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Guidelines for linking HBM and health studies

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Table of contents

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2. Background

HBM and health studies, namely health examination surveys (HES), have several common components both in the planning and the preparation phase of the study, as well as in the implementation phase, namely with regard to survey contents and to fieldwork. For planning and preparation phases, for example, common features can be found in sampling, ethical and data protection, personnel requirements, and training of the survey staff. Both study types include questionnaires which can have several common modules, health measurements and collection of biological samples such as blood and urine. Sample selection and requirements for the fieldwork site as well as recruitment of participants also share several common features.

Additional to all common features and protocols there are also specific issues/protocols from HBM and HES which differ. Therefore, the aim of these guidelines and SOPs is to provide recommendations on how HBM and HES could be combined at a national level to obtain the best synergies on fieldwork logistics, data collection and costs.

These guidelines are based on comparison of the existing HBM and HES protocols.The guidelines and SOPs for HBM studies are based on some of the deliverables (ready and under preparation) within the HBM4EU project[1], experience from COPHES/DEMOCOPHES[2,3,4,5,6,7,8] and HBM protocols/recommendations[9] For HESs the guidelines and SOPs are taken from the EHES[10,11]. The main purpose has been to identify survey phases and contents of the survey protocols which are common in both HBM and health studies, i.e. easily merged, and where differences exist. When protocols for HBM and HES were similar, common parts are described as recommendation for combined HBM and health survey. When differences in the protocols were observed, recommendations aims to highlight the minimum key components required for both parts (HBM and HES). For differing parts, case-by-case decisions are needed in each study to ensure that study aims are fulfilled.

[1] https://www.hbm4eu.eu/result/publications/
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3. Guidelines

3.1 Planning and preparation of the survey

3.1.1 Sampling

Within HBM4EU, in order to derive representative HBM data, the country is set as a primary sampling unit (PSU). To attain an entire European coverage within HBM4EU, a European maximal scenario would be sampling in each of the participating EU countries (PSUs). However, this scenario would be really expensive. In order to derive representative HBM data more cost effectively, the number of PSUs has been defined as a minimum of 12 European countries. These countries need to be distributed over all geographical regions in Europe. Four geographical regions (clusters) are defined according to the United Nations geo-scheme for Europe: Northern Europe, Eastern Europe, Southern Europe and Western Europe.

The sampling domains for which at least specified reliability is desired in Europe are gender and age groups. The seven age groups that are targeted within the HBM4EU surveys are: 0-2y, 3-5y, 6-11y, 12-19y, 20-39y, 40-59y and 60-79y. No further general inclusion and exclusion criteria are set. However, for specific biomarker measurements, additional recruitment and sampling conditions may be set out.

In EHES, the main aim is to obtain a nationally representative sample for each country among the adult population aged 25-64 years.

For individual countries which plan to combine HBM and HES, it is important to understand the requirements for the sampling in both domains and make their decisions based on these requirements.

3.1.1.1 Terminology

The following terms are commonly used in relation to sampling. Provided definitions are mainly from Porta 2008[12] and Rao 2000[13].

Target population	The collection of individuals about which inferences are desired.
Sampling frame	A source of material or device from which a sample is drawn. It is a list of all those who can be sampled. It may include individuals, households, dwellings, institutions etc.
Exclusion criteria	Pre-defined criteria used to exclude some members/groups of the target group. For example people who don't speak the main language(s) of the country etc.
Sample size	Number of individuals to be selected to the sample. This is a number to be invited to the study, not the number of participants.
Eligibility	Pre-defined criteria for sampled individuals and their eligibility. Sometime sampling frames include persons who, by definition of the target population, no longer belong to the sample and should be excluded due to

[12] Porta M (Ed.) A Dictionary of Epidemiology. 5th edition. 2008. Oxford University Press
[13] Rao PSRS. Sampling methodologies with applications. 2000. Chapman & Hall/RCR

	ineligibility. For example, person may have died or moved out of study area or he/she may be wrongly recorded to the sampling frame.
Sampling scheme	A detailed description of what data will be obtained and how. Sampling scheme should include information about how many stages it includes and which sampling methods, i.e. random sample, stratified random sample, convenience sample etc. is used in each stage.
Primary Sampling Unit	In multi-stage sampling, the 1st stage sampling unit. Often this is a geographical area.
Secondary Sampling Unit	In multi-stage sampling, the 2nd stage sampling unit. Often this is an individual.
Participation rate	Proportion of the eligible samples who have participated to the study.

3.1.1.2 Requirements for sampling by HBM and HES

In the Table 1 we provide requirements for HBM studies in general, not only for those planned under HBM4EU, and for health studies based on EHES recommendations.

Table 1. General requirements for sampling by HBM and HES

	HBM	HES
Definition of target population (geographical coverage, age, etc.)	General population of people with permanent residence in the country/study area.	At least: All person aged at least 25 years and at most 64 years and having permanent residence in the country.
	Age group 0-79 years.	Preferably also: 18+ without upper age limit.
	Optional, depending on substances of interest: specific occupational groups or hot-spots based on known pollutant concentrations.	
Exclusion criteria	Depends on substances of interest.	None.
Sampling frame	Depends on national availability and legal possibilities to use different sampling frames. Whenever possible, a central file with the most recent and best coverage of the people in the target population should be used. Ideally this would be a	Depends on national availability and legal possibilities to use different sampling frames. Whenever possible, a central file with the most recent and best coverage of the people in the target population should be used. Ideally this would be a

	HBM	HES
	population register.	population register.
	Occupational groups could be sampled through unions or workplace.	
Sample size (N of persons to be invited)	At least 500 persons/country, depending on participation rate. I.e. data from at least 300 participants is expected.	At least 4,000 persons/country
	Possibly more if broad coverage of different ages including children and adults	
Eligibility criteria	Within defined age group, alive and still living in the study area.	Within defined age group, alive and still living in the study area.
Sapling scheme	Two-stage sampling	Two-stage sampling
	PSU: Study area/geographical area	PSU: Study area/geographical area
	SSU: people, addresses, household or dwellings depending on available sampling frames	SSU: people, addresses, household or dwellings depending on available sampling frames
	For sampling of children and adolescents schools /kindergartens can be used for SSU	
Expected participation rate	60%	70%

3.1.1.3 Recommendation for sampling when combining HBM and HES

The sample should serve the needs for both HBM and HES aims. The recommendation for combined HBM and HES is:

- **The target population:** General population aged at least 25-64 years, but preferably 0-79 years whenever feasible. National coverage with both urban and rural areas.
- **Exclusion criteria:** For HES, all population groups, also institutionalized (in elderly homes, etc.) are important to obtain results which represent the entire target population. Sometimes, it may be difficult to reach for example institutionalized persons but they should not be excluded by default from the sample. For HBM no particular exclusion criteria is needed prior to the sampling but some particular profiles must be excluded a posteriori and sufficient information for these needs to be collected in questionnaires for example.
- **Sampling frame:** Best available sampling frames in the country which also has as much other information (at least contact information) as possible.

- **Sample size:** Since national HES requires a large sample size to be able to provide representative and reliable information about health of the population, it may not always be feasible to conduct HBM study on entire sample of 4000 persons per country. Therefore, HBM study could be conducted in a sub-sample of the large sample. This sample should include at least 500 persons in the age group(s) relevant for the substances of interest. A sub-sample should be a random sample of the large sample to ensure its representativeness.
- **Eligibility criteria:** Within defined age group, alive and still living in the study area.
- **Sampling scheme:** Two-stage random sample where the PSU is a study area or other geographically defined area and the secondary sampling unit (SSU) is an individual within PSU.
- **Participation rate:** Each study should aim to as high participation rate as possible, ideally at least 60%. It is well known that selection to the surveys is selective for socio-demographic factors as well as for health and health behaviours. If participation rates are low, this will effect on representativeness of the results. Therefore, it is better to target available resources to recruitment and not to increase sample size.

3.1.2 Ethics and data protection

Both HBM and health studies have to follow the same ethical principles and data protection regulations/legislation. When planning the combined HBM and health study, national acts regulating the status and/or rights of the patients and national medical research acts has to be followed. Also other national ethical principles of research involving humans and international biomedical research guidelines have to be taken into account.

For HBM studies, D1.5 Legal and ethical policy document provides guidelines related to the required ethical approvals and data protection actions. Similar guidelines for health studies are available from the EHES[14].

In all studies, ethical approval has to be obtained from a relevant ethics committee. Required documents for an ethical approval proposal vary between countries and sometimes even between ethics committees within a country. It is therefore, important to find out early in the planning process which documents are needed. In some countries, a separate data protection approval has to be obtained, while in some countries these are part of the ethical approval.

A written informed consent is required from all study participants before any measurements or biological sample collection can be initiated. Informed consent, together with information letter/notice/leaflet, has to provide enough details that the participant understands in what he/she is getting involved in and that his/her participation is voluntary and he/she can withdraw at any time. Participants also have to have a change to ask clarifying questions before signing the informed consent.

For data protection, national regulations and institutional guidelines have to be followed, safeguarding all personal data of the survey participants.

3.1.3 Required personnel

Organization of the HBM study and HES requires a lot of personnel for different tasks on study coordination, fieldwork, sample and data handling and processing as well as in reporting. The number and qualifications of required personnel is also dependent on the contents of the study,

[14] Tolonen H (Ed). EHES Manual, Part A. Section 4. Legal and ethical aspects. 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

sample size and how the fieldwork and survey logistics are organized. There may also be national requirements, for example for persons drawing blood samples, which effect on required personnel.

3.1.3.1 Personnel requirements by HBM and HES

Table 2 will provide generic listing of required personnel for HBM studies and HES.

Table 2. Personnel requirements by HBM and HES

	HBM	HES
Coordinator	Project leader/Principle investigator(s)	Project leader/Principle investigator(s)
		Survey coordinator
	Fieldwork supervisor	Fieldwork supervisor
	ICT support for fieldwork team(s) if ICT systems are used	ICT support for fieldwork team(s) if ICT systems are used
Fieldwork	Qualifications and number of fieldwork team members is dependent on included measurements, sample size and its geographical extend, and length of the fieldwork.	Qualifications and number of fieldwork team members is dependent on included measurements, sample size and its geographical extend, and length of the fieldwork.
	• Nurses	• Nurses
	• Laboratory personnel (in some countries it is required that blood samples are drawn by certified phlebotomists)	• Laboratory personnel (in some countries it is required that blood samples are drawn by certified phlebotomists)
	• Interviewers (if self-administered questionnaires are not used)	• Interviewers (if self-administered questionnaires are not used)
		• Survey physician (in many countries this is a requirement but does not need to be on the field can be also in the central coordinating office)
Sample handling and processing	Laboratory personnel	Laboratory personnel
Data handling and processing	Data-entry clerks	Data-entry clerks
	ICT experts (data management)	ICT experts (data management)
	Scientists	Scientists

	HBM	HES
Reporting	Scientists	Scientists
	Public health experts	
		Public relations (PR) expert
		Possibly also graphical designer (in house or subcontracting)

3.1.3.2 Personnel recommendations for combined HBM and HES

HBM or HES studies individually may require similar human resources. The recommendation for combined HBM and HES study is:

- **Coordination:** Any combined study should ideally be carried out by a single central structure that provides oversight and overall coordination of the study (project leader). It could be ministries or public health agencies for example. The project leader should be responsible for the overall management of all HBM or HES aspects of the study in terms of study planning, fieldwork implementation, final report and field experience feedback.

  The principal investigator/survey coordinator should be responsible for the proper implementation on the field of the study protocol and follow-up of standard operational procedures.

- **Fieldwork:** Each field supervisor should be responsible for the fieldwork organization in a defined geographical area or at the national level depending on the local survey organization. He/she coordinates aspects from logistics to the data collection, under the responsibility of the principal investigator. The collection of biological samples and physical measurements must be carried out by trained personnel who are trained specifically for this purpose during the training seminars planned as part of the study (nurses, phlebotomists, laboratory personnel). In the case where the questionnaires are administered by an interviewer, this must be done in a standardized way.

- **Sample handling and processing:** The handling and processing of the biological samples is carried out under the coordination of the laboratory manager. He/she is responsible for the proper progress of biological analysis (and also storage), the strict application of SOPs and the compliance with the specifications that the laboratory has underwritten for the study.

- **Data handling and processing:** The handling and processing of the overall final data is carried out in collaboration with ICT experts, scientists and/or public health experts. Statistical analysis should be done under a defined statistical analysis plan in close collaboration with qualified statisticians, scientists and public health experts.

- **Reporting:** The dissemination of the results and final reports can be presented in different volumes or sub-volumes according to the HBM and HES components, in order to make it more easily readable. To get wider visibility for the results, scientists should work together with PR experts and graphical designers.

3.1.4 Training of the personnel

Training of the personnel both on the central coordinating office and on the fieldwork team(s) is essential for the success of the HBM studies and HESs. Training is one of the components of the quality assurance of the study and will help to ensure high quality data collection.

3.1.4.1 Requirements for HBM and health studies

Table 3 highlights training requirements for HBM and HES.

Table 3. Key components of the training for HBM and HES

	HBM	HES
Entire survey personnel	Purpose and aims of the survey	Purpose and aims of the survey
	Legal and ethical aspects (data protection, protection of privacy)	Legal and ethical aspects (data protection, protection of privacy)
	Design of the survey	
		Survey organization
	Recruitment strategy	Recruitment strategy incl. importance and tools for promoting high participation rates
	Importance and methods of standardized operating procedures	Importance and methods of standardized operating procedures
	Quality assurance procedures	Quality assurance procedures
	Data management system	Data management system
	Publicity and communication strategy	Publicity and communication strategy
Fieldwork personnel		Communication skills
	Interviewing techniques	Interviewing techniques
	Motivating participants	Motivating participants
	Safety issues (biological and occupational)	Safety issues
		Giving feedback to participants
		Consulting survey physician(s) and supervisor(s)
	Specific training for those collecting and handling biological samples	Specific training for those collecting and handling biological samples
		Specific training for those carrying out specific health measurements such as blood pressure, anthropometric measurements etc.

3.1.4.2 Recommendations for training when combining HBM and health studies

The training requirements for HBM and HES are the same for the general parts of the study which concern the entire staff involved in the survey process (see Table 3.)

All parties involved in the survey process should be aware of the overall aims and processes of the study and what is their precise place in the global chain of the study.

For fieldwork personnel specific training for:

- Communication skills;
- Interviewing techniques;
- How to motivate reluctant participants;
- How to give feedback to the participants;
- When and how to consult survey physician and supervisors;
- Safety issues related to both measurements and especially collection of biological samples but also when meeting invitees who might behave violently.

Each person conducting measurements and/or collecting biological samples needs to go through detailed training for standardized protocols and re-training/certification may be needed if survey takes a long time. For health measurement recommended by EHES, the training material is available online[15] and can be used in national training.

It is recommended to organize a training seminar/workshop before the start of the combined HBM and HES. Everyone involved with the study should participate to this training seminar/workshop. Training would include theory on standardized procedures and practical training on appropriate techniques. The survey organizer/leader is responsible for organization the required training and making sure that everyone has required knowledge, also taking into account possible national requirements (regulations/guidelines) before starting the work.

3.2 Survey content

3.2.1 Questionnaires

In both HBM studies and HES, background and supporting information for objective measurements is collected using questionnaire(s). For HBM some of the questions may be specific for the substance of interest.

3.2.1.1 Key questionnaire topics for HBM and health studies

Table 4 lists the main topics of questions, not specific wordings of individual questions, which at least should be included to HBM studies and HESs. HBM questionnaires need to include a set of questions to identify potential sources of exposure to the chemicals of interest from occupational activities, diet, household environment, hobbies, domestic exposures and individual behaviours. For HESs, topics on *italic* are commonly included to a national HES but are not listed as core questions in the EHES recommendations.

This table also lists only items on actual survey questionnaire, not items to be recorded during the study visit such as measured height and weight.

[15] EHES Training materials. http://www.ehes.info/training_materials/index.htm

Table 4. Key questionnaire topics for HBM and HES

		HBM	HES
Contents	SES background	Sex	Sex (if not obtained from sampling frame)
		Age/date of birth	Age/date of birth (if not obtained from sampling frame)
		Marital status (additional information)	Marital status
		Education	Education
		Labour status	Labour status
		Employment status and profession	-
		Household composition (optional information)/Family structure	Household composition
		Income	Income
		Nationality and/or place of birth	-
		Ethnic origin (if accepted by national legislation)	-
		Area of residence	-
		Workplace area/address	-
	Health status	General health	General health
		-	Diagnosed chronic/long standing illnesses
		Medical history	*Medical history*
		Family health related history	-
	Functional capacity	-	Limitation of daily living
	Use of health care services	Visits to the doctor	*Visits to the doctor*
		Previous hospital admissions	-
		Prescription of medicines by a doctor	Prescription of medicines by a doctor
		-	Measurement of blood pressure, blood cholesterol and glucose by a health professional
	Anthropometrics	Self-reported height and weight (only if not measured)	Self-reported height and weight
	Lifestyle*	Smoking	Smoking
		Alcohol consumption	*Alcohol consumption*
		Sun exposure	-
		Physical activity	*Physical activity*
		Occupational activities and exposures (depending on chemical substance)	-
		Sedentary behaviours	*Sedentary behaviours*
		Diet (depending on chemical substance also data on packaging, cooking process and hygiene)	*Diet*
		Consumption of locally produced foods	-

	HBM	HES
	Individual and domestic uses of chemicals (depending on chemical substance)	-
	Living environment (in terms of environmental exposure: industries, farms, traffic)	-
	Hobbies	-
Mode of data collection	Self-administered or interview depending on national practices and the setting of the fieldwork	Self-administered or interview depending on national practices and the setting of the fieldwork

*This includes, for the needs of HBM studies, questions to identify potential sources of exposure to chemical substances of interest.

3.2.1.2 Recommendations for included questionnaire topics when combining HBM and health studies

The questionnaire for combined HBM and HES should include at least the key questions needed to fulfil the needs of both study types. At the same time it should be ensured that questionnaire does not get too long and is too burdensome for the participant. Therefore, the following list of questions/questionnaire modules includes only those which are common in both HBM and HES. For HBM and HES specific questions, decision about included questions has to be made case-by-case depending on study specific aims and national monitoring/research needs. For example, for HBM module, substance specific questions should be added based on list of included substances. Similarly for HES module, some health examinations may require a specific set of questions to provide required background information. At least following questions/questionnaire modules should be included:

- From SES background: sex, age/date of birth, marital status, education, labour status, household composition, income.
- From health status: general health and medical history which could to some extend also be obtained through diagnosed chronic/long standing illnesses.
- From use of health care services: prescription of medicines by a doctor.
- Anthropometric: self-reported height and weight. Note: This is important to collect in addition to measured height and weight for validation purposes and for possible non-response adjustment.
- Lifestyle: smoking, alcohol consumption, physical activity, sedentary behaviours, diet.

For data collect mode, it is not possible to provide only one solution since best and most cost-effective way may vary considerably between countries. In some countries self-administered questionnaires are frequently used either as paper or web questionnaires. On the other hand, in some countries interviews, face-to-face or telephone, are more commonly used data collection methods. This depends also strongly on general organization of the survey and available staff.

3.2.2 Collection of biological samples

3.2.2.1 Requirements for the collection of biological samples in HBM and health studies

For health surveys, EHES provides a minimum set of biological samples to be collected, allowing the analysis of lipids and glucose. Also collection of urine is highly recommended to allow analysis of sodium intake in the population. For HBM the preferred biological matrix depends on the compounds to be measured. The most frequently used sample types are either blood or urine but

also other matrices may be useful. However, for linking HBM to HES or other health studies, blood and urine are most likely the most widely accessible sample types.

Table 5. Requirements for the collection of biological samples in HBM and HES

	HBM	HES
Sample types	Blood (serum, plasma, whole blood)	Blood (serum, plasma, whole blood)
	Urine (preferably 24h pool but first morning void and random spot may be used)	Urine (preferably 24h)
Pre-analytic requirements	Participants	Participants
	• Blood: None	• Blood: Fasting glucose, lipoprotein fractions and triglycerides require at least 8 hours fasting (and at most 14 hours).
	• Urine: for collection of first morning void it is relevant to note the time of the collection as well as the time of the void prior to the collected. For 24 hour pools note the time of the last void before start of collection and the time of the last void collected.	
	Equipment	
	• Equipment used for sample collection (e.g. tubes, needles, containers etc.) should preferably be tested for if it contain/leak the compounds to be analysed and thus could be a source of contamination of samples. If contamination is detected the source should, if possible, be replaced.	
Amount	Blood:	Blood:

	• plain serum gel tube (9/8 ml)	• plain serum gel tube (9/8 ml) • fluoride-citrate tube (5/3 ml) • EDTA tube (9 ml) whole blood for DNA • EDTA tube (9 ml) plasma for vitamins, antioxidants etc. • EDTA tube (3ml) whole blood for HbA1c
	Urine:	Urine:
	• At least one 2 ml, preferably more for long term storage	• At least one 2 ml, preferably more for long term storage
Sample collection	Blood:	Blood:
	• Sitting posture preceded by 10-15 min rest.	• Sitting posture preceded by 10-15 min rest.
	• From the arm that was not used for blood pressure measurement, i.e. from left arm.	• From the arm that was not used for blood pressure measurement, i.e. from left arm.
	• Avoiding prolonged venous occlusion by tourniquet.	• Avoiding prolonged venous occlusion by tourniquet.
	Blood and urine: • Field blank samples* should preferably be collected in parallel with sampling of the biological samples.	
Sample handling and processing on the field	Blood:	Blood:
	• Before centrifugation, make sure that the blood has clotted in the plain serum and plasma tubes (at least 20 minutes).	• Before centrifugation, make sure that the blood has clotted in the plain serum tube (at least 30 minutes at room temperature).
	• Centrifugate tubes at room temperature (20-25^{o}C) for 10 minutes at 2000rpm. Plain serum tubes within 30-60 minutes from venipuncture. Plasma tubes within 60 minutes from venipuncture.	• Centrifugate tubes at room temperature (20-25^{o}C) for 10 minutes at 2000rpm. Plain serum tubes within 30-60 minutes from venipuncture. Plasma tubes within 60 minutes from venipuncture.
	• Immediately after centrifugation transfer serum/plasma into storage tubes.#	• Immediately after centrifugation transfer serum/plasma into storage tubes.
	Urine:	
	• Transfer into storage tubes.	

	• For 24 hour urine: measure and record the volume of the full pool before transferring aliquotes into storage tubes.	
Sample storage on the field	Blood and urine:	Blood:
		• If samples are not transferred immediately to the lab, freeze samples on the field.
	• Samples should be frozen as soon as possible but can be kept at 4-8°C for up to 24h.	
	• Long term storage at least -20°C but preferably -70°C or less	• Long term storage: Samples frozen at -20°C should be analyzed within 6 months. For longer storage, at -70°C or less.
		Urine:
		• At least -20°C but for long term storage preferably -70°C
Sample transfer	Either the primary or secondary receptacle must be leak proof.	The sample boxes should be packed in leak proof secondary box.
	For liquids, add enough absorbent to the primary containers.	Secondary box should have enough absorbent material.
	For frozen or refrigerated samples, place dry ice/refrigerant packs outside of secondary packaging.	The frozen samples in their respective storage boxed should be backed on dry ice to be transferred to the laboratory.
		National regulations concerning transport/mailing of biological samples needs to be followed.

* Field blank samples= a “blank” matrix (e.g. purified water or artificial serum or urine certified to be clear of the compounds to be analysed), which is handled the same way as the biological samples during sampling and sample handing in the field. Field blank samples are included randomly in order to track contamination of samples originating from ambient conditions during sampling and sample handling.

For some compounds (e.g. phthalates) it may be relevant to inhibit in vitro metabolism/degradation of the compound by denaturation of serum enzymes immediately after transfer of serum to storage tubes. If denaturation agent (usually acid) is added to the storage tubes this should be recorded as well as marked on the tubes.

3.2.2.2 Recommendations for collection of biological samples when combining HBM and health studies

Combined HBM and HES study should consider at least key requirements from both HBM and HES to allow collected samples to be used for the analysis of biomarkers for both HBM and health purposes. Therefore, following is recommended:

- **Sample types to be collected:** Blood (serum, plasma and whole blood) and urine (preferably 24 h urine)
- **Pre-analytic requirements:** From participants, fasting is required for some health related biomarkers such as fasting glucose and triglycerides. For urine collection (the first morning void or 24 h pool), the timing of the void needs to be instructed and recorded. When collected samples are used for HBM analysis, contamination of the samples by equipment used for sample collection should be avoided.
- **Amount:** For blood at least plain serum gel tube (9/8 ml), fluoride-citrate tube (5/3 ml), EDTA tube (9ml) whole blood, EDTA tube (9 ml) plasma, EDTA tube (3 ml) whole blood and 2 ml of urine should be collected. It is highly recommended to collect more, whenever possible, for long-term storage.
- **Sample collection:** Blood sample is draw on sitting posture after 10-15 minutes rest from the arm that was not used for blood pressure measurement, i.e. from left arm. A prolonged venous occlusion by tourniquet is avoided. When collected samples are used for HBM analysis, it is recommended to collect field blank samples in parallel with sample collection.
- **Sample containers:** Accurate information on the material of the tubes used for blood or urine sample collection should be provided since it may impact on the measured concentrations of some particular specific chemicals depending on the materials used by the manufacturer (especially in the context of multi-pollutant analysis from the same samples).
- **Sample handling and processing on the field:** After blood samples have been drawn and before centrifugation plain serum tubes are allowed to clot at least 30 minutes in room temperature. Tubes are centrifugated at room temperature (20-25 ^{o}C) for 10 minutes at 2000 rpm. Immediately after centrifugation, samples are transferred (serum/plasma) into storage tubes. Spot urine samples are transferred into storage tubes. For 24 h urine samples, the full volume of the sample is measured and recorded before transferring sample into storage tubes.
- **Sample storage on the field:** Samples should be frozen as soon as possible already on the field. For long term storage, -70^{o}C or less is preferred.
- **Sample transfer:** When frozen samples are transferred, dry ice should be used. Frozen samples are packed on leak proof containers. National regulations concerning transport/mailing of biological samples needs to be followed.

3.2.3 Health examinations and analysis of biomarkers

Health examinations and biomarkers are a core part of the HES. In HBM chemical related biomarkers are in key role and often some objective health measurements are also included. See Appendix 1. for more information about health measurements included to previous combined HBM and health studies (namely HES). Appendix 2 provides background information for required biological matrixes for different priority chemicals.

3.2.3.1 Requirements for health examination and biomarker for HBM and health studies

Table 6 provides the key health examinations and analysis of biomarkers for HBM studies and HESs.

Table 6. Key health examinations and analysis of biomarkers in HBM and HES

	HBM	HES
Anthropometric measurements	Mandatory:	Mandatory:
	• Height	• Height
	• Weight	• Weight
		• Waist circumference
	In order to calculate BMI and assess corpulence of individual.	
	Additionally:	Additionally:
	• Waist circumference	
		• Hip circumference
		• Body composition by bioimpedance
Clinical measurements	Mandatory:	Mandatory:
	• Blood pressure	• Blood pressure
	Additionally:	Additionally:
	• Osteodensitometry	
		• Lung function measurement
		• Cognitive function test
		• Physical activity/fitness test and measurements
		• Ultrasound tests of thyroid and bone density
Biological measurements	Mandatory:	Mandatory:
	• Volume of urinary creatinine	
	• Cotinine (sensitive biomarkers for exposure to tobacco smoke)	
		• Total and HDL cholesterol
		• Glycose if fasting samples collected otherwise glycated haemoglobin (HbA_{1c})

	HBM	HES
	Also useful in order to collect an adequate volume of blood from individual in respect for good health condition for him/her.	
	Additionally (useful to maximise the possibilities to interpretive levels of exposure for metals and to link to potential health issues):	
	• Iron status (blood ferritin and trans-ferritin)	
	• Iodine status (T4, TSH)	
	• Glycated haemoglobin (HbA_{1c})	
	• Biomarkers of renal dysfunction (some contaminants being quantified in urine)	

3.2.3.2 Recommendations for health measurements and analysis of biomarkers when combining HBM and health studies

Combined HBM and HES study should include at least those measurements which are mandatory for both domains:

- Anthropometrics: height and weight, and waist circumference.
- Clinical measurements: blood pressure.
- Biological measurements: Volume of urinary creatinine, cotinine, total and HDL cholesterol and glucose and/or glycated haemoglobin (HbA_{1c}).

Obviously all additional measurements which can be included to the combined study will provide valuable information about health and health determinants of the target group. The number and type of additional measurements should be considered carefully in each survey to avoid unnecessary burden for participants. In selection of health measurements and analysed biomarkers, a criteria developed by the EHES[16] for the selection of health measurements could be used. Then each included additional measurement should fulfil following eight points:

1. Public health importance
2. Clear interpretation of the results,
3. Availability of international standards
4. Practicality, easy to administer
5. Surveys as the primary source of information
6. Cost of the survey
7. Ethical acceptability

[16] Tolonen H (Ed.) EHES Manual. Part A. Section 5. Selecting the questionnaire modules, measurements and biological samples. 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

8. Acceptability to the participants

However regarding the specificity of this kind of combined HBM andHES studies, it appears necessary to add some specific criteria to take into account that health measurements have to be selected to answer HES and HBM aims. Therefore, some additional criteria have been proposed.

We checked from existing major studies combining heath studies and HBM (Esteban/France, GerES/Germany, but also NHANES/USA, CHMS/Canada and Knhanes/Korea) which health measurements were more frequently collected. Most of the core physical health measurements (blood pressure and anthropometric measures) included in the EHES were also included in the major European and international studies combining HES and HBM. However, there was a great heterogeneity in regard to other physical measures such as those relating to hearing (audiometry), respiratory function (spirometry), physical activity (accelerometry), or even dental and ophthalmological examinations.

Regarding biological measurements, blood is the main biological matrix used in the EHES for the determination of most of the biomarkers of interest. Urine as a biological matrix is more involved in the determination of the additional indicators. Both blood and urine, the most common matrices used, appear each necessary for various measurements.

Additional criteria for combined HBM/HES studies:

Criteria	Rationale
Substance has potential for detrimental health effects	The health measurement needs to be interpretable in relation with the health effect, known or suspected, caused by exposure to one prioritized substance of interest.
Compatibility with matrices used	The biological measurement should be feasible within a biological matrix used in HBM4EU (Blood or Urine).
Existing data from HES/HBM studies	This criterion is relevant in order to establish time-trends or spatial trends for health parameters. The measurement should have already been done in many existing HBM/HES surveys in Europe.
Potential for biomarker of effect	The health measurement should be assessed in order to know if it had a potential to become a biomarker of effect that can be directly linked to a specific health effect. Biomarker of effect could be useful for researcher in order to link exposure and health effect.

3.3 Requirements for the fieldwork site

HBM studies and HES can be conducted in many types of locations such as health care centres, specially established examination clinics, mobile units, home of the participant, etc. Each of the fieldwork sites has their pros and cons.

3.3.1.1 Requirements for fieldwork site on HBM and health studies

In HBM studies and HES, some measurements have special requirements which should be taken into account when fieldwork site is selected. These requirements are summarized in Table 7.

Table 7. Requirements for fieldwork site on HBM and HES

	HBM	HES
Blood pressure	Quiet room with comfortable temperature	Quiet room with comfortable temperature
Anthropometrics	Privacy	Privacy
Collection of biological samples	Room where potential external contamination can be avoided	

3.3.1.2 Recommendations for fieldwork site when combining HBM and health studies

In general, fieldwork site should be organized so that it is easily accessible for participants also by public transportation. For persons with functional limitations, easy access by elevators/ramp would be needed.

Since some measurements have special requirements, these should be taken into account to ensure that measurements are not compromised due to setting on which they are taken. Blood pressure measurement requires quiet room with comfortable temperature as any sudden loud sounds and too cold temperature may affect the blood pressure levels. Also if blood pressure is measured using auscultation method, all noise from the other rooms or corridor may disturb the measurement. For all anthropometric measurements participants are asked to undress and therefore privacy is required.

Room where biological samples and collected and handled should be one where potential contaminations can be avoided.

3.4 Recruitment of the participants

Successful recruitment of the participants is a key for any HBM study of HES. Each study has their own recruitment strategy based on study design, target population, available funds, previous experience etc. Same basic principles apply to both HBM studies and HESs.

Recruitment strategy should be well planned before hand and required resources should be allocated for that. The strategy should include components related to publicity of the study, format and timing of contact attempts, and supporting material used during the recruitment. The use of incentives (financial or gifts) has been found to increase participation rates in many studies and could be considered.[17] However, it may also introduce selection bias if some specific population groups such as more deprived people are more prone to participate due to offered incentives but this varies considerably between countries. In some countries use of incentives (financial/gifts) in population studies is not allowed by ethics committees/national legislation. Therefore, other formats of promotion should be considered.

Publicity of a study is important to raise people's awareness. How this is done depends on study design and country. If study is organized as a random sample of the population through specific examination clinics, announcements on media such as local newspapers and radio, as well as through social media are often good choices. Also providing posters about the study to public places such as health care centres, libraries, community houses etc. could be used. Nowadays, internet and social media are increasingly used for publicity. Study should have their own internet

[17] Edvards PJ, Roberts I, Clarke MJ et al. Methods to increase response to postal and electronic questionnaires (Review). The Cochrane Collaboration. Wiley&Sons, Ltd. 2010

page and in some countries communities/cities have their own Facebook/Twitter accounts which could be used to distribute information about the study.

The first personal contact can again be by mail, telephone or as a personal visit depending on country. Most important for the 1st contact is that invitee receives all the relevant information to make a decision about participation. This usually means that an invitation letter together with information leaflet is provided for the invitee. In some countries, also informed consent is send together with information leaflet allowing invitees to read that at home before participating to the study. If person is not reached by the 1st contact or he/she is reluctant to participate but does not refuse explicitly, re-contacts are made. Number, format and timing of the re-contact depend on study and available resources. Sometimes also national regulations/legislation may limit the possible number and format of re-contacts.

Each contact attempt should be recorded together with information about who, how, when and what was the outcome.

For recruitment, at least invitation letter, information leaflet/notice, and informed consent are needed. If resources allow, study web site, advertisement material such as posters, banners to be used in social media, short leaflets etc. could be prepared to promote the study.

4. Appendices

Appendix 1. Health measurements included to EHES and previous combined HBM and health studies

Type of health measurements	EHES[18]		Esteban (France)[19,20]	GerES IV (Germany)[21,22]	CHMS (Canada)[23]	NHANES (USA)[24]	KNHANES (Korea)[25]
	Measure	Rationale (if measured)					
A. Physical measurements							
A1. Blood pressure	Yes (core measurement)	Elevated blood pressure is one of the key risk factors for cardiovascular diseases, dementia and some kidney diseases. Population level measurement of blood pressure is used to estimate prevalence of hypertension and to monitor changes in the blood pressure levels in the population	Yes (and pulse rate)	Yes (and pulse rate)	Yes	Yes	Yes

[18] 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:SIBN:978-952-302-700-8, URL: http://urn.fi/URN:ISBN:978-952-302-700-8

[19] Etude Esteban (étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition). PROTOCOLE 09/2012

[20] Balicco A, Oleko A, Szego E and al. Esteban design: A cross-sectional health survey about environment, biomonitoring, physical activity and nutrition (2014–2016). Toxicol Anal Clin. 2017 Dec;29(4):517-37

[21] Schulz C, Seiwert M, Babisch W et al. Overview of the study design, participation and field work of the German Environmental Survey on Children 2003-2006 (GerES IV). Int J Hyg Environ Health. 2012 Jul;215(4):435-48

[22] Kurth BM, Kamtsiuris P, Hölling H et al. The challenge of comprehensively mapping children's health in a nation-wide health survey: design of the German KiGGS-Study. BMC Public Health. 2008 Jun 4;8:196

[23]Second and third reports on Human Biomonitoring of Environmental Chemicals in Canada. www.santecanada.gc.ca/biosurveillance

[24] According only to the 2016 NHANES Health Measurements (https://www.cdc.gov/nchs/data/nhanes/survey_content_99_16.pdf; www.cdc.gov/nchs/data/nhanes/nhanes_15_16/2016_hm_list.pdf)

[25] Kweon S et al. Data resource profile: the Korea National Health and Nutrition Examination Survey (KNHANES). Int J Epidemiol. 2014;43(1):69-77.

A2. Anthropometric measures	Height	Yes (core measurement)	Adult height reflects the interplay of genetic endowment and various early-life experiences and exposures such as fetal, dietary, social and psychological circumstances. Height will be used when calculating Body Mass Index (BMI), which is a widely used way to measure obesity (a known risk factor for many chronic diseases, eg. type 2 diabetes, hypertension and dyslipidemia)	Yes	Yes	Yes	Yes	Yes
	Weight	Yes (core measurement)	Used when calculating Body Mass Index (BMI), which is a widely used to measure obesity	Yes	Yes	Yes	Yes	Yes
	Waist circumference	Yes (core measurement)	Used as an indicator of abdominal obesity (associated with the risk of CVD incidence and type 2 diabetes)	Yes (in adults only)	Yes	Yes	Yes	Yes
	Hip circumference	Yes (additional measurement)	Used in combination with waist circumference when calculating waist-to-hip ratio (WHR), useful to evaluate the abdominal body fat distribution, as compared to the gluteofemoral one (relating to the buttocks and thighs) one. Abdominal adiposity distribution is associated with an increased risk of cardiovascular disease (CVD) risk factors, events and morbidity.	Yes (in adults only)	Yes	Yes		No

A3. Functional capacity tests	Handgrip test	Yes (additional measurement)	Handgrip strength is an indicator of upper body strength. It is also used as an indicator of overall muscle strength in population studies. It correlates with overall physical fitness and is also a predictor of mortality.	No				
	Timed chair stand test	Yes (additional measurement)	Test of lower extremity and central strength, especially muscle strength, balance and coordination but other functional domains are also involved, such as endurance.	No				
	Hearing test (audiometry)				Yes		Yes	Yes
	Respiratory function test (spirometry)	No	_	Yes (pulmonary function test, in adults only)		Yes (lung function testing)		
A4. Physical function	Physical activities (accelerometer)	No	_	Yes	Yes			
	Aerobic fitness	No	_	No		Yes (physical fitness)		Yes (cardiovascular fitness)
Dental examination							Yes	Yes
Ophtamology					Yes		Yes	Yes
B. Biological measurements								

B1. Blood sample collection (whole blood, serum, plasma)	Yes (core measurement for some health indicators)	Core measurements: Serum total cholesterol, HDL-cholesterol, Plasma glucose, Whole blood HbA1c Additional measurement: Serum triglycerides, apolipoproteins A1 and B, DNA extraction from whole blood, nutritional biomarkers, environmental exposure, antibodies for infectious diseases, and others). The role of blood lipids composition is very similar with that of blood pressure (High serum total and HDL cholesterol are major risk factors of cardiovascular diseases) ; Increased glucose level or HbA1c may indicate insulin deficiency or insulin resistance which indicates risk for diabetes (glycated haemoglobin reflects the time-averaged blood glucose concentration during the previous 2-3 months, but is more expensive than fasting blood glucose measurement)	Biological specimen collection of blood (26-88 ml): Complete Blood Count (CBC) including hemoglobin, fasting glucose, serum creatinine, lipid profile (total cholesterol, HDL cholesterol, calculated LDL, fasting triglycerides), Ferritin and transferrin (women), plasma folate (childbearing women), whole blood HbA1c, environmental biomarkers prioritized; specific IgE antibodies	Yes (2 ml for children aged 3-6, 6 ml for children aged 7-14): heavy metals, Persistent organic pollutants (POPs)	Whole Blood (EDTA tube): acrylamide, metals and trace elements, methylmercury, Whole Blood (washed grey tube): volatile organic compounds (VOCs); Plasma: organochlorines, polychlorinated biphenyls (PCBs), polybrominated flame retardants (PBB & PBDEs), Perfluorinated compounds (PFCs); Serum: lipids: triglycerides & total cholesterol,	Yes: anemia, nutrition status, high-sensivity C-Reactive Protein, exposure to environmental metals and trace elements, infectious diseases tests, total cholesterol/HDL, triglycerides/ LDL, kidney and liver function, hormones, sexually transmitted diseases, glucose, fluoride	Yes: Cholesterol(total), Triglycerides, Glucose(fasting), Glycohaemoglobin, Insulin, hepatitis, metals and trace elements measurement, Anemia, kidney function, allergy

B2. Urine sample collection	Spot urine sample Overnight urine sample 24-hours urine sample	Yes (additional measurement)	Priori intended for the measurements of sodium (Na), potassium (K), creatinine, albumin and iodine (I). The intake of sodium (consumed as common salt) is associated with elevated blood pressure	Biological specimen collection of first morning urine (totality in children, 200 ml in adults):	Morning urine: heavy metals and trace elements, phthalates, Bisphenol A, Dialkyl phosphates, Pyrethroids, Chlorophenols, PAH metabolites, nicotine and cotinine, stress hormones	Spot urine sample: creatinine, fluoride, metals and trace elements, nicotine metabolite, environmental phenols, polycyclic aromatic hydrocarbon metabolites (PAHs) and benzene metabolites, specific gravity	Spot urine sample: exposure to chemicals and metals, kidney function test, sexually transmitted diseases (chlamydia, trichomonas)	Yes: protein, glucose, blood, creatinine, ketone, bilirubin, gravity, pH, microalbulmin, nitrite, cotinine, sodium, urobilinogen
B3. Scalp hair sample		No	_	Scalp Hair sample (about 50 mg or 2-3 mm thick):				
B4. Others (saliva, nail, breast milk, deciduous teeth…)							Saliva: HPV	

Appendix 2. Biological measurements and health-related effects to the chemical exposure for the 1st priority chemicals of the HBM4EU

Prioritized chemicals substances	Information about a biological matrix previously used for the measurement in the studies	Health-related effect (known or suspected) due to the exposure to the chemical substance
Phthalates and Hexamoll® DINCH	Phthalate metabolites are present in every urine sample investigated	• DEHP, DnBP, DiBP and BBzP classified are reproductive toxicants (cat 1B of CLP); • Direct additive effects of the mixtures of individual phthalates on the foetal testosterone production and the course of pregnancy
Bisphenols	BPA has been quantified in blood	• Bisphenol A (BPA) is an endocrine disruptor • Associated with increased risk for cardiovascular disease, miscarriages, decreased birth weight at term, breast and prostate cancer, reproductive and sexual dysfunctions, altered immune system activity, metabolic problems and diabetes • Associated with increased risk for cognitive and behavioural development in young children.
Per-/polyfluorinated compounds	Numerous studies have reported human exposures to PFAS from the concentrations in blood or breast milk (mostly PFOS and PFOA)	• PFOS and PFOA are classified as carcinogenic (Cat2, suspected human carcinogens), reprotoxic (Cat 1B, presumed human reproductive toxicants), Lact, and toxic to specific target organs • Potential adverse health consequences in humans at current exposure levels to some PFASs: increased risk of miscarriage, reduced fetal growth and increased weight and reduced fertility among offspring as a result of early life exposures; Postnatal exposures associated with thyroid hormone imbalances and reduced immune response to vaccination
Flame retardants	• *For pre- and postnatal exposure assessments of BrominatedFRs, breast milk, cord blood, and maternal blood plasma are typically analysed[26];*	• PBDEs and HBCDs have potential neurotoxic, endocrine, and carcinogenic effects • Evidence of Firemaster 550 as an endocrine disrupting compound and

[26] Gill U, Chu I, Ryan JJ, Feeley M. Polybrominated diphenyl ethers: human tissue levels and toxicology. Rev Environ Contam Toxicol. 2004;183:55-97

Prioritized chemicals substances	Information about a biological matrix previously used for the measurement in the studies	Health-related effect (known or suspected) due to the exposure to the chemical substance
	• *OrganophosphorusFRs and PhosphateFRs has been measured in urine samples, respectively in a Swedish and Californian population*[27],[28].	obesogen
Cadmium and chromium	• Cd is common quantified in blood and/or urine samples; levels in urine are widely accepted as a measure of the body burden and the cumulative amount in the kidneys, plasma. • In HBM studies, elevated levels in blood or urine can be indicative of Cr(VI) exposures. However, measuring chromium in RBCs, and determining the ratio with levels in plasma/serum, may be a more specific indicator for Cr(VI) exposure. To separate plasma/serum from RBCs, fresh (preserved but never frozen) blood has to be available.	• Cd is primarily nephrotoxic and carcinogenic to humans (Group1) lung, endometrium, bladder, and breast; seems to increase the risk of common cardiovascular events; causes bone demineralisation. • Cr(VI) is carcinogenic to humans (Group 1) (lung cancer, nose cancer, nasal sinus cancer); Cr(VI) compounds are mutagenic and known to cause male and female reproductive toxicity, and developmental toxicity; Cr(VI) is a respiratory toxicant and can adversely affect the hematopoietic system. It causes skin sensitization, such as in contact with contaminated leather.
PAHs	Methods already exist for the determination of some PAHs (such as BaP) in urine; further methodological developments may be necessary however	• Many PAHs are known or suspected carcinogenic and mutagenic compounds
Aniline family		• Aromatic amines may cause methemoglobinemia in humans • Aniline and many of its derivatives are known or suspected human carcinogens (e.g. bladder carcinogens 2-naphtylamine and benzidine)
Chemical mixtures	–	–
Emerging substances	• Matrices to focus are urine, blood, breast milk, cord blood • Alternative matrices (hair, nails, or meconium) may also be investigated	–

[27] Norén E, Larsson E, Littori M, Maxe M, Jönsson BA, Lindh CH. Biomonitoring of organophosphorus flame retardants in a Swedish population – Results from four investigations between years 2000-2013. http://www.imm.ki.se/Datavard/Rapporter/RapportOPFR20170411-Avtal2215-15-002.pdf

[28] Dodson RE, Van den Eede N, Covaci A, Perovich LJ, Brody JG, Rudel RA. Urinary biomonitoring of phosphate flame retardants: levels in California adults and recommendations for future studies. Environ Sci Technol. 2014;48(23):13625-33