



science and policy  
for a healthy future

HORIZON2020 Programme  
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## Criteria for feasibility studies

### Additional Deliverable Report

### AD 11.2

### WP 11 - Linking HBM, health studies and registers

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# 1 Authors and Acknowledgements

This document has been prepared in collaboration with all involved partners.

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## 2 Background

The HBM4EU project aims at the coordination and harmonisation of existing and planned HBM (human biomonitoring) initiatives in 26 countries, including 22 European Member States and three associated countries, as well as Switzerland. The specific focus of the HBM4EU Project is on linking research to evidence-based European policymaking. HBM4EU will generate knowledge on chemical exposure levels in the population and their health effects.

National HBM initiatives are managed by leading HBM experts in Europe. It is encouraged to make existing data available for research within HBM4EU, and to the broader research community, stakeholders, and policy makers. In addition, new HBM data, i.e. data generated during the project with HBM4EU co-fund, will be used for research during the course of the project.

In parallel to HBM studies, in many European countries, health examination surveys (HES), surveys with physical measurements and collection of biological samples such as blood and urine, together with questionnaires are conducted. The European Health Examination Survey<sup>1</sup> was established in 2010 to coordinate these national HESs in Europe. Between 2000 and 2017, a national HES has been conducted in 15 European countries<sup>2</sup> and in many countries smaller, regional or disease specific surveys have been carried out.

Since for both HBM studies and HESs, the data collection phase through fieldwork is one of the largest cost categories, and needed infrastructures are very similar, potential to combine these two studies has been considered. In some countries such as Germany and France, this combination has already been done. This also increase collaboration between environmental and health professionals and ministries.

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<sup>1</sup> <http://www.ehes.info>

<sup>2</sup> [http://www.ehes.info/national/national\\_hes\\_status.htm](http://www.ehes.info/national/national_hes_status.htm)

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### 3 Aims

The aim of the document is to provide a minimum set of criteria to be fulfilled by all feasibility studies conducted under Task 11.4. In this document feasibility studies mean surveys combining both HBM and health studies with physical examinations.

The **aim** of these feasibility studies is to assess the **opportunities and obstacles** encountered when combining two similar but still in some respect different survey types. Opportunities and obstacles are expected to include **practical/logistic, financial and scientific** benefits and short comings.

For many areas of survey organisation such as

- sampling including definition of sample size, selection of sampling frame and sampling scheme;
- recruitment of invitees;
- research ethics and data protection including obtaining ethics approval and informed consent;
- data management; and
- questionnaire design and administration;

HBM and health studies are using very similar methods which could be easily combined. Also for many quality assurance/control measures similarities can be seen between HBM and health studies.

For other areas such as requirements related for the collection and storage of biological samples, contents of the questionnaires, or included physical examination, differences exists. When requirements and/or protocols of two studies differ, decisions have to be made to find a balance between requirements. These decisions have to be justified and support the aims of the combined study.

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## 4 Criteria

### 4.1 Eligibility and timing of the studies

#### Criteria:

- Feasibility studies will be conducted only in countries which do not have experience in combining HBM and health studies in the past.
- Feasibility studies will be conducted in connection with already planned/starting surveys/studies.
- Fieldwork will take place in 2019.

#### Eligibility

Previously, in some countries such as Germany and France, large HBM studies are conducted in connection to the national health examination surveys. Experiences from these studies will be collected separately and therefore there is no need to conduct a feasibility study in such countries.

Extent of previous experience may vary considerably between countries. In some countries national monitoring programmes (health and/or HBM) and/or epidemiological/exposomics studies are in place with well-functioning survey infrastructure while in other countries smaller scale research projects on health and/or HBM have been conducted with more limited infrastructure.

In this context, infrastructure means knowledge and tools to

- select proper sampling frame, sample size and draw representative sample;
- recruit survey/study invitees;
- questionnaire preparation, administration, checking, data-entry and storage;
- equipment and skills to conduct clinical examinations;
- equipment and skills to draw biological samples;
- measure exposure burden in biological samples;
- obtain ethical approval and follow data protection regulations;
- secure data handling and storage, and
- obtain funding for survey/study.

Countries with different previous experience and available infrastructures should be included to feasibility studies to ensure that as extensive experiences as possible will be obtained. In general, countries could be classified to following three categories:

1. Country has experience in organising health studies with clinical measurements but has not conducted HBM studies previously.
2. Country has experience in organising HBM studies but has not conducted health studies with clinical measurements previously.
3. Country has no experience in health studies with clinical measurements or HBM studies.

The fieldwork of feasibility studies should take place in 2019. This means that feasibility studies should be planned a part of the studies/surveys already under planning/preparation.

## Timing

Estimated time lines for the feasibility studies are given below:

Action	2018				2019				2020			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Launch of the call												
Proposals for the call												
Decision on call outcome												
Preparation for a feasibility study												
Fieldwork of a feasibility study												
Laboratory analysis												
Data checking and preparation												
Transfer of data to IPCheM												
Self-evaluation report by countries												
Final evaluation report												

## 4.2 Target population and sample selection

### Criteria:

- Geographical coverage of the target population including area(s), sex, age groups: To be defined together with WP8
- Sample size: at least 200, if feasible 400
- Sampling frame: Depends on the availability of sampling frames in a country. Priority is to use sampling frames which are most up-to-date and are regularly updated.
- Sampling scheme: Multistage, random probability sample
- Target participation rate: 60%

### Target population

Representative sample for target population is required for both HBM and health studies. In general, target population should be general population but this may differ depending on included priority chemicals and more specific research questions.

For health surveys, EHES recommends to include general adult population (at least 25-64 years, preferably 25+ years).<sup>3</sup>

For HBM, the recommendation by WP8 is that target population for HBM4EU should cover all ages between 0 and 79 years.

<sup>3</sup> Tolonen H (Ed.) EHES Manual. Part A. Planning and preparation of the survey. 2nd edition. National Institute for Health and Welfare, 2016, Directions 2016\_13. URN:ISBN:978-952-302-700-8, URL: <http://urn.fi/URN:ISBN:978-952-302-700-8>

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For feasibility studies, covered age group needs to be defined based on measured priority chemicals and available infrastructures within participating countries. In ideal case, different feasibility studies would cover different age groups to allow evaluation of opportunities and obstacles between age groups.

## Sample selection

### *Sample size*

For health studies, EHES recommendation for pilot studies (similar to feasibility studies) is 200 persons, with at least 25 persons in each 10-year age group-sex domain (for age group 25-64 years). Sample should be stratified by age group and sex. For national, full-size studies it has been recommended to have a minimum sample size of 4000 persons.<sup>4,5,6</sup>

For HBM studies, HBM4EU recommends that each participating country collects data from at least 300 participants (150 men and 150 women). Depending on expected participation rate, the sample size has to be at least 500 (60% participation rate). HBM4EU recommendation is to stratify the sample by sex, age group and socio-economic class<sup>7</sup>.

Since a national HBM and health studies should include persons from urban and rural populations, feasibility studies should include at least two samples each, one from an urban and one from a rural area (for the latter, depending on the country situation, proximity to health centres may even require two different subgroups). For each of the two samples, 200 subjects should be randomly selected. With an expected participation rate of 60%, this would leave 120 subjects per sample to be interviewed and possibly examined.

A sample size of 200 subjects is based on power calculations<sup>8</sup> and allowing best possible combination of sample size needs for both HBM and health studies. This number would allow for obtaining prevalence estimates of reasonable precision (i.e., not differing by more than 7.5% in absolute terms from the true underlying population prevalence rate with 90% certainty). A sample size of 120 would also allow for detecting, with a probability of 90%, at least one case with a condition shared by only 2% of the underlying population.<sup>9</sup>

Subsequent larger scale national studies require large (at least 4.000) random probability sample. The respective samples should cover different geographic regions and faithfully represent important subgroups such as socio-economic classes and characteristics of the underlying populations, with a specific focus on vulnerability profiles.

### *Sampling frame*

Availability and coverage of sampling frames will vary between countries and target population. Always the best available sampling frame should be used, taking into account possible legal and practical requirements/limitations. The sampling frame should be recently updated and include also contact information for people.

<sup>4</sup> Tolonen H (Ed.) EHES Manual. Part A. Planning and preparation of the survey. 2nd edition. National Institute for Health and Welfare, 2016, Directions 2016\_13. URN:ISBN:978-952-302-700-8, URL: <http://urn.fi/URN:ISBN:978-952-302-700-8>

<sup>5</sup> Tolonen H et al (Eds.) Recommendations for the Health Examination Surveys in Europe. National Institute for Health and Welfare, 2008, Kansanterveyslaitoksen julkaisu B21/2008. Available at: <http://urn.fi/URN:ISBN:978-951-740-838-7>

<sup>6</sup> Lemeshow S, Hosmer DW JR, et al. Adequacy of sample size in health studies. 1990. World Health Organization.

<sup>7</sup> UNESCO. International Standard Classification of Education. ISCED 2011. Available at: <http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf>

<sup>8</sup> Thomson SK. Sampling. 2<sup>nd</sup> edition. 2002. Wiley, pp.41-44

<sup>9</sup> Poulson OM, Holst E, Christensen JM. Calculation and application of coverage intervals for biological reference values. A supplement to the approved IFCC recommendation (1978) on the theory of reference values. Pure & Appl. Chem. 1997; 69(7): 1601-1611

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### *Sampling method*

Probability sampling should be used when selecting a sample. In ideal case, multistage random sampling should be selected. If several geographical areas can be included to a feasibility study, geographical area (e.g. urban vs. rural) should be used as primary sampling unit (PSU). Then from persons living in the PSU, samples are selected.

### *Target participation rate*

Feasibility studies should target to a high participation rate as possible to avoid bias due to selection bias caused by non-participation. A target participation rate should be 60%. If lower participation rate is expected, it is recommended to use available resources on recruitment of invitees rather than increasing of sample size.

## 4.3 Questionnaire modules to be included

### **Criteria:**

A minimum set of questionnaire modules to be included:

- Background questions on socio-demographic status, occupation
- Self-reported anthropometric data
- Lifestyle questions on smoking (tobacco use, passive smoking, smokeless tobacco use) and dietary consumption including alcohol consumption)
- General health status and medical history including use of medications
- Minimum European Health Module (incl. self-perceived health, chronic morbidity and activity limitations)
- Physical activity and sedentarity
- Occupational exposures
- Home and household environment
- Domestic exposures and leisure & DIY activities
- Chemical-specific questions related to high exposure burden (lifestyle, behaviour, food consumption etc.)

HBM and health studies both need questionnaires to gather information on participant's background characteristics and behaviour in order to interpret collected data. Some specific questions to HBM surveys might be useful for understanding data coming from health studies and vice versa.

In feasibility studies, it will be assessed how questionnaires needed for HBM and health studies could be combined. This has at least two dimensions:

1. When both HBM and health studies have same questionnaire modules but individual questions differ, how to combine these? Which questions to use in combined questionnaire and why? Or is there possibly some other formulation of the questions which would provide required information for both needs (HBM and health)?
2. How many and how long HBM or HES specific questionnaire modules can be included to combined questionnaire without making questionnaire too long (burdensome) for participant?

Questionnaire modules to be included can be classified into three groups:

1. Questionnaire modules needed for both HBM and health studies.
2. Questionnaire modules needed for health studies only.

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3. Questionnaire modules needed for HBM studies only. Due to the specificities of the sources of exposure to prioritised chemical substances, specific items might be added in modules thereafter depending of the state-of-the-art information available. A specific attention should be devoted to pathologies or health indicators known or suspected to be linked with an exposure burden from a prioritised chemical substance.

For HBM specific questionnaire modules, standardised HBM4EU questionnaires recommended by WP7 should be used. For health specific questionnaire modules, questions recommended by the EHES and European Health Interview Survey should be used. Deviations from standardised questionnaires need to be justified and documented.

For common questions needed for both HBM and health studies, the final decision on the used questions will be made by the Principle Investigator of the study. Justifications for the decisions have to be documented.

### 4.3.1 Modules common to both HBM and health studies

#### General background information

<b>Demographic and socio-economic information</b>	<ul style="list-style-type: none"> <li>• Age (year of birth)</li> <li>• Sex</li> <li>• Education (categorised according to ISCED-2011)<sup>10</sup></li> <li>• Socio-professional category (according to the ISCO-08)<sup>11</sup> (ILO)</li> <li>• Socio-economic status (SES): additional information on household incomes, health insurances, home ownership, household size, etc.</li> <li>• Family status (married status, household composition, number of children, etc.)</li> <li>• Nationality, place of birth</li> </ul>
<b>Current occupation (basic information)</b>	<ul style="list-style-type: none"> <li>• Employment: business/public sector, activity sector, date of arrival in the company or number of years in business, workplace</li> </ul>
<b>Anthropometric data</b>	<ul style="list-style-type: none"> <li>• Self-reported data (height, weight)</li> </ul>

#### Lifestyle information related to smoking

<b>Tobacco exposure</b>	<ul style="list-style-type: none"> <li>• Status of tobacco consumption (current, in the past, never, in the last 48 hours)</li> <li>• Smoking periods and duration (the start and end dates) Type and consumption behaviour (frequency of tobacco smoking, indoor/outdoor, inhalation or not)</li> <li>• Semi-quantitative evaluation of the type of tobacco smoked (number of cigarettes/day, grams/week)</li> <li>• Passive exposure and frequencies (for non-smokers and former smokers): items relating to the exposure to the tobacco smoke (e.g. number of hours exposed/day, place of exposure)</li> </ul>
<b>Smokeless tobacco behaviour</b>	<ul style="list-style-type: none"> <li>• Use of the electronic cigarette, frequencies, types</li> <li>• Use of others tobacco substitutes (nicotine patches or medicines)</li> </ul>

**Note:** For children, a special attention should be devoted on the environmental passive exposure to smoke related to tobacco use by their relatives.

<sup>10</sup> UNESCO. International Standard Classification of Education (ISCED). Available at: <http://uis.unesco.org/en/topic/international-standard-classification-education-isced>

<sup>11</sup> ILO. International Standard Classification of Occupation (ISCO). Available at: <http://www.ilo.org/public/english/bureau/stat/isco/>

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## Dietary consumptions

Usually food frequency questionnaire on the last 12 months, detailed food questionnaire for 3 days selected on a week, or detailed food questionnaire on the last 48 hours are used to collect information on dietary consumptions. EFSA recommendation is to use 24 hour recall.<sup>12</sup>

<b>Beverages (including water and alcohol consumptions)</b>	<ul style="list-style-type: none"> <li>Type, frequencies and semi-quantitative assessment of the consumptions of water, non-alcoholic beverages (fruit juices, tea, coffee, traditional beverage) or alcohols (wine, beer, liqueur, spirits)</li> <li>List of last consumptions</li> </ul>
<b>Food products (fruits and vegetables, meat, fishes and sea products, cereals, eggs, chocolate, milk and dairy products, etc.)</b>	<ul style="list-style-type: none"> <li>Source of food (industrial, gardens, “organic farming”, etc.)</li> <li>Cooking process and hygiene (crude, barbecue, canned food, etc.)</li> <li>Packaging of food (specifically plastics)</li> <li>Frequencies and semi-quantitative assessment of the consumptions</li> <li>Last consumptions (adjustable for some specific products)</li> <li>Specific diets (lose/gain weight or for specific disease or other reasons such as vegan, vegetarian)</li> </ul>

### 4.3.2 Modules specific to health studies

#### General health status and medical history

<b>General health status (diseases diagnosed by physician, especially during the last 12 months)</b>	<ul style="list-style-type: none"> <li>Longstanding illness (anaemia, asthma, chronic obstructive pulmonary, CVD, diabetes, hyper/dyslipidaemia, hypertension, liver dysfunction, osteoarthritis, renal dysfunction, stomach ulcer, thyroid dysfunction, etc.)</li> <li>History of medical measurements by a health professional for some health indicators: e.g. blood pressure, cholesterol, glucose or glycated haemoglobin</li> <li>Allergies: rhinitis, dermatitis, food allergy, etc.</li> <li>Cancers and family history of cancers: (lung, breast, bladder, kidney, prostate, colorectal, endometrial, liver, melanoma, leukaemia, pancreatic, thyroid, non-Hodgkin lymphoma, etc.)</li> <li>Information on physiological status, fertility and reproduction (e.g. menopausal status, menstruation, pregnancy, gravidity and parity, fertility problems, etc.)</li> <li>Mental health problems</li> <li>Infectious diseases (gastroenteritis, flu, HIV/AIDS, acute respiratory disease, hepatitis, other sexually transmitted disease, etc.)</li> <li>In addition: items relating to the physical and dental health (wearing of prosthesis, wearing of the dental amalgams, etc.)</li> </ul>
<b>General self-perceived health (using standard short questions of EHIS) (EUROSTAT)</b>	<ul style="list-style-type: none"> <li>Individual self-health perception</li> <li>Longstanding illness or health problem</li> <li>Recent limitations in daily activities due to a health problem</li> </ul>
<b>Medical history and use of health medical services (in particular during the last 12 months)</b>	<ul style="list-style-type: none"> <li>Hospitalisations and biological exams (date/period, number, duration, reasons)</li> <li>Follow up/consultation by a specialist physician or a dentist/orthodontist (date/period, reasons)</li> <li>History of self-use/solicitation of the care services</li> </ul>

<sup>12</sup> <http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2014.3944/epdf>

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<b>Use of medications (over the counter and prescribed medication)</b>	<ul style="list-style-type: none"> <li>• Medication consumptions (if relevant): name of medications, frequencies, times, etc. (specify if medical prescriptions)</li> <li>• Dietary supplements (herbal medicines, vitamins, etc.)</li> <li>• Contraceptive pills or other hormones</li> <li>• Other medications or drugs consumed (name, reason, frequency)</li> </ul>
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### Physical activity and sedentarity (especially during the last 7 days)

	<ul style="list-style-type: none"> <li>• Type and name of activities (sports, walking or others)</li> <li>• Intensity of activities (vigorous, moderate), frequency and duration</li> <li>• Place of activities (indoor/outdoor, at home, in workplace, in a centre, in the wild, etc.)</li> <li>• Time spend sitting/day at work and home</li> </ul>
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Note: The items of the physical activity module must be based on the internationally standardised questionnaire for physical activity like IPAQ (International Physical Activity Questionnaire) and RPAQ (Recent Physical Activity Questionnaire)

### 4.3.3 Modules more specific to HBM studies

#### Occupation (including unemployment)

*For children, collect at least some general information related to the occupation of parents and tutors or nurses.*

<b>Current occupational exposures</b>	<ul style="list-style-type: none"> <li>• Occupations and workplace: activity sector, workstations, tasks in the company and duration, time spent at work and time of day, work in open or close environment and time spent per day</li> <li>• Transport: transport modes from home to workplace, time spent in transports,</li> <li>• Exposures to chemical substances in the professional environment (gases and vapours, cleaning products, metals, plastic products, biocides, etc.) and to the dusts (organics, inorganics): frequency, last exposure</li> <li>• Exposure to the prioritised substances selected and/or their potential sources of exposure: phthalates and DINCH; bisphenols A, S, F; per/polyfluorinated compounds; flame retardants; cadmium; chromium; polycyclic aromatic hydrocarbons; anilines and MOCA</li> </ul>
<b>Past occupations and exposures</b>	<p>On the same approach that for the current occupation and exposure</p> <ul style="list-style-type: none"> <li>• Employment: business/public sector, general type of activities, date of arrival in the company or number of years in business</li> <li>• Occupation and workplace: period/date of the occupation, activity sector, workstations, tasks in the company and duration, time spent at work and time of day, work in open or close environment and time spent per day</li> <li>• Exposures to various chemical substances in the professional environment (gases and vapours, cleaning products, metals, plastic products, biocides, etc.) and to the dusts (organics, inorganics): frequency, last exposure</li> <li>• Exposure to the prioritised substances selected and/or their potential sources of exposure: phthalates and DINCH; bisphenols A, S, F; per/polyfluorinated compounds; flame retardants; cadmium; chromium; polycyclic aromatic hydrocarbons; anilines and MOCA</li> </ul>

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## Home and Household environment

<b>Home characteristics</b>	<ul style="list-style-type: none"> <li>• Place (city), postal code, address (if possible)</li> <li>• Type of residence (apartment, house, etc.), level of floor if concerned</li> <li>• Dwelling characteristics: surface and coverings, year of building, renovations and redecorations, floorings, etc.</li> <li>• Date of entering in the house and information about the previous houses and periods of living in the habitat during the last years (to be specify)</li> <li>• Internal characteristics of the habitat (painting, fireplace, heating and ventilation, softener water, etc.)</li> <li>• External characteristics of the habitat (backyard/garden, swimming pool, etc.)</li> </ul>
<b>Living environment</b>	<ul style="list-style-type: none"> <li>• Type of locality (urban/semi-urban/rural)</li> <li>• Industrial environment (plant/industry in the vicinity of home and distance, incinerators, rubbish dump, etc.)</li> <li>• Agricultural environment (presence of agricultural fields, extend, type of cultures, etc.)</li> <li>• Traffic (high traffic road, railway, airports)</li> <li>• Distance to home</li> </ul>

## Domestic exposures and Leisure & DIY activities

<b>Domestic exposures (type and frequency, recent exposure)</b>	<ul style="list-style-type: none"> <li>• Use of household products (disinfectant, dishwasher, cooking accessories, etc.)</li> <li>• Use of various specific chemicals (mode, frequency)</li> <li>• Cleaning activities (type of activities)</li> <li>• Use of domestic biocides (insecticides, herbicides, rodenticides, fungicides)</li> <li>• Time spent inside the house</li> <li>• Pets at home (type of animals, use of pest controls)</li> </ul>
<b>Leisure and do-it-yourself activities (type and frequency, recent exposure)</b>	<ul style="list-style-type: none"> <li>• Example of leisure and/or D-I-Y activities : use of wood stains and varnishes, welding, model making, art painting, enamelling and ceramic activities, stripping or sanding of paintwork or woodwork, rifle shooting, tanning activities, gardening, activities in a park or walking area, etc.</li> </ul>
<b>Cosmetics (type and frequency, recent exposure)</b>	<ul style="list-style-type: none"> <li>• Products use for washing (type of product, application on hair/skin, etc.)</li> <li>• Products use for makeup (type of product, application on hair/skin, etc.)</li> <li>• Other products and use</li> </ul>

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## 4.4 Biological samples to be collected

### Criteria:

- Samples to be collected: blood and/or urine depending on covered age group and included priority chemicals
- Sample collection, handling and storage should follow standardised procedures proposed for HBM4EU and EHES.
- Whenever possible, part of the collected samples should be stored (biobank) for future use.
- Samples should be analysed in the laboratories fulfilling the QC/QA requirements set out by HBM4EU for HBM biomarkers and EHES for health biomarkers (primarily for lipids, glucose and HbA<sub>1c</sub>).
- Analysed biomarkers:
  - Health: lipids, glucose, HbA<sub>1c</sub> and whenever possible extraction of DNA
  - HBM: 1<sup>st</sup> priority chemicals to extend they are feasible (depending on amount of available samples and funding)

Collected biological samples should serve the needs of the analysis for HBM and health biomarkers. In ideal case, additional samples are also collected and stored for future use.

### Samples to be collected

For health studies, EHES recommends to collect at least: one plain serum gel tube (9/8 ml); one fluoride-citrate plasma tube (5/3 ml); one EDTA whole blood tube (9 ml); one EDTA plasma tube (9 ml); and one EDTA whole blood tube (3 ml). Plain serum is needed to analyse lipids and lipoproteins, fluoride-citrate plasma to analyse glucose, clotting factors and adhesion molecules, EDTA whole blood to do DNA extraction and glycated haemoglobin (HbA<sub>1c</sub>), and EDTA plasma to analyse vitamins and antioxidants. If sodium intake, which has high importance for health studies due to increasing prevalence of hypertension, is to be measured, 24h urine should be collected.<sup>13</sup> For health studies, at least lipids, glucose and HbA<sub>1c</sub> should be measured. Extraction of DNA is highly recommended and other biomarkers should be measured based on national needs and available funding.

For HBM studies, to be able to assess exposure burden of specific chemicals in the human body, the selection of the adequate biological matrix is crucial. The knowledge of the toxicokinetic of the target chemical is required. Blood and urine are the most common matrices employed in HBM surveys. Generally it can be summarised that the more volume you can get, the more analysis can be performed. The exact amount of samples needed depends on the analytical method and analysed priority chemicals. Therefore, required amount of samples will be sorted out in collaboration with WP9.

For example, in the German Environmental Specimen Bank (ESB)<sup>14</sup>, 150ml venous blood from the participants is collected from which 80ml whole blood and 18ml plasma are stored.<sup>15</sup> For immediate analysis, 20ml whole blood and 2,5ml plasma are needed. For 24-h urine, a volume of 180ml is stored per participant and 14ml of 24-h urine is used for the analytical part. As ESB was established to follow time trends of exposure to chemicals, amounts collected are much higher than it might be needed for feasibility studies in HBM4EU.

<sup>13</sup> Tolonen H (Ed.) EHES Manual. Part A. Planning and preparation of the survey. 2nd edition. National Institute for Health and Welfare, 2016, Directions 2016\_13. URN:ISBN:978-952-302-700-8, URL: <http://urn.fi/URN:ISBN:978-952-302-700-8>

<sup>14</sup> <https://www.umweltprobenbank.de/en/documents>

<sup>15</sup> Schröter-Kermani C, Gies A, Kolossa-Gehring M. The German Environmental Specimen Bank. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2016;59(3):368-72

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There are different matrices available with different advantages and disadvantages for HBM<sup>16</sup>:

Matrix	Advantage	Disadvantage	Chemical groups that can be analysed
24-hour-urine Morning urine Spot urine	Non-invasive, collection at home No volume limitation Metabolite analysis	Volume and concentration variability	Metals, trace elements, metabolites, organic compounds, tobacco
Blood, serum, plasma	In contact with the whole organism and in equilibrium with organs and tissues Widely studied morphology and well established SOPs for sampling	Invasive; trained staff and special material required Volume limitation Ethical constraints Special conditions for transport and shipment	POPs, metals/trace elements, organic compounds, tobacco
Hair	Non-invasive, minimum training required for sampling No special storage requirements or transport Information about short and long term exposure Segmental analysis	Difficulty in differentiating internal/external exposure Potential variations with colour, hair care or race	Metals/trace elements, POPs, organic compounds, tobacco
Saliva	Non-invasive, easy collection	Lower concentrations, requires sensitive analytical techniques Flow variation The use of stimulant or absorbent pads can interfere with analysis Less documented for HBM applications	Metals/trace elements, organic compounds, POPs, tobacco
Breast milk	Information about mother and child Slightly invasive Enriched in lipophilic compounds	Restricted at certain period of life Depuration during lactation should be considered in interpretation	POPs, metals/trace elements, organic compounds, tobacco

<sup>16</sup> Esteban M, Castaño A. Non-invasive matrices in human biomonitoring: a review. Environ Int 2009; 35(2): 438-49

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Matrix	Advantage	Disadvantage	Chemical groups that can be analysed
Nails	Non-invasive, easy collection  No special storage requirements or transport	Difficulty in differentiating internal/external exposure (toenails are less exposed)	Metals/trace elements, tobacco

Other matrices can be used, but are less common in HBM surveys.

### Pre-analytic factors

For health studies, several issues has to be taken into account in the pre-analytic phase; fasting, posture during the sample drawing, use of tourniquet, effect of physical training and seasonal variation.<sup>17</sup>

For HBM studies, before the examination, the participants are asked to behave like every day and stay to their regular patterns of behaviour concerning diet, sport, use of cosmetic products etc.

In feasibility studies balance between pre-analytic requirements, such as fasting, between HBM and health studies have to be sorted out.

### Sample collection, handling and storage

Sample collection, handling and storage should be conducted following the standardised protocols for HBM and health<sup>18,19</sup> studies.

### Analytic phase

For analysis of the health biomarkers, the requirements defined by EHES is that used laboratory has a documented quality management system (ISO/IEC 17025 for Testing and Calibration Laboratories or ISO 15189.2007 for Medical Laboratory Standards) and should be accredited.

For analysis of the HBM biomarkers, used laboratories have to fulfil the selection criteria of the laboratories defined by ISCIII (deliverable D9.3 due M9).

<sup>17</sup> Tolonen H (Ed.) EHES Manual. Part A. Planning and preparation of the survey. 2nd edition. National Institute for Health and Welfare, 2016, Directions 2016\_13. URN:ISBN:978-952-302-700-8, URL: <http://urn.fi/URN:ISBN:978-952-302-700-8>

<sup>18</sup> Tolonen H (Ed.) EHES Manual. Part A. Planning and preparation of the survey. 2nd edition. National Institute for Health and Welfare, 2016, Directions 2016\_13. URN:ISBN:978-952-302-700-8, URL: <http://urn.fi/URN:ISBN:978-952-302-700-8>

<sup>19</sup> Tolonen H (Ed.) EHES Manual. Part B. Fieldwork procedures. 2<sup>nd</sup> edition. National Institute for Health and Welfare, 2016, Directions 2016\_14. URN:ISBN:978-952-302-701-5, URL: <http://urn.fi/URN:ISBN:978-952-302-701-5>

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## 4.5 Health measurements to be included

### Criteria:

- A minimum set of health measurements to be included irrespectively of chemicals of interest. These include:
  - Anthropometric measurements
    - Height and weight
    - Waist and hip circumference
  - Blood pressure
- For specific chemicals and sub-populations, additional health measures may be relevant to be included (see table below).

From health examination part, a minimum set of health measurements to be included would be those covering the core measurements of the EHES: anthropometric measurements (height, weight, waist circumference) and blood pressure. For these measurements, standardised protocols of the EHES should be used. Currently also many functional capacity and cognitive tests are commonly included to health surveys.

For some of the priority substances of HBM studies, other measurements may be more relevant than e.g. blood pressure. Included health measurements should be relevant to known or suspected adverse effect pathways for the compounds to be measured. Proposed health measurements vary by age group. In table below, key measurements are highlighted in **bold**, others are relevant for example for reproductive effects or for neurodevelopmental effects and highly recommended to be included whenever feasible.

Pregnant women	<ul style="list-style-type: none"> <li>• Body fat distribution</li> <li>• Fasting blood glucose (see Section 4.4)</li> <li>• Glycated haemoglobin (HbA<sub>1c</sub>) (see Section 4.4)</li> <li>• Lipids (triglycerides, HDL and LDL) (see Section 4.4)</li> <li>• Thyroid hormones (TSH, T3, T4, fT3, fT4)</li> <li>• Ultrasound of the thyroid gland</li> </ul>
Newborn	<ul style="list-style-type: none"> <li>• <b>Birth weight and height</b></li> <li>• <b>Head circumference</b></li> <li>• Anogenital distance</li> <li>• Penile length (boys)</li> <li>• Reproductive hormone levels at age of 2-4 months (testosterone, inhibin B)</li> <li>• Body fat distribution</li> <li>• Fasting blood glucose (see Section 4.4)</li> <li>• Glycated haemoglobin (HbA<sub>1c</sub>) (see Section 4.4)</li> <li>• Lipids (triglycerides, HDL and LDL) (see Section 4.4)</li> </ul>
Children	<ul style="list-style-type: none"> <li>• <b>Pubertal staging</b></li> <li>• <b>Body fat distribution</b></li> <li>• Bone density (e.g. DXA)</li> </ul>

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		<ul style="list-style-type: none"> <li>• <b>Fasting blood glucose (see Section 4.4)</b></li> <li>• <b>Glycated haemoglobin (HbA<sub>1c</sub>) (see Section 4.4)</b></li> <li>• <b>Lipids (triglycerides, HDL and LDL) (see Section 4.4)</b></li> <li>• Thyroid hormones (TSH, T3, T4, fT3, fT4)</li> <li>• Neurodevelopmental tests</li> <li>• Cognitive tests</li> <li>• Immune response to specific vaccines</li> </ul>
Adults	Men	<ul style="list-style-type: none"> <li>• Reproductive hormones (androgens, Luteinizing hormone (LH), estradiol, sex hormone binding globulin (SHBG), inhibin B, follicle stimulating hormone (FSH))</li> <li>• Body fat distribution</li> <li>• Bone density</li> <li>• Sperm parameters</li> <li>• Functional capacity tests</li> <li>• Fasting blood glucose (see Section 4.4)</li> <li>• Glycated haemoglobin (HbA<sub>1c</sub>) (see Section 4.4)</li> <li>• Lipids (triglycerides, HDL and LDL) (see Section 4.4)</li> <li>• Thyroid hormones (TSH, T3, T4, fT3, fT4)</li> <li>• Ultrasound of the thyroid gland</li> </ul>
	Women	<ul style="list-style-type: none"> <li>• Body fat distribution</li> <li>• Bone density</li> <li>• Ovarian ultrasound</li> <li>• Functional capacity tests</li> <li>• Serum anti-müllerian hormone (AMH)</li> <li>• Fasting blood glucose (see Section 4.4)</li> <li>• Glycated haemoglobin (HbA<sub>1c</sub>) (see Section 4.4)</li> <li>• Lipids (triglycerides, HDL and LDL) (see Section 4.4)</li> <li>• Thyroid hormones (TSH, T3, T4, fT3, fT4)</li> <li>• Ultrasound of the thyroid gland</li> </ul>

And some of them are more relevant for specific chemicals while others may be relevant for several chemicals.

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Chemical groups	Suspected MoA and health effects	Study populations	Recommended measured health outcomes
phthalates and Hexamoll® DINCH bisphenols flame retardants	Reproductive effects  (anti-androgenic, estrogenic, anti-estrogenic)	Pregnant women/ Newborns	Birth weight and length, head circumference, anogenital distance, penile length (males), reproductive hormone levels at 2-4 months of age: testosterone, inhibin B)
		Children	pubertal staging body fat distribution bone density (e.g. DXA)
		Adult men	reproductive hormones (androgens, LH, estradiol, SHBG, inhibin B, FSH) body fat distribution bone density (sperm parameters) functional capacity tests
		Adult women	body fat distribution bone density (ovarian ultrasound) functional capacity tests serum anti-müllerian hormone (AMH)
Phthalates bisphenols	Obesogenic and metabolic effects	Pregnant women/ newborns	body fat distribution fasting blood glucose
		Children	glycosylated hemoglobin (HbA1c)
		Adult men	lipids (triglycerides, HDL and LDL)
		Adult women	Newborns: birth weight and length
per- /polyfluorinated compounds	Thyroid hormone effects	Pregnant women/ newborns	Maternal: thyroid hormones (TSH, T3, T4, fT3, fT4), ultrasound of the thyroid gland Newborns: birth weight and length, head circumference
		Children	Thyroid hormones Neurodevelopmental tests Cognitive tests

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Chemical groups	Suspected MoA and health effects	Study populations	Recommended measured health outcomes
		Adult men	Thyroid hormones Ultrasound of the thyroid gland
		Adult women	Thyroid hormones Ultrasound of the thyroid gland
per- /polyfluorinated compounds  PAHs	Immunesystem effects	Pregnant women/ newborns	
		Children	Immune response to specific vaccines
		Adult men	
		Adult women	
phthalates  bisphenols  flame retardants	Neurodevelopmental effects /neurodegenerative effects	Pregnant women/ newborns	
		Children	Neurodevelopmental tests Cognitive tests
		Adult men	
		Adult women	
PAHs  Cadmium and chromium	Carcinogenic	Pregnant women/ newborns	
		Children	
		Adult men	
		Adult women	
Cadmium and chromium  PAHs	Lung, liver, kidney effects	Pregnant women/ newborns	
		Children	
		Adult men	
		Adult women	

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## 4.6 Quality assurance measures

### Criteria:

- Surveys have to follow agreed SOPs for HBM and health measurements to the extent it is feasible under national circumstances. All deviations have to be documented and justified.
- Survey organisers have to demonstrate that they have participated to training related to HBM surveys and measurements of health surveys. Also training for the fieldwork personnel has to be organised.
- For the analysis of HBM biomarkers, a laboratory qualified by HBM4EU QC/QA programme has to be used.
- For each feasibility study, at least one external audit visit by persons designated by WP11, Task 11.4 leader will be organised and a written audit report will be prepared. All partners organising a feasibility study have to agree with this.

In all feasibility studies, agreed SOPs (see detailed recommendations above for questionnaire, collection and storage of biological samples, and health measurements) for different phases of the survey have to be followed. Obviously in feasibility studies, some adjustments may be needed when we are combining HBM and health studies, which may have overlapping or contradicting requirements. All deviations and amendments to the agreed SOPs have to be documented and justified.

To ensure correct use of provided SOPs in each survey, both survey organisers and actual fieldwork personnel has to be trained. Survey organisers require training to have common understanding of used SOPs. Centralised training will be organised under WP2, Task 2.5 and partners conducting feasibility studies are obliged to participate to this training.

Fieldwork personnel require detailed training of how SOPs are used in local settings. Organises of the surveys are responsible for providing this training and providing documentations that training has been organised, fieldwork members have participated to it and what was the contents of the training.

## 4.7 Data protection and ethical approval

### Criteria:

- Partner responsible for organisation of the survey will obtain all required ethical and data protection approvals before the start of the fieldwork.
- All required ethical and data protection approvals with related documents (information material and informed consent) will be provided to Lisbeth E. Knudsen (Task 1.5 leader) before starting of the fieldwork.

All feasibility studies have to follow EU and national legislation related on data protection and ethical conduct in health related studies. Details are provided in the D1.5 Legal and ethics policy document. Ethical approval has to be obtained from relevant ethics committee prior to the start of the survey fieldwork and required documents have to be provided to the Task 1.5 leader Lisbeth E. Knudsen.

A written informed consent has to be obtained from all participants before any physical measurements or sample collection is conducted. Survey team on the field and central office is

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responsible for ensuring data confidentiality and data security, i.e. safeguarding the personal information provided by survey participants.

## 4.8 Providing data to IPChem

### Criteria:

- Newly generated HBM data will be made available through IPChem.
- Newly generated combined HBM and health data will be made available for HBM4EU consortium, through HBM4EU data repository.
- Required data transfer agreements will be prepared before data transfer takes place and provided to Lisbeth E. Knudsen (Task 1.5 leader).

In the Grant Agreement, under WP10 (Task 11.5), it has been stated that all new HBM data generated under HBM4EU project will be made available through IPChem<sup>20</sup>. This covers also HBM data generated in feasibility studies.

Since feasibility studies will also include health data which is not covered by IPChem but would be needed by many WPs on their assessment of health impacts of chemical exposures, a separate HBM4EU data repository will be established under WP10 together with JRC. The technical details for data transfer to IPChem and HBM4EU data repository, including data transfer agreements, are included to the Data policy, prepared by WP10 as deliverable D10.1.<sup>21,22</sup>

## 4.9 Documentation and reporting obligations

### Criteria:

Each Partner conducting a feasibility study has to provide following documents/reports in English for the evaluation:

- Information letter/material for invitees
- Informed consent form
- Other supporting material used in recruitment/on the field
- Study plan and protocol
- Used questionnaire(s)
- Self-assessment on opportunities and obstacles

Each feasibility study will be evaluated for opportunities and obstacles resulting in combining HBM and health examination survey. To be able to do this, documentation of entire survey process and report of the outcome is required in English. The documentation of the survey process includes:

- Material required to obtain ethical approval and approval by data protection authorities (if nationally required) for the survey;
- Information letter/material provided for survey invitees;
- Informed consent form;
- Other possible supporting material used in recruitment and/or during the fieldwork;

<sup>20</sup> <https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html>

<sup>21</sup> <https://www.hbm4eu.eu/wp-content/uploads/2017/08/Deliverable-10.1-Data-Management-Plan-August-2017.pdf>

<sup>22</sup> [https://www.hbm4eu.eu/wp-content/uploads/2017/03/HBM4EU\\_Deliverable\\_D10.1\\_Data-policy\\_v1.0\\_20170731\\_Annex.pdf](https://www.hbm4eu.eu/wp-content/uploads/2017/03/HBM4EU_Deliverable_D10.1_Data-policy_v1.0_20170731_Annex.pdf)

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- Study plan and protocol incl. description of sample and sampling procedures, recruitment method, flow of the fieldwork, detailed SOPs for the measurements and sample collection, handling and transfer, description of data protection procedures etc.
- Used questionnaire(s).
- A self-assessment on opportunities and obstacles resulted from the feasibility study.

## 4.10 Funding

Feasibility studies are expected to be carried out in connection with existing/planned HBM or health studies, providing basic infrastructure for the studies. From HBM4EU, additional costs for including HBM/health module will be covered to the extent specified in the Internal Call. Costs covered by HBM4EU will have 50% funding rate (50% EU funding/50% own contribution) as stated in the Paragraph 7.4.2 of the Consortium Agreement (version 1, 2016-11-03).