



The questionnaire design process in the European Human Biomonitoring Initiative (HBM4EU)

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ABSTRACT

Background: Designing questionnaires is a key point of epidemiological studies assessing human exposure to chemicals. The lack of validated questionnaires can lead to the use of previously developed and sub-optimally adapted questionnaires, which may result in information biases that affect the study's validity. On this ground, a multidisciplinary group of researchers developed a series of tools to support data collection within the HBM4EU initiative. The objective of this paper is to share the process of developing HBM4EU questionnaires, as well as to provide researchers with harmonized procedures that could help them to design future questionnaires to assess environmental exposures.

Methods: In the frame of the work package on survey design and fieldwork of the HBM4EU, researchers carried out procedures necessary for the development of quality questionnaires and related data collection tools. These procedures consisted of a systematic search to identify questionnaires used in previous human biomonitoring (HBM) studies, as well as the development of a checklist and evaluation sheet to assess the questionnaires identified. The results of these evaluations were taken into consideration for the development of the final questionnaires.

Results: The main points covered by each of the sections included in HBM4EU questionnaires are described and discussed in detail. Additional tools developed for data collection in the HBM4EU (e.g. non-responder questionnaire, satisfaction questionnaire, matrix-specific questionnaire) are also addressed. Special attention is paid to the limitations faced and hurdles overcome during the process of questionnaire development.

Conclusions: Designing questionnaires for use in HBM studies requires substantial effort by a multidisciplinary team to guarantee that the quality of the information collected meets the study's objectives. The process of questionnaire development described herein will contribute to improve the harmonization of HBM studies within the social and environmental context of the EU countries.

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1. Introduction

Epidemiological studies or surveys aimed at assessing environmental exposures need to find the most accurate methods for data collection. Questionnaires are often deemed the best choice and are among the most widely used methods to collect relevant information for studies (Gillham, 2000) as compared to other methods such as collecting information from official registers. As the development of questionnaires is a key process in the preparation of HBM studies, special attention should be paid.

Questionnaires can provide useful information on the main sources and determinants of exposure to environmental chemicals, along with data on the duration, time window (past, recent or current exposure) and frequency (Nieuwenhuijsen, 2005). When combined with exposure data, questionnaires can help to better reflect past and longer-term exposure patterns. In addition, in the absence of measured exposure data, questionnaires can provide a surrogate measure of the exposure (Ozkaynak et al., 2005). The information obtained by questionnaires offers a wide variety of potential uses. Data can inter alia be used directly or converted to create new and more complex variables, such as exposure indexes (Nieuwenhuijsen, 2008). Moreover, questionnaires can serve purposes other than just collecting information with which to assess exposures, such as gathering data on potential confounding factors or on health effects.

In general, it is preferable to use validated questionnaires (i.e. those that have demonstrated adequate reliability and validity) when they are available. But in the field of environmental epidemiology the number of validated questionnaires is very limited. Although a few attempts have been made to study the potential of a questionnaire to predict the magnitude of exposure to environmental chemicals in e.g. pregnant women (Eskenaazi et al., 2013), children (English et al., 2015; 2019) or the general population (Nomura et al., 2016), considerable work remains to be done in this field.

Therefore, questionnaires for new studies must often be designed and developed by the researchers conducting the study. When this is the case, researchers must determine which features the questionnaire should have, depending on research objectives, study population and resources available in terms of staffing, expertise, finance and time. Based on these features, researchers must then decide what information will be obtained using the questionnaire and how it will be administered (e.g. self-completed, face to face or telephone interviews). Other aspects such as structure, wording or layout, selection of individual questions, among others, also need to be considered. Developing questionnaires is a key process in the preparation of HBM studies (Fiddicke et al., 2021). Only well-designed questionnaires that fit with the study's aims and needs will provide valid and useful information. Therefore, special attention must be paid to the process of designing and drafting questionnaires.

The European Human Biomonitoring Initiative (HBM4EU) is a joint initiative of 30 countries, the European Environment Agency and the European Commission co-funded under Horizon 2020. It was launched in 2017 for the purpose of coordinating and advancing human biomonitoring (HBM) in Europe. The Initiative's primary objective is to gather evidence of the real exposures of citizens to chemicals and their possible health effects, and to support policymaking in this area (Ganzleben et al., 2017). Another key goal of HBM4EU is to harmonize procedures for HBM in order to provide policymakers and researchers with comparable data regarding levels of human exposure to environmental chemicals across the EU. The Initiative also seeks to bring human biomonitoring studies into better alignment and to produce a European dataset (Gilles et al., 2021) (more information on the European HBM Platform and alignment of surveys at EU level is available at <https://www.hbm4eu.eu/the-project/european-hbm-platform/>).

HBM4EU has its own strategy for the prioritization of substances to be studied, to aid in the selection of substances that will be studied within the scope of this project (Ougier et al., 2021). Existing gaps in

knowledge regarding chemical exposures led to the definition of two sets of priority substances that might cause adverse health impacts of relevance at the European level (supplementary table 1). More information about the prioritization strategy is available at <https://www.hbm4eu.eu/objectives-of-the-prioritisation-strategy/>.

The objectives of HBM4EU also include "the elaboration of harmonized questionnaires to collect information on individual characteristics of the participants regarding age, sex, body mass index, socio-economic class, general health and on different exposure sources and pathways, as well as specific sampling information to allow the interpretation of biomarker values". All of the foregoing objectives point to the need to develop tools with which to collect information in a standardised manner, to facilitate the use of such tools in aligned studies (those conducted in a collaborative framework within HBM4EU) (Gilles et al., 2021), and to ensure the comparability of results across geographic regions and time-points.

The aim of this article is to describe the process of developing a standardised questionnaire to be used within the framework of the Human Biomonitoring Initiative in Europe (HBM4EU) as well as other questionnaire-based tools for collecting relevant information in this project. The activity reported herein attempts to respond to the needs of: 1) elaborating comprehensive and agreed materials which cover all the information necessary to adequately characterize exposure to priority substances in the HBM4EU project; and 2) providing well-designed and structured tools to collect information that allow for more efficient data analysis. The article also discusses the experience gained by researchers during the elaboration of these tools, so as to increase the transparency of the procedures used to develop questionnaires assessing environmental exposures.

2. Methods

A group of multidisciplinary researchers with expertise, inter alia, in environmental epidemiology (n = 7), toxicology (n = 6), occupational epidemiology and health (n = 4), food safety (n = 5) and health sciences (n = 10), conducted a far-reaching project to develop a battery of questionnaire-based tools for collecting relevant information for HBM4EU. All professionals and institutions involved in this process are listed in supplementary tables 2 and 3.

A well-defined process was followed to design and develop the questionnaires (Fig. 1). Firstly, a number of sequential steps were carried out to define the general content of the questionnaire. Subsequently, next steps were undertaken in parallel to obtain the final questionnaires. The main stages of this process are described in detail in the following subsections.

2.1. Elaboration of a checklist

This is an early step in the process of questionnaire development that specifies domains or blocks of information that deserve to be included in the questionnaire (sociodemographics; exposure sources; health endpoints; confounders/effect modifiers) (Table 1). Participating researchers took the time to agree upon a checklist that included the following six blocks of information: i) sociodemographic information; ii) residential environment and home exposures; iii) diet; iv) lifestyle; v) occupational exposure: occupational history and current and retrospective exposure to chemical compounds at work; and vi) health. Within each section general items were addressed in broad brushstrokes. Further details about the checklist and the general items are shown in Table 1.

2.2. The search for questionnaires

An online search was conducted to identify questionnaires already used in relevant human biomonitoring studies performed worldwide. The search strategy was based on the following two methods.

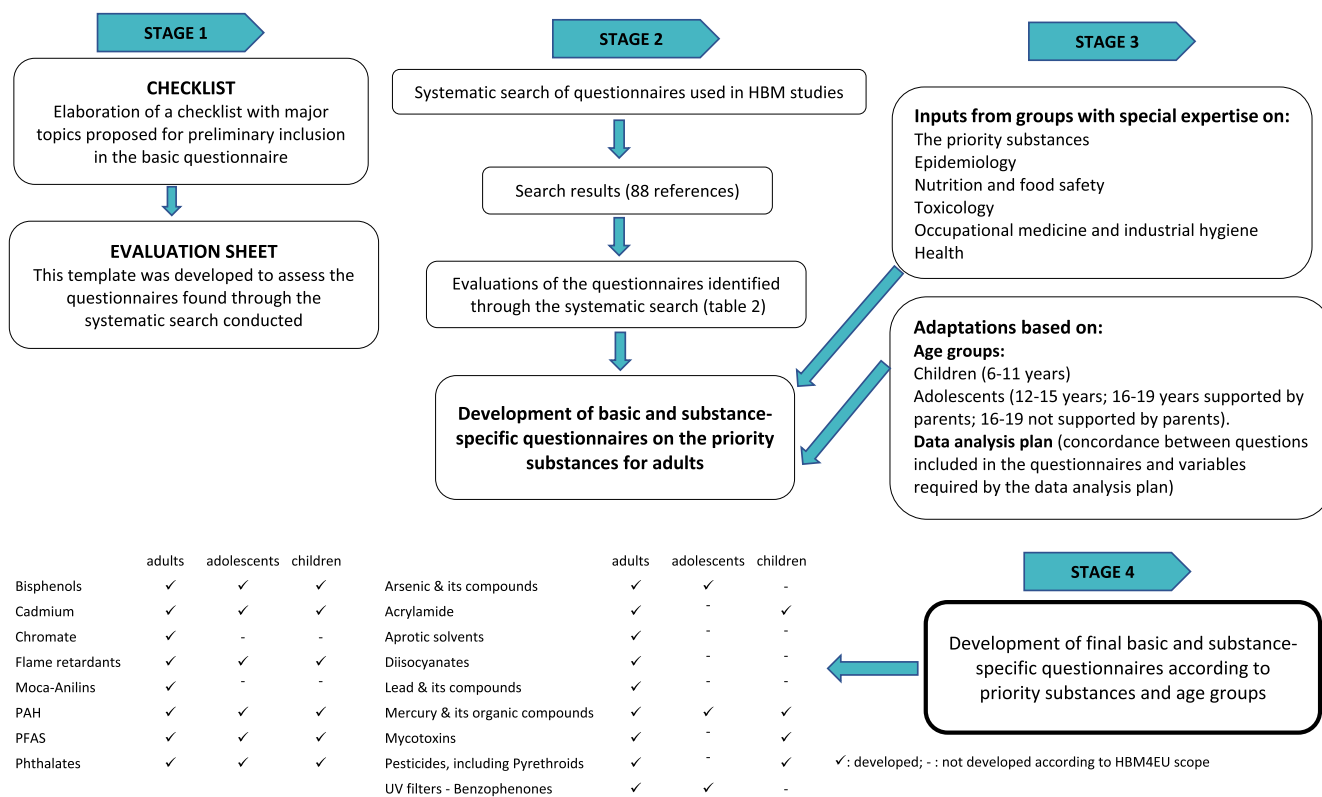


Fig. 1. Summary of the main stages followed for the elaboration of the questionnaires in the frame of HBM4EU.

2.2.1. Systematic search

A systematic search was carried out in PubMed, Web of Science, Scopus and EMBASE, using an appropriate combination of free keywords pertaining to human biomonitoring programmes and questionnaires: human biomonitoring, programme, survey, environment OR environmental, general population, questionnaire design, questionnaire development, epidemiological questionnaire. The following inclusion criteria were established: articles in English or any other EU language spoken by the researchers involved in this work (Spanish, Portuguese, German, Italian, French and Finnish) published in scientific journals in the last 10 years with an available abstract and reporting information on well-established HBM programs in the general population, as well as on the design and use of questionnaires. The search was completed in February of 2017.

Altogether, 108 references were identified in Pubmed, 83 in Web of Science, 289 in Scopus, and 139 in EMBASE. After exclusion of duplicates, a total of 88 references meeting the inclusion criteria remained. Their abstracts were peer-reviewed by two members of the Andalusian School of Public Health (EASP) team to determine whether they contained information of interest to the objectives of this review. Then articles deemed to contain relevant information were entirely read to gather more information on the questionnaires used in the surveys.

2.2.2. Other information sources

We also checked review articles and book chapters not identified via database searches but that were found in the bibliography of the articles reviewed and in web browser searches. Official websites of the institutions leading HBM programmes and other online resources were consulted to gain access to the questionnaires used in the aforementioned studies. Likewise, a search of the grey literature (official reports, national or regional HBM programs, among others) was performed via Open Grey.

2.2.3. Search results

This search strategy produced a total of 27 HBM programmes and 14 epidemiological studies and other resources useful for evaluating sociodemographic characteristics of the population and potential human risks associated with environmental exposures to chemicals. Table 2 summarised the HBM programmes, other resources and epidemiological studies identified through the systematic search. The table also notes whether the corresponding questionnaires were available for further evaluation (this is not shown for epidemiological studies, since none of the questionnaires used in these studies were revealed in the scientific publications or their supplementary material).

2.3. Evaluation sheet

Based on the checklist described in section 2.1, an evaluation sheet template was developed to assess the questionnaires found through the systematic search conducted previously, in order to identify those questions that best fit each item on the checklist. These questions were given further consideration for inclusion in the harmonized questionnaires for HBM4EU.

The Excel file containing the evaluation sheet had six sections, each one corresponding to a type of information included in the checklist: i) sociodemographic information; ii) residential environment and home exposures; iii) dietary habits; iv) lifestyle; v) occupational exposure; vi) health. For every item (each row of the Excel file) within each section, evaluators answered five questions (each column of the Excel file) about the content of the original questionnaire. Extra rows were available at the end of each section for the evaluator to make observations on each topic or the entire questionnaire. Sections of the evaluation sheet are shown in Table 3.

Nine evaluators from institutions involved in this project were selected based on their expertise and language skills to perform the evaluation of the original questionnaires using the evaluation sheet template. The five points to be addressed by the reviewers were: 1) Was

Table 1
Preliminary items covered by the checklist which were then included in the basic questionnaire.

I. Sociodemographic information	II. Residential environment and home exposures
Birth date/ Age	Area of residence (e.g. urban, suburban, countryside)
Sex	Living environment (e.g. agricultural area, industrial area)
Birth place (municipality, region, country, PC)	Dwelling type (e.g. flat, house)
Race/ethnicity	Dwelling characteristics: (e.g. size, year of building, materials)
Current address	Traffic-related questions
Time living in... (country/municipality/study area, current residence)	Heating and air conditioning systems
Education (according to International Standard Classification of Education (ISCED))	Energy source used for cooking (e.g. gas)
Household members (number, age, relationship)	Cleaning habits (including cleaning products and insecticides)
Current employment situation (all household members)	Pets at home (including insecticides)
Household income levels (monthly)	
Occupational category (according to international ISCO-08 coding system)	
Occupational social class (based on validated classification systems for each country)	
III. Diet	IV. Lifestyle
Food frequency questionnaire (last 12 months)	Smoking
24-hour food consumption	Physical activity
Water consumption (including origin and frequency)	Daily activity (including journeys and indoor and outdoor activities)
Source of food (e.g. homemade food, bar or restaurant)	Frequency of use of hygiene products and cosmetics (e.g. perfums, moisturizing creams and makeup)
Ways of cooking food	Hobbies (e.g. crafts, DIY activities)
Supplementation: vitamins and minerals	
Special diets	
V. Health	VI. Occupational exposure: occupational history and current and retrospective exposure to chemical compounds at work
Anthropometric measurements: weight, height, contour waist and skin folds	Working life (including occupations, activity sector, tasks and duration)
Weight changes	Exposure to chemical compounds at work (retrospective and current exposures)
Diagnosed acute and chronic diseases	
Allergies	
Consumption of medications	
Vaccinations	
Reproductive history: fertility problems, abortion, pregnancy, children, breastfeeding	
Dental health (including dental fillings and other treatments)	
Body modifications (e.g. piercings, implants, tattoos)	

information available in the original questionnaire (yes/no); 2) Question formulation; 3) Do you think the question is adequately formulated for inclusion in the HBM4EU questionnaire?; 4) Do you consider this question appropriate for HBM4EU objectives?; 5) Content validity; and an additional area for Observations. The evaluators received instructions as to the input they should give for each question of the evaluation sheet, based on the content of the original questionnaire.

Evaluations were thoroughly reviewed and summarized by the Escuela Andaluza de Salud Pública (EASP, Granada, Spain) team who had expertise in the fields of epidemiology, toxicology, food safety, occupational health and biomonitoring surveys. Relevant information

was compiled so that it could be incorporated into the standardized HBM4EU questionnaires.

2.4. Justification of formal and technical aspects of the questionnaires

The elaboration of a questionnaire is a complex process that entails several critical steps. Defining basic features of the questionnaire is one such step, since aspects, such as the structure, wording or layout, among others, depend directly on the features previously defined. In this regard, the way the questionnaire is to be administered has significant implications on its design. The questionnaire can be self-completed by the participants (paper or online) or based on an interview (face to face interview, telephone interview), in which the information is collected using traditional formats or digital aids (Computer Assisted Personal Interview-CAPI; Computer Assisted Telephone Interview-CATI; Computer Assisted Self-Interviewing-CASI; Computer Assessed Web Interview-CAWI).

The design of a questionnaire intended to be completed by the respondents must be simpler and clearer than a questionnaire administered by trained interviewers, which often includes complex structures such as jump rules (Mathers et al., 2007). In the case at hand, bearing in mind the aims and characteristics of HBM4EU, as well as the pros and cons of the different questioning methods, it was agreed to undertake the design of a questionnaire to be administered by means of a face to face interview. This method of administration is well-suited to meeting some of the most relevant requirements of questionnaire-based data collection in the framework of HBM4EU and aligned studies. The HBM4EU requires the collection of a wide range of information in an accurate and objective manner. The administration of the questionnaire by trained interviewers: 1) improves the validity of the information collected –compared to that collected by a self-completed questionnaire– since the interviewer can provide clarification or other resources to respondents (e.g. visual resources, scales) that allow to obtain more accurate and unbiased answers; and 2) increases response rates –compared to those obtained with self-completed questionnaires– because this type of questionnaire can take quite a while to complete (45–60 min) (Mathers et al., 2007). Furthermore, this method provides certainty regarding who is answering the questionnaire and it can be useful in assessing the veracity of certain answers (e.g. questions about the residential environment), among other factors (Mathers et al., 2007).

As for other basic features of HBM4EU questionnaires, such as the type of questions, a combination of closed and open questions was considered necessary. Also, general guidance on the wording was provided before the questions were drafted. Efforts were made to use: i) clear wording (technical terms were removed when possible or at least explained); ii) specific questions (when, what exactly); iii) questions with a single answer; iv) positive phrasing; and vi) neutral language (not offensive or emotional) (Fiddicke, 2018).

3. Results and discussion

This section describes the main features of the instruments developed for data collection to meet the information demands of HBM4EU. It includes a detailed description of the main sections of the basic and substance-specific questionnaires elaborated on the basis of the evaluation of questionnaires previously used for HBM studies (section 2.3 and 2.4). Subsequent updates and adaptations of these questionnaires are also addressed here. Likewise, general considerations on these instruments are discussed throughout this section.

3.1. Basic and substance-specific questionnaires

These questionnaires had the most weight for data collection under HBM4EU. The basic questionnaire was developed to collect all the necessary information concerning individual characteristics of adults respondents, in terms of sociodemographics and lifestyle, occupation

Table 2
Summary of HBM programmes, epidemiological studies and other resources identified through the systematic search.

HBM programmes			
Title (year)	Country	Link	Questionnaire accessibility
Pollutants in humans (2008–2011)	Austria	http://www.umweltbundesamt.at/en/	n.a.
Canada Health Measures Survey (CHMS) (2007–2017)	Canada	http://www.hc-sc.gc.ca/ewh-semt/contaminants/human-humaine/chms-ecms-eng.php	O
National Survey of Persistent Organic Pollutants in Human Milk in China (2005)	China	http://www.chinafoodsafety.net/detail.aspx?id=16441E47E7C025CEB156558B18113F5852100BC370FF75A5	n.a.
Human Biomonitoring Project (CZ-HBM). Environmental health monitoring system (2009–2016)	Czech Republic	http://www.szu.cz/topics/environmental-health/human-biomonitoring?highlightWords=biomonitoring	P
COPHES/DEMOCOPHES project (2009–2012)	Europe	http://www.eu-hbm.info/democophes	O
ESBIO (2005–2007)	Europe	http://cordis.europa.eu/result/rcn/44527_en.html (questionnaire available under request in this web site)	n.a.
Flemish Environment and Health Study. FLEHS I (2002–2006); FLEHS II (2007–2011)	Flanders	http://www.milieu-en-gezondheid.be/English/contact.html#3	n.a.
Elfe: etude longitudinale française depuis le enfance (2011)	France	http://www.elfe-france.fr/index.php/en/	n.a.
The French National Survey on Nutrition and Health-ENNS (2006–2007)	France	http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Nutrition-et-sante/Enquete-s-et-etudes/ENNS-etude-nationale-nutrition-sante	n.a.
German Environmental Survey-GerES V (2014–2017)	Germany	http://www.umweltbundesamt.de/en/topics/health/assessment-environmentally-related-health-risks/german-environmental-survey-geres	P
Human Biomonitoring of Environmental Chemicals in Israel (2012)	Israel	http://www.health.gov.il/NewsAndEvents/SpokemanMessages/documents/dover_27092012_3.pdf	O
Programme for biomonitoring the Italian population exposure-PROBE (2011).	Italy	http://www.ccm-network.it/progetto.jsp?id=node/604&idP=740	P
Japan Environment and Children's Study-JECS (2011)	Japan	https://www.env.go.jp/en/chemi/hs/jecs/about_the_study/index.html	n.a.
The Russia Longitudinal Monitoring Survey (1994–2017)	Russia	http://www.cpc.unc.edu/projects/rhms-hse/data/questionnaires	O
National human biomonitoring programme in Slovenia (2007)	Slovenia	http://www.nijz.si/en	n.a.
Korean National Survey for Environmental Pollutants in the Human Body (KorSEP) (2005–2017)	South Korea	http://www.nier.go.kr/NIER/egovEngIndex.jsp	n.a.
Korean National Environmental Health Survey (KoNHES) (2012–2014)	South Korea	http://www.nier.go.kr/NIER/egovEngIndex.jsp	O
BIOAMBIENT (2009–2010)	Spain	http://democophes.blogs.isciii.es/category/biomonitorizacion-espana/	O
Catalan Health Interview Survey (2010–2017)	Spain	http://web.gencat.cat/es/actualitat/detall/Enquesta-de-salut-ESCA-2017	O
Andalusian Biomonitoring Program (2012–2014)	Spain	http://www.easp.es/	O
Canarias Health Survey (2015)	Spain	http://www.gobiernodecanarias.org/istac/temas_estadisticos/sociedad/salud/estadodesalud/C00035A.html	O
Swedish environmental health questionnaire surveys (2004–2016)	Sweden	https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/public-health-reporting-and-statistics/	n.a.
National Health and Nutrition Examination Survey-NHANES (2011–2012).	USA	https://www.cdc.gov/nchs/nhanes/nhanes2013-2014/questionnaires13_14.htm	O
Biomonitoring California (2011–2012)	USA	http://www.biomonitoring.ca.gov/	n.a.
Epidemiological studies			
Title	Country	Reference	
Human biomonitoring of heavy metals in the vicinity of non-ferrous metal plants in Ath, Belgium	Belgium	Fierens S. et al., 2016	
Body burden of cadmium and its related factors: a large-scale survey in China	China	Ke S. et al., 2015	
Tentative reference values for environmental pollutants in blood or urine from the children of Kinshasa.	Congo	Tuakuila J. et al., 2015	
The Danish National Health Survey 2010. Study design and respondent characteristics	Denmark	Christensen A. et al., 2012	
Blood and urinary levels of metals and metalloids in the general adult population of Northern France: The IMEPOGE study, 2008–2010.	France	Nisse C. et al., 2017	
A biomonitoring study on blood levels of beta-hexachlorocyclohexane among people living close to an industrial area	Italy	Porta D. et al., 2013	
Serum concentrations of persistent organic pollutants (POPs) in the inhabitants of a Sicilian city	Italy	Amodio E. et al., 2012	
Exposure Assessment to Environmental Chemicals in Children from Ciudad Juarez, Chihuahua, Mexico	Mexico	Ochoa-Martinez AC. et al., 2016	
A review of Human Biomonitoring studies of trace elements in Pakistan	Pakistan	Waseem A. et al., 2016	
Human exposure to heavy metals in the vicinity of Portuguese solid waste incinerators—Part 2: biomonitoring of lead in maternal and umbilical cord blood.	Portugal	Reis MF. et al., 2007	
Biomonitoring of PCDD/Fs in populations living near Portuguese solid waste incinerators: levels in human milk.	Portugal	Reis MF. et al., 2007	
Linking EDCs in maternal Nutrition to Child health (LINC study) - protocol for prospective cohort to study early life exposure to environmental chemicals and child health.	The Netherlands	de Cock M. et al., 2016	
	UK	Bevan R. et al., 2013	

(continued on next page)

Table 2 (continued)

HBM programmes			
Title (year)	Country	Link	Questionnaire accessibility
Reference ranges for key biomarkers of chemical exposure within the UK population.			
Human Fetal Exposure to Triclosan and Triclocarban in an Urban Population from Brooklyn, New York		USA	Pycke BF. et al., 2014
Other resources			
Title	Institution	Link	Questionnaire accessibility
Population and social conditions statistics	EUROSTAT	http://ec.europa.eu/eurostat/web/main	O
The Pancake Project	EFSA	https://www.efsa.europa.eu/en/supporting/pub/en-339	O
INTERGROWTH-21st. The International Fetal and Newborn Growth Consortium	University of Oxford	http://www.intergrowth21.org.uk/default.aspx	O

O: online availability; P: provided after consultation with the institution; n.a.: not available

Table 3

Example of topics and sections included in the evaluation sheet template.

Does the questionnaire include questions on...?	Yes/No	Question formulation	Suitability*	Appropriate formulation**	OBSERVATIONS
1. Sociodemographic characteristics?					
1.1. Birth date or Age					
1.2. Sex					
1.3. Birth place					
1.4. Residential history					
...					
2. Residential environment and/or home exposures?					
2.1. Area of residence					
2.2. Living environment (including proximity to "hot spots")					
2.3. Dwelling type					
2.4. Dwelling characteristics					
...					
3. Dietary habits					
3.1 Food frequency consumption					
3.2 Food treatment and conservation					
3.3. Cooking habits					
...					
4. Lifestyle					
4.1 Smoking habits					
4.2. Daily activity					
4.3. Use of cosmetics and hygiene products					
...					

*According to HBM4EU objectives and the available scientific evidence, is this question suitable (in terms of content) to be included in the questionnaire? (No/Yes/Yes, but with changes). Justify the answer

** Is the question adequately formulated (in terms of wording and conception) to be included in HBM4EU questionnaire? (No/Yes/Yes, but with changes). Justify the answer

and health-related factors. Substance-specific questionnaires were focused on the identification and proper characterization of the sources of exposure to the priority substances. Both the basic and the substance-specific questionnaires were designed to assist in the interpretation of the results obtained from future HBM studies. Supplementary table 4 includes the direct links to these questionnaires.

The basic features described in the previous section were considered for developing the questionnaires. The instruments also included questions identified at the time of evaluating existing questionnaires used in previous studies (section 2.3). Questions proposed by partners due to their relevance in the study of the first and second set of priority substances were included as well.

Specific questionnaires were elaborated by partners/experts from eight European countries, according to their particular expertise in the fields of epidemiology, toxicology, occupational epidemiology and health, food safety and the health sciences. This work was supported by reference groups with special expertise on each of the priority substances, to check that all the relevant information was adequately covered by the substance-specific questionnaires.

At a more detailed level, questions to be included in the basic and the substance-specific questionnaires were selected following a strategy for

each of the previously established sections of the questionnaire (socio-demographic characteristics, residential environment and home exposures, dietary habits, lifestyle, occupational exposures and health), as explained below. At this point, it should be clarified that the reason why some questions could seem to be repetitive throughout the basic and specific questionnaires (e.g. smoking habits) is that they provide both personal information relevant for the study, and on determinants of the exposure to one or more priority substances (a factor can be source of exposure to several priority substances). It should be also noted that, for the first set of priority substances, substance-specific questions were included in different sections throughout the basic questionnaire. This approach was later modified: for the second set of priority substances, as a result of certain improvements made to facilitate administration of the questionnaire and of the selection of target substances, questions on each substance were addressed in its own section.

Sociodemographics. With regard to sociodemographic characteristics, great importance was given on the inclusion of updated versions of international and standardised classifications of education level ([International Standard Classification of Education \(ISCED\)](http://uis.unesco.org/en/topic/international-standard-classification-education-isced), 2011, available at: <http://uis.unesco.org/en/topic/international-standard-classification-education-isced>), employment status or professional categories,

(International Labour Organization's International Standard Classification of Occupations-ISCO, 2008), available at <https://www.ilo.org/public/english/bureau/stat/isco/>, and economic activities (NACE Rev.2, available at <https://ec.europa.eu/eurostat/web/products-manuals-and-guidelines/-/ks-ra-07-015>). Still, novel questions had to be included as well, to cover topics that had been inadequately addressed by other studies, like residential history or family context. This section also included questions that required further adaptation to the national context of the different countries (e.g. income levels), so as to provide more representative data about national socioeconomic contexts.

Residential environment and home exposures. This block included a variety of questions aimed at collecting general information on housing characteristics, and on topics related to specific sources and determinants of exposure for the HBM4EU priority substances linked to the residential environment. Questions on home age, type or size/living surface of the house, where it is located (e.g. city centre, suburb, rural areas), type of house (e.g. flat, detached house, farmhouse), ventilation and cleaning habits (including cleaning products), or proximity to facilities considered as potential sources were included in this section. Concerning the ambient, questions on traffic, heating and cooling systems at home and energy sources were integrated.

Diet. There is strong evidence that diet contributes to the levels of exposure to several groups of chemicals in the general population, such as persistent organic pollutants (Arrebola et al., 2018; Domingo and Nadal, 2017; González-Alzaga et al., 2018 Jun; Manzano-Salgado et al., 2016), heavy metals (Berglund et al., 2015; Castaño et al., 2015 Aug; Malavolti et al., 2020 Nov), pesticides (González-Alzaga et al., 2020 Jul; Papadopoulou et al., 2019) and mycotoxins (Carballo et al., 2019 Jun). For this reason, a dietary section was included in HBM4EU questionnaires to assess the overall dietary habits of participants, as well as to identify the main predictors of the diet-related exposure. It included a food frequency questionnaire (FFQ) along with questions addressing foods and drinks, such as habits in terms of food preparation and conservation (e.g. type of packs, type of cookware...), food and drink origin (e.g. home-made food, meals eaten outside home...), source of drinking water, consumption of dietary supplements, among others. FFQs have been widely used in epidemiological studies to assess the relationship between diet and disease, as well as the role of food items as determinants of exposure to environmental chemicals (Pérez Rodrigo et al., 2015; Vioque et al., 2016). Despite their known potential limitations especially reproducibility and validity in assessing past exposure (Cade et al., 2002 Aug; Vioque et al., 2016), FFQs are widely used as efficient and cost-effective dietary assessment methods (Beck et al., 2020; Palacios et al., 2017; Voortman et al., 2020). FFQ includes a list of foods (and drinks) that allows researchers to find out how often each item is consumed by the interviewee in broad terms such as number of times per day/per week/per month, etc. (Cade et al., 2002; Margetts and Nelson, 1997).

Since the list of foods and drinks should be chosen according to the objectives of the study, HBM4EU partners with expertise in nutritional epidemiology and food safety performed a thorough search for foods and drinks that might be potential sources of exposure to priority substances, as well as on the most representative foods and drinks of the total diet. General European Food Safety Authority (EFSA) guidelines on FFQs and the assessment of dietary habits were also used as reference for this section (European Food Safety Authority, 2014). A broad representation of the main foods and drinks of the total diet, as well as those known to be sources of the exposure to the priority substances, were addressed in this section.

Food and drink items were grouped into the following categories: fish, meat, dairy products (not skimmed) and eggs, cereals, fats, vegetables and fruits, snacks and other foods/drinks. The FFQ had nine options according to individual frequency consumption of each item in the prior four weeks: (nearly) never, 1–3 times per month, once per week, 2–3 times per week, 4–6 times per week, once per day, 2–3 times per day, ≥ 4 times per day and don't know.

The potential contamination of meals by transfer of priority chemicals from food containers or cookware to food or drinks (e.g. canned meals, plastic packaging, use of microwave oven), as well as habits aimed at reducing the residues of these chemicals in the meals (e.g. washing and drying food), are addressed in this section. Likewise, organic food consumption habits were also considered for inclusion in the questionnaires.

Lifestyle. Lifestyle habits have been identified as important determinants of exposure to environmental chemicals (Becker et al., 2007). Likewise, some factors related to lifestyle may act as confounders and effect modifiers. Smoking habits, the use of certain cosmetics and hygiene products, cleaning patterns, handling electronic devices or spending time in high traffic areas, among other factors, have been found to be predictors of the exposure to different chemicals, such as heavy metals (e.g. cadmium, lead, mercury) (Berglund et al., 2015; Borowska and Brzóska, 2015 Jun; Echeverría et al., 2019; Wennberg et al., 2017), phenols and phthalates (Husøy et al., 2019; Philippat et al., 2015) or flame retardants (Bastiaensen et al., 2019; Sugeng et al., 2018). The potential sources of exposure to the priority substances were addressed in this section. The questionnaire finally included questions specifically adapted to each of the substances and sought to collect data on smoking habits (using key questions from the standardised questionnaire for tobacco surveys; Global Adult Tobacco Survey Collaborative Group (GATS), 2011), alcohol consumption, activity patterns (time spent in different places, both indoors and outdoors), cleaning habits, handling of substances in hobbies or DIY activities, frequency of use of cosmetic and hygiene products, among others.

Occupation. Occupational exposure may result in exposure levels several times higher than those associated with environmental or consumers' exposure. It is therefore very important to have reliable occupational data, as it can be useful in explaining potential outliers (individuals with high exposure levels in general population surveys in adults). The sources and pathways of exposure to chemical substances can differ considerably depending on whether the exposure takes place in environmental or occupational settings. The tools and methodology used to collect information on occupational exposures can also be different from those used in studies assessing environmental exposures (Semple, 2005). For this reason, experts in occupational medicine were involved in the elaboration of this section of the questionnaire, to ensure that all the specific issues concerning occupational exposure to the priority substances were properly addressed. General questions about the interviewee's current job and employment history were included in the questionnaire, asking about the activity sector in which the person worked (following the Statistical Classification of Economic Activities in the European Community-NACE Rev.2), the job description and time spent in the position. To evaluate potential occupational exposure to specific priority substances, occupational experts developed a list of occupational tasks/activities with known exposure to priority substances. When respondents said they performed these tasks as part of their job, more detailed questions were asked about duration (hours/day) and frequency (days/week) of the task/activity, about any preventive and collective protective measures taken, and the use of personal protective equipment (if yes, further details on protective gears were requested using free text). The information collected in this section allows exploration of the potential differences in exposure levels to priority substances between individuals with and without occupational exposure. This means addressing not just statistically significant differences but also toxicologically relevant differences between the two groups.

Health. To contribute to the HBM4EU objective of generating evidence of the exposure of citizens to the priority substances and the health effects that such exposure might have, a section on health was also included in the questionnaires. This section contained questions about general diseases or conditions diagnosed by a doctor, including age at diagnosis, and questions about specific symptoms potentially associated with exposure to the priority substances. It will help establish

links between human biomonitoring data and health information, which can be used to support policymaking. The aim is to improve health and well-being of the population, including vulnerable groups, such as pregnant women, children and people with chronic diseases.

There is evidence that certain health-related issues, such as weight change, pregnancy, breastfeeding, pharmaceutical consumption and having implants or dental amalgam fillings, among others, may contribute to the individual's exposure to lipophilic chemicals, such as Persistent Organic Pollutants-POPs (Jansen et al., 2017), mercury (Bjørklund et al., 2017) or bisphenols (Marzouk et al., 2019). For this reason, the questionnaires also covered health issues that might act as determinants of exposure to the priority substances.

3.2. Adaptations of HBM4EU questionnaires to different age groups and data analysis plan

The questionnaires developed in the HBM4EU framework were conceived to collect information on individual characteristics in a systematic way to provide information on the exposure levels of people living in Europe to prioritized substances, as well as the main sources and determinants of these exposures.

The information provided by these questionnaires is essential for the statistical analysis of the results of this project, since it will allow the major variables related to exposure to target chemicals to be identified. It was thus critical a close interaction between the group in charge of questionnaire development and those in charge of data analysis and management. Basic and substance-specific questionnaires were finished by 2019 and then updated in 2020 to improve data harmonization between the information included in the questionnaires and the information required by the data analysis plan. This was done to ensure that all the relevant information needed for data analysis is provided by the questionnaires.

The final version of the questionnaires developed for adults were adapted to specific age subgroups set by HBM4EU for a better characterization of exposure to the priority substances. Bearing in mind the potential variability among the age groups related to diet (e.g. food items specifically consumed by children, serving sizes) and lifestyle (e.g. hobbies, activity patterns), the questionnaires for adults were adapted in 2020 to cover specific sources of exposure to these substances in children and in adolescents. According to age subgroups established by HBM4EU, one version for children (6–11 year old) and three versions for adolescents (12–15 year old, 16–19 year old supported by parents and 16–19 year old not supported by parents) were created.

3.3. Development of additional instruments for questionnaire data collection

a. Interviewer manual

Because the interviewer can directly affect the quality of the information collected by a questionnaire (Fink, 2015), it is necessary to develop instruments focused on the standardised administration of the questionnaires. The interviewer manual is needed to ensure the standardised conduction of the interview and to minimize probing, but it plays an especially important part in HBM4EU, because the questionnaires are to be administered in several aligned studies in different countries.

This manual includes general instructions on how to administer the questionnaire (e.g. question formulation, answer interpretation), as well as background information that justifies the inclusion of each question. Supplementary table 4 includes the direct link to this document.

Additionally, Standard Operating Procedures (SOPs) on quality assurance for recruitment and fieldwork were developed within HBM4EU. These included, among other things, guidelines to select and train interviewers, as well as, to assist them to administer questionnaires. These documents are available at HBM4EU online library (<https://www.hbm4eu.eu/mdocs-posts/standard-operation-procedure-sop/>).

sop/).

b. Serving size gallery

Information on the frequency of consumption of the main food groups is essential for a proper characterization of dietary habits. Reporting dietary habits faces certain limitations, such as recall bias and the difficulty of identifying serving sizes. Previous studies aimed at estimating dietary intake have used serving size galleries to minimize the effect of these limitations (Forster et al., 2014; Pisani et al., 1997; Riordan et al., 2018). A gallery of pictures of the serving sizes of the main food items was included in the food frequency questionnaire, to facilitate questionnaire administration. It was annexed to the questionnaires.

c. Satisfaction questionnaire

Future HBM studies could largely benefit from information on the level of satisfaction and the experience of participants in previous studies. Such information could be used to address weaknesses identified in those studies. This feedback might also lead to improved participation rates, which is a key point in HBM studies, as these rates can affect the validity and utility of the results. A satisfaction questionnaire was created to collect data on participants' perception of the entire process of the study in which they participated. This questionnaire is intended to provide relevant information to future studies, not only aligned studies of the HBM4EU, but HBM studies in general. Data concerning the level of satisfaction of participants can be used to detect limitations in the study and to make suggestions to improve upcoming biomonitoring studies. Issues such as respondents' previous information about the study, how they were invited to participate, their contact with the staff, their views on the questionnaires and the facilities were addressed by this questionnaire, which also asked for their views on the usefulness of the study, their willingness to participate in future research and aspects that should be improved, to name a few. Supplementary table 4 includes the direct link to this document.

d. Non-responder questionnaire

As discussed earlier, questionnaires in HBM studies can be used to document the exposure and potential exposure sources of the participants (Nieuwenhuijsen, 2005; National Research Council-NRC-, 2006). Some HBM studies, e.g. GerES (Kolossa-Gehring et al., 2012); CMHS (Haines et al., 2017), are designed to collect representative data for a defined part of the population. If representative data is the goal, achieving a high response rate is vital (Stoop, 2004). Response rates in epidemiologic studies have been on the decline in the past years and this was interpreted as likely to continue (Galea and Tracy, 2007). So, methods and tools must be used to counter any potential bias in study data and its interpretation that might arise from missing participants. A questionnaire designed specifically for potential participants that refuse participation, a so-called non-responder questionnaire (NRQ), is such a tool. The NRQ is administered to individuals who were invited to participate in the HBM study but chose not to. It can ask for reasons for refusal, of course, but it can also include a small number of questions about the individual's situation in relation to suspected exposure sources. It has been shown that trends in prevalence detected in the results of a survey can be overestimated compared to when the results have been adjusted by information gathered from a non-responder questionnaire (Karvanen et al., 2016).

Since it is a tool with which to analyse the study's data in relation to a potential non-responder bias, a non-responder questionnaire should deliver data that is directly comparable to the main questionnaire used in the study. This means that a non-responder questionnaire needs to be a flexible adaptation of the study's main questionnaire.

In order to develop a concept for the design of a non-responder questionnaire in the scope of HBM4EU, an interview with the expert involved in questionnaire design and study conduct for the German Environmental Surveys (GerES) in the past decades was conducted in 2018. This was accompanied by literature screening and analysis of pre-existing non-responder questionnaires from large HBM studies such as GerES (Schulz et al., 2021; 2007) and the feasibility study to coordinate

and perform HBM on a European scale COPHES/DEMOCOPHES (Den Hond et al., 2015; Joas et al., 2012). The final concept was handed in for review by a multidisciplinary expert group tasked with the development of questionnaires in the HBM4EU work package for study design and fieldwork preparation. The concept discusses the importance of non-response analysis and provides recommendations for NRQ design. It also lists some example questions that can be used to create a NRQ in HBM4EU. These questions can only be considered examples, as they need to be carefully adapted to the questions of the main questionnaire. They are split into two groups; one is considered essential and one is optional, or substance-related.

According to the Concept, essential questions for a NRQ would be those that cover the criteria used in the original selection of the gross sample, such as age and sex plus, if not asked elsewhere, the person's reason for declining participation. Region as a selection criterion is assumed to be covered because the contact information of the participant is available during the selection process. Optional questions for a non-responder questionnaire would depend heavily on the focus of the study's main questionnaire (and the substances of interest). They could, for example, address the most important factors for bias or certain exposure routes of high interest and should be carefully selected by experts directly involved in study and questionnaire design.

By offering recommendations and examples rather than a complete questionnaire, the concept provides an approach that can be used by studies outside HBM4EU to develop a NRQ suitable for their own project and questionnaire. Supplementary table 4 includes the direct link to this document.

e. Matrix-specific questionnaires

HBM studies involve the collection of biological samples and researchers must have information about the sample collection process to accurately determine the level of exposure to the target substances. Considering that the substances detected have different chemical characteristics, their concentrations in human biological samples can be affected by conditions that occur in a specific time frame before sample collection. For these reasons, and also to promote the use of a standardised method of data collection, matrix-specific questionnaires have been developed for each on the priority substances to accompany the main questionnaire. These questionnaires were designed to collect information on the main sources of exposure to the priority substances (mainly food consumption, daily activity and lifestyle) just prior to the sampling, since metabolism affect the concentrations in urine or blood samples in a time-dependent manner. The time frame covered by these questionnaires ranged from 24 to 72 h to 60 days, depending on the substance and its metabolism in the human body (while many non-persistent substances have short half-lives of a few hours, no differences over one week can be found for persistent chemicals). Information regarding sample collection (e.g. date and time, fasting conditions, type of urine sample (e.g. spot sample, 24 h urine, first morning urine) or volume collected) were also covered by these questionnaires. Supplementary table 4 includes the direct link to this document.

3.4. Challenges of developing questionnaires for HBM studies

The development of questionnaires revealed several challenges. Future HBM studies could benefit from this experience, which could help to minimize critical aspects of these studies.

One of the main challenges was that the questionnaires were not developed for a single, pre-defined study for a selected single substance, but rather they had to follow an overarching design that can serve as a basis for many aligned studies on different chemicals and to be applied in different countries. Considerable effort was made to establish a well-defined strategy to guide the standardised elaboration of the questionnaires. In addition, the contribution of many European partners (see supplementary table 3), and the need to collect a wide range of information on individual characteristics and on sources and exposure factors, involved the elaboration of lengthy documents. Drafting the final

versions of the questionnaires posed a great challenge, as they had to include all the relevant questions, and, at the same time, be practical in terms of administration to respondents (e.g. reasonable completion time and easy comprehension). To address this matter, partners provided background information in the interviewer manual to justify each of the questions included in the questionnaires, so that irrelevant questions could be discarded.

Another major challenge was the need to harmonize the questions included in the basic and substance-specific questionnaires to be adapted them to the needs of the data analysis plan of HBM4EU. Partners devoted much work to check that the high number of variables required by this data analysis plan were provided by the questionnaires.

An additional hurdle that had to be overcome during the elaboration of the questionnaires was how to address personal or sensitive information (e.g. ethnicity, income level, medical history, etc.). In this regard, questions that could make participants feel uncomfortable were carefully evaluated in terms of how they were formulated, as they could lead to a lower response rate.

The development of reliable dietary questionnaires is often one of the most challenging aspects of dietary epidemiology. Among the issues that arose during the development of dietary questionnaires was the period of time of food consumption that should be covered by the questionnaire, which can range from the past 24 h to an entire year. It was decided that a period of 4 weeks was suitable to estimate in a representative manner the intake of foods that might be associated with exposure to priority substances. A second major challenge in this area was the evaluation of frequency and amount of food and beverages intake, since perceptions vary greatly. For this reason, we included a gallery of pictures specifying the average weight of each portion to aid in the accurate completion of this semi-quantitative food-frequency questionnaire. Detailed frequency options were offered, which included nine possible responses (Faggiano et al. 1992). Another critical question was the need to ensure a correct estimate of the intake of prioritized substances through the evaluation of dietary habits. At the same time, the overall number of questions was kept as low as possible, in order to increase the accuracy of the dietary ascertainment and to limit the difficulties related to completing a long dietary questionnaire such as this one. A dedicated section for all prioritized substances along with specific additional questions for each individual contaminant was also developed and included in the questionnaire, in a flexible way in order to allow its adaptation to the assessment of new substances in future projects. Finally, some difficulties were encountered in tailoring the questionnaire to different age groups, in particular children and adolescents.

Regarding questions on occupational exposures, the most critical aspect was drafting questions that were short but that also addressed the matter adequately and sufficiently. This is obviously to ensure the questionnaire was not particularly long and also to reduce the problem of non-responders or inaccurate responses. To identify exposures to priority substances the toxicokinetics of the xenobiotics had to be taken into account, in particular the half-life of the substance. Doing so prevents irrelevant exposures from being considered, which would cause bias in the interpretation of the bio-monitoring results. Finally, it is important to keep in mind that we might not have identified all potential occupational exposure sources for the priority chemicals, due to lack of data. Therefore, the lists of occupational tasks/activities –especially in the case of lesser known substances– may not cover everything, although they have been made as comprehensive as possible.

Challenges still pending include the validation of the questionnaires and reassessing them for computer-assisted interview, if needed, since they were designed for pen and paper administration. Moreover, the questionnaires would need to be redrafted if in the meantime new findings arise that make some questions obsolete or bring about the need for more questions (e.g. novel exposure determinants, confounding factors or adjustment variables).

A comparison between this and other similar articles addressing the process of development questionnaires for HBM studies was made. For

that purpose, an exhaustive search was carried out in PubMed in January 2020, limited to scientific articles conducted in humans and published in the last 10 years, using a combination of key words pertaining to questionnaire design process in the frame of HBM studies. The search terms included human biomonitoring, environmental exposures, questionnaire development, questionnaire design, questionnaire elaboration, data/information collection, tool/instrument for data/information collection. This search produced a total of 232 references and their abstracts were peer-reviewed by EASP team, although no close reference to our experience was found. This search only produced articles reporting the use of questionnaires as an instrument to gather information for the study, and, in some cases, a brief summary of the main sections or questions of the questionnaires was included. By contrast, several references were found addressing the validation of questionnaires (English et al., 2015; Zani et al., 2015), as well as the development of questionnaires in the frame of health surveys (Bollweg et al., 2020; Sørensen et al., 2013) but they were not specifically linked to HBM. The scarce literature found during this process should serve to underline the importance of bringing more visibility to the procedures for questionnaire development in HBM studies.

4. Conclusions

Developing questionnaires is a key process in the preparation of HBM studies. This process requires a substantial effort to ensure the adequate collection of the information needed for a proper characterization of the exposure to environmental chemicals. Our experience of questionnaire development in HBM4EU revealed the need to rely more on well-defined strategies and standardised procedures for questionnaire development to be used in HBM studies. This becomes particularly important when performing multi-country and multi-centre studies, to facilitate the comparison of results. Information on the methodologies followed for questionnaire development should be given a higher profile in future HBM studies. More accessible questionnaires could also facilitate the exchange of experiences and the improvement of procedures for data collection.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2021.107071>.

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