HBM4EU list of priority substances.

No	Single substance or group of substances	Substance(s) considered for the scoring	Overall priority score	Substance Category
1	Lead (and its compounds)	Lead	70.3	A
2	Mercury (and its organic compounds)	Mercury Methylmercury	56.0 54.2	A B
3	Arsenic inorganic compounds	Inorganic arsenic compounds, including diarsenic trioxide	74.2	B
4	Acrylamide	Acrylamide	69.4	B
5	Mycotoxins	Aflatoxin B1 Deoxynivalenol Fumonisin B1	63.4 51.4 47.4	B C C
6	Pesticides	Chlorpyrifos Dimethoate Pyrethroids Permethrin Glyphosate Fipronil	62.5 61.6 61.2 60.0 52.0 45.6	B C B B B C
7	UV filters - Benzophenones	Benzophenone-3	51.0	B
8	Aprotic solvents	N,N-dimethylformamide 1-methyl-2-pyrrolidone	49.6 42.8	B B
9	Diisocyanates	4,4-MDI, 2,4-TDI & 2,6-TDI	53.2	C

may have structural similarities or the same analytical methods, offering the possibility for work packages to include a set of substances (i.e. a group) in their programmes in a rational way. The online survey for

nominating substances in the second prioritisation round suggested that a possible rationale for including several substances in a single group may be based on a similar toxicological profile or similar uses. However, a rationale for grouping substances based on similar uses can possibly lead to the nomination of a wide group of substances of very different types, making it difficult to work on all of them within the project. Therefore, more relevant rationales for grouping substances, e.g. common analytical methods is recommended (e.g. all species of inorganic arsenic such as arsine, arsenate, dimethylarsinic acid (DMA), methylarsonic acid (MMA) may all be measured by a single speciation method).

Secondly, regarding the scoring method for groups of substances, a legitimate discussion was raised on the scoring of a “representative” lead substance of the group. An alternative approach consists in considering a “worst-case scoring”, performed on the most harmful characteristics identified for substances within the group. Because there may be significant differences across substances within a group, due for example to the heterogeneity in data availability, the most cautious approach should always prevail when considering risk assessment. This enhances the need of a robust and well-justified rationale behind the nominations of groups, as mentioned above.

Thirdly, the likelihood that a specific substance is part of a mixture of daily life exposure could additionally be taken into account as a parameter to score the exposure criterion.

Finally, regarding the overall nomination process, interesting suggestions have been made to improve its efficiency. Indeed, each entity nominating substances had to complete the entire online survey for each substance/substance groups (with an upper limit of 5 nominations). The survey is a time-consuming procedure that had to be completed even if the nominated substance may not be selected in the final prioritisation process. It was therefore suggested that each nominating entity first

provides initial expression of interest. Then, a short list of substances would be set on the basis of the interest of the nominating entities and shared with them, to allow coordinating efforts on providing the relevant documentation for a substance or group of this list.

4. Discussion

It is the first time that a pan-European HBM project has been implemented, with currently 30 countries being part of the initiative already (North Macedonia and Estonia joined the initiative in 2020). The prioritisation process had to propose a method allowing the selection of substances of common priority across participating countries, the EC and a range of stakeholders, but also to determine the research efforts needed at national levels.

4.1. Comparison with other chemical prioritisation process

The HBM4EU prioritisation process can be compared to other substance prioritisation activities at the EU level, for example the EU Directive 2000/60/EC, commonly known as the EU Water Framework Directive (WFD) (Daginnus et al., 2011). This was also a policy-oriented prioritisation process for monitoring chemicals in water bodies. The process for the WFD was finalised with Decision 2455/2001/EC on the first list of priority substances and is revised and updated every 6 years. Under the WFD, priority substances are identified based on a two-year consultation process for which a combined monitoring-based and modelling-based priority-setting procedure has been developed. Background documents are produced for the priority substances as well as a procedure for the identification of priority hazardous substances. An expert advisory group, consisting of experts from Member States, European Free Trade Association (EFTA) countries, the Scientific Committee on Toxicity, Ecotoxicity and the Environment (SCTEE), the European Chemicals Bureau and stakeholders from industry, water suppliers and environmental groups, are consulted. In the WFD, substances are prioritised taking into account (Bodar et al., 2003): 1) risk assessments carried out under existing chemically relevant EU Directives and Regulations, e.g. ECHA and the European Food Safety Authority (EFSA) (Bodar et al., 2003; ECHA 2016; EFSA 2009; EU Regulation No 528/2012); 2) targeted risk-based assessments focusing on aquatic ecotoxicity and human toxicity *via* the aquatic environment; 3) simplified risk-based assessments based on intrinsic hazards, widespread environmental contamination, production volumes and use patterns. The priority list of substances under the WFD focuses only on single substances (Daginnus et al., 2011; Faust et al., 2019; INERIS 2009).

Similar to the WFD, the time for implementation of the proposed HBM4EU prioritisation process is quite long (approximately 1 year). The HBM4EU prioritisation process also includes consulting an expert group, as well as with partners participating in the project, i.e. policy makers, scientists and stakeholders who nominated substances to be included for monitoring and research activities within the project. This approach aims to ensure the legitimacy, credibility and societal relevance of the process. Within HBM4EU, a stakeholder workshop was also conducted to address public concerns, a step that was not included in the WFD priority-setting process.

In contrast to the WFD, the HBM4EU priority-setting process did not include any type of risk assessment studies, nor did it focus only on single substances, cf. group of priority substances on mixtures, emerging chemicals, flame retardants, PAHs and pesticides.

In Europe, other national biomonitoring programmes are also known to have a priority strategy for substances that share some similarities with that of HBM4EU.

In France, the National Nutrition and Health Survey (ENNS) was conducted in 2006–2007 to meet the objectives on biomonitoring, chronic disease surveillance and nutritional surveillance. More recently, the Grenelle I Act (No. 2009–967 of August 3, 2009) led to the

development of a French National Biomonitoring programme, in which two distinct studies were designed: 1) the Health Study on Environment, Biomonitoring, Physical Activity and Nutrition (called “Esteban”), which is a nationwide cross-sectional survey of the mainland population aged 6–74 years and 2) the ELFE cohort (Longitudinal Study from Childhood) constituting the perinatal component of the French National Biomonitoring programme (Balicco et al., 2017; Dereumeaux et al., 2016; Fillol et al., 2014; Fréry et al., 2012). The prioritisation process relies on members of government agencies to validate an initial list of pollutants and on a group of French-speaking and international HBM experts to establish the selection criteria, to rate the chemicals using a graded score and to review, validate and establish a provisional final list. The final list is reviewed, revised and recommended by an “emerging risk” group of the National Environmental Health Plan (PNSE).

In Belgium, Flanders has established the Flemish Environment and Health Study (FLEHS) (Schoeters et al. 2012, 2017). The prioritisation of chemicals was based on international lists and expert advice using weighted scoring, followed by a step-by-step procedure implemented to first categorise criteria and then select and score the chemicals. Scientific experts and the strategic advisory board for the Ministry of Environment, Health and Energy and the Socio-economic Board (representatives of employers and employees) were asked to make recommendations.

Germany has one of the longest running HBM programmes in Europe. The German Environmental Survey (GerES) has been running since 1985, and its prioritisation strategy is based on existing international lists and further information on hazardous chemicals and the degree of exposure of the general public in Germany and expert judgments (government authorities, industry and science sectors) (Kolos-Gehring et al. 2012b, 2017; Schulz et al. 2007, 2017). The selection of chemicals for GerES also focuses on a cooperation project between the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) and the German Chemical Industry Association (VCI) to select new substances and to develop new analytical HBM methods.

In Canada, the Canadian Health Measures Survey (CHMS) prioritisation approach is based on expert advice (workshop of experts), stakeholder consultations *via* questionnaires, and the Health Canada regulatory programme needs mandated by the Chemicals Management Plan. The process was adapted and adjusted during each of the first three cycles of the CHMS (Haines et al., 2017).

In the US, the main HBM programme is NHANES, running since the 1970s (CDC 2009, 2019). It comprises a participatory approach led by the Center for Disease Control (CDC) *via* notices in the Federal Register to establish criteria for inclusion or removal of chemicals and for the nomination of chemicals to measure in the biomonitoring program as part of NHANES. An expert panel of outside reviewers and CDC scientists scores nominated individual chemicals or categories of chemicals using weighted criteria to categorise these into five priority groups. Another recent initiative is the Environmental Influences on Child Health Outcomes (ECHO) by the US National Institutes of Health. With multiple cohorts of participating children, it will take into account longitudinal studies to investigate environmental exposures (including chemicals) on child health and development. It will investigate the exposure to about 200 chemicals already present in NHANES as well as new chemicals. ECHO’s prioritisation strategy is based on database and literature research for chemicals in environmental media and in consumer products that are potentially toxic, and that have not been measured in NHANES (Pellizzari et al., 2019).

4.2. Specificity and limitation of the HBM4EU chemical prioritisation process

With different types of approaches for each country and HBM programme, there are some commonalities that were taken into account and adapted to the objectives of HBM4EU. The aim of the HBM4EU initiative is not only to measure the internal exposure to well-known

substances in the European population, but also to focus on human exposure to lesser known or emerging substances for which analytical methods are not yet available, and toxicological and exposure data is currently insufficient.

As an H2020 project, HBM4EU addresses societal challenges to health and well-being for European citizens. It is a main objective of the project to bridge the divide between science and policy at the European level and to generate results that meet the knowledge needs of EU policy makers. Priority was therefore given to the nomination of substances by members of the EU Policy Board, with the aim of delivering on this key objective. Input from the National Hubs was also highly valued and helped to ensure that the project also serves the knowledge needs of national policy makers and to determine whether national and European level priorities are aligned. Selected substances are the subject of research at European level. It is therefore important that HBM4EU addresses knowledge gaps on chemical exposure and resulting health impacts that have relevance at the European level and that can generate results that benefit the pan-European population. Substances that are exclusively of local or national concern were therefore not considered. Input from the Stakeholder Forum made it possible to assess the social relevance of research activities on nominated substances and drew in additional evidence and knowledge. As such, the strategy for the prioritisation of substances was not based entirely on scientific evidence. It was also guided by an imperative to produce knowledge in support of policy making at European level.

A literature review was carried out to discern and adapt the prioritisation strategy from international experiences. The prioritisation criteria that were selected and used for the scoring and the whole prioritisation process needed to be streamlined, also including time restrictions. During the prioritisation process, substances were allocated to categories reflecting the availability of existing data on hazard and exposure. The substance's regulatory status and availability of analytical methods to perform HBM were also taken into account. The aim was to ensure that HBM4EU focused not just on well-known and -studied substances, but also covered ones with limited data. Indeed, the particularity of this project in comparison to other biomonitoring programmes is that it includes also research activities dedicated, for example, to the identification of biomarkers of effect or the development of analytical methods. Therefore also, when data gaps have been identified for certain hazards or exposure parameters during the scoring step, a Low score was attributed instead of a null score to avoid "disadvantaging" lesser-known substances during the ranking of the substances. This special attention to have lesser-known substances included in the second priority list has the merit to constitute an anticipatory approach by generating knowledge on data poor substances.

Despite efforts made to implement an objective and systematic scoring method, expert judgment was inevitable to score some parameters, in particular for data-poor substances. For example, the CLP classification was considered for scoring some endpoints (i.e. an objective score relying on solid evidence), but where no official classification has been proposed, then evidence identified in the peer-reviewed literature were considered. In this case, the expert's judgement has a more prominent influence on the given score. Nevertheless, each given score was discussed with a panel of experts from a variety of fields of expertise, in order to reduce the subjectivity in the scoring. The evaluation of societal concern can also be liable to some subjectivity. Scoring this criterion relied mainly on the stakeholder's reflections and information about the substances captured during a stakeholder workshop (including whether NGO campaigns related to the substances were recently conducted), but also on lists established by diverse stakeholders. In this consideration however, the weight given under the prioritisation process to the scoring of societal concern was lower (20%) than the ones given to the scoring of hazards and exposure characteristics (40% each). However, to help define this societal concern, it may be worth better considering differences in terms of occupational health aspects versus the general population or environmental aspects. Specific

questions on such aspects can be asked before prioritisation in the survey used by the entities to nominate substances, to provide further arguments in support of the nomination of substances or groups of substances. Finally, every step of the process, justifications of the choices made and results are fully documented on the HBM4EU webpages, in order to account for the choices made in a completely transparent way.

4.3. Reflections for a further refined chemical prioritisation process

Steps for a further refined prioritisation strategy are presented below:

- 1) Pre-nomination step: the EU Policy Board, the Stakeholder Forum as well as the National Hubs provide an initial expression of interest for up to 5 substances or groups of substances together with a rationale for nominating them.
- 2) Long list of nominated substances/groups: this list will be publicly available and will collate all the nominated substances/groups of substances and the nominating parties who nominated them.
- 3) Short list of nominated substances: based on the long list of nominated substances/groups of substances, partners involved in the prioritisation process will produce a short list of approximately 25 substances/groups, ranked according to the number of times they were nominated and to who nominated them (i.e. following the same criteria used during the second round of prioritisation, as mentioned above).
- 4) Compiling data: after producing and sharing the short list, nominating parties will have 2 months to complete the online survey requesting information related to the prioritisation criteria. Based on the information provided in the survey on each nominated substances/groups of substances, background documents will be produced within 3 months. In the meantime, a Stakeholder Forum workshop will be organised to evaluate the societal concern of the substances/groups of substances on the short list.
- 5) Scoring and ranking process: the substances/groups of substances of the short list will be scored and categorised by experts, on the basis of the information gathered in the background documents, allowing for the elaboration of a ranked list of prioritised substances.

Before the end of the HBM4EU project, a third round of prioritisation will be run based on the feedback and suggestions for improvement presented in this paper. This work will then benefit any follow-up HBM initiative that takes place. Currently, discussions are ongoing for the set-up of a partnership under Horizon Europe, the European Partnership for the Assessment of Risks from Chemicals (PARC).

5. Conclusion

To prioritise chemicals for inclusion in a European-wide HBM initiative, a structured and transparent process was developed using a participatory approach. Prioritisation must reflect the selection of chemicals of interest considering the diversity of needs for such initiative, as also the policy needs from the participating countries and agencies and the current concerns of European citizens. The prioritisation strategy for substances and substance groups developed in HBM4EU served to guide biomarker selection for the biomonitoring studies initiated in HBM4EU and the associated research to improve interpretation of biomarker data in terms of health risks and exposure sources. The process was considered to be transparent and science-based, as shown by the feedback that was obtained.

The strategy for the second round of prioritisation of HBM4EU priority substances was implemented over a one-year period (from July 2017 to June 2018). The list of prioritised substances and their respective selected CGLs was approved by the HBM4EU Governing Board composed of the programme sponsors in the participating countries, the European Chemicals Agency (ECHA), the EEA and EFSA in July 2018,

after which research activities could start. The second list included acrylamide, aprotic solvents, arsenic, diisocyanates, lead, mercury, mycotoxins, pesticides (including chlorpyrifos, dimethoate, pyrethroids, glyphosate and polyethoxylated (POE)-tallow amine, and fipronil), and a type of UV filters (benzophenones).

To further maintain harmonised and comparable results of prioritisation processes, we recommend that any future HBM project take this prioritisation process into account. The prioritisation strategy developed under HBM4EU, as well as the third list of priority substances, can be used in any follow-up HBM initiative.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijheh.2021.113778>.

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