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Report on opportunities and obstacles of combining HBM and health studies, availability of health studies with biological samples, availability of administrative registers, and guidelines for combining HBM and health studies

Deliverable Report

D 11.1

WP 11 - Linking HBM, health studies and registers

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Abbreviations

Al	Aluminium
ANSP	Agence Nationale de Sante Piblique
AT	Austria
EHES	European Health Examination Survey
BDE	Decarbomodiphenyl ether
BE	Belgium
BG	Bulgaria
BHA	Beta hydroxy acid
BPA	Bisphenol A
BRIDGE Health Project	BRidging Information and Data Generation for Evidence-based Health Policy and research
Cd	Cadmium
CH	Switzerland
Co	Carbon monoxide
COPHES	Consortium to Perform Human Biomonitoring on a European Scale
Cr	Chromium
CRP	C-reactive protein
CVD	Cardiovascular disease
CY	Cyprus
CZ	Czech Republic
DDE	Dichlorodiphenyldichloroethylene
DE	Germany
DEP	Azieda Sataria Locale Roma
DEXA	Duel-energy X-ray absoptiometry
DK	Denmark
EE	Estonia
EL	Greece
ES	Spain
ESTEBAN	Étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition
EU	European Union
FI	Finland
FIOH	Finnish Institute of Occupation Health
FMUL	Faculdade de Medicina da Universidade de Lisboa

FR	France
GerES	German Environmental Survey
GP	General practitioner
HbA_{1c}	Glycated hemoglobin
HBM4EU	Human Biomonitoring for EU
HBM	Human BioMonitoring
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
HES	Health Examination Survey
Hg	Mercury
HDL	High density lipoprotein
HHF	Hellenic Health Foundation
HR	Croatia
HU	Hungary
I	Iodine
IBMT	Fraunhofer Gesellschft zür Foerderung der Angewandten Forschunge E.B.
ICD	International Classification of Diseases
ICT	Information and communicaitons technology
IE	Ireland
IgE	Immunoglobulin E
IHIS	Ustav Zdrovotnickych Informaci a Statistiky Ceske Republiky
INSA	National Institute of Health Dr. Ricardo Jorge
IPCheM	Information Platform for Chemical Monitoring
IL	Israel
IS	Iceland
ISS	Istituto Superiore di Sanità – The Italian National Institute of Health
IT	Italy
KI	Karolinska Insitutet
LDL	Low density lipoprotein
LT	Lithuania
LU	Luxembourg
LV	Latvia
Mn	Manganese
MOH-IL	Israel Ministry of Health
MS	Member State

MT	Malta
MUW	Medizinsche Universitaet Wien
Na	Sodium
NHC	National Hub Coordinator
NHCP	National Hub Contact Point
Ni	Nickel
NIPH	Norwegian National Institute for Public Health
NL	Netherlands
NO	Norway
PAH	Polycyclic aromatic hydrocardons
Pb	Lead
PBDE	Polybrominated diphenyl ethers
PCB	Polychlorinated biphenyl
PE	Polyethylene
PFAS	Per- and Polyfluoroalkyl Substances
PI	Principle Investigator
PIC	Personal Identification Code
PL	Poland
POP	Persistent organic pollutant
PP	Polypropylene
PR	Public Relations
PSU	Primary Sampling Unit
PT	Portugal
QA	Quality Assurance
RegionH	Regionl Hovedstaden – The Capital Region of Denmark
RO	Romania
SDU	Suddansk Universitet
Se	Selenium
SE	Sweden
SES	Socioeconomic status
SI	Slovakia
SK	Slovenia
SOP	Standardized Operating Procedure
SPT	Skin prick test
SSU	Secondary Sampling Unit

Ta	Tantalum
THL	National Institute for Health and Welfare
UBA	Umweltbundesamt
UK	United Kingdom
UMU	Umeå University
WIV-ISP	Institut Scientifique de Sante Publique

Introduction

The European Human Biomonitoring Initiative (HBM4EU) is a joint effort of 28 countries (24 European Member States, three associated countries and Switzerland), the European Environment Agency and the European Commission, co-funded under Horizon 2020.

The main objective of HBM4EU is to use human biomonitoring (HBM) to assess human exposure to chemicals in Europe in order to better understand the associated health impacts and to improve chemical risk assessment. HBM4EU will generate knowledge on chemical exposure levels in the population and their health effects.

In parallel to HBM studies, health examination surveys (HES) are conducted in many European countries. HES are surveys where information collected by questionnaire(s) is complemented with information obtained by physical measurements such as blood pressure and anthropometric measurements, and by analysis of biomarkers from biological samples. The European Health Examination Survey (EHES)[1] was established in 2010 to coordinate the development of national HESs in Europe. Between 2000 and 2017, 15 European countries[2] have conducted a national HES and in many countries smaller, regional or disease specific surveys have been carried out.

Since for both HBM studies and HESs, data is collected through fieldwork which is one of the largest expenses for such studies and needed infrastructures are very similar, the potential to combine these two types of studies has been considered. This could result in more cost-effective ways to conduct health and environmental monitoring. In some countries, such as Germany, Israel and France, this combination has already been done at national or regional level.

Human biomonitoring and health studies have a lot of similarities in terms of the infrastructure and procedures required for their implementation. However, in practice, the opportunity for adding a HBM module to an ongoing/planned health study (and vice versa) is rarely used. Reasons for this may be multifarious and may differ from country to country, and between different study settings.

This report will look at different aspects related to combining HBM and health studies, together with possibilities for mortality and morbidity follow-up through linkage to administrative registers. Also possibilities to use biological samples collected in previous health studies and stored for future use in biobanks for analysis of HBM biomarkers will be reviewed. Therefore, this report has four main parts:

- Part A. Opportunities and obstacles of combining HBM and health studies
- Part B. Availability of administrative registers and possibilities for their use in HBM studies
- Part C. Guidelines for linking HBM and health studies
- Part D. Criteria for the use of existing biological samples from health studies for HBM analysis

Feasibility studies will be conducted on the integration of HBM and health studies, in order to identify further both synergies and obstacles that can emerge during the preparation and implementation of fieldwork studies in different settings and across different national infrastructures. A workshop to explore the synergies and obstacles related to the combination of HBM and health studies will be organized in June 2018. In coming years, this report will be updated based on knowledge gained from feasibility studies.

[1] http://www.ehes.info
[2] http://www.ehes.info/national/national_hes_status.htm

Part A - Opportunities and obstacles of combining HBM and health studies

1 Authors and Acknowledgements

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

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2 Background

Task 11.1 aims to evaluate the opportunities and obstacles of combining ongoing and/or planned health studies (health examination surveys (HES), cohort studies, dietary surveys, occupational studies, etc.) and HBM. An inventory of the recently conducted, ongoing and planned health studies, which could be linked to an HBM study, was performed and will be updated in coming years in collaboration with the National Hubs. For this, 2 to 5 studies per participating country were identified by the National Hub Contact Points (NHCPs), coordinated by the National Hub Coordinator (NHC). The inventory also includes information about existing biological samples collected in these studies and stored in biobanks for future use (in collaboration with WP7, Task 7.1 which will conduct an inventory on HBM studies). This inventory will be updated annually.

On the other hand, there are countries that have already conducted studies combining HBM and HES. Experiences from these studies (Germany, France and Israel) will be analysed, and obstacles and outcomes will be summarised in the report.

The settings for conducting HES and/or HBM differ from country to country and the experience from countries where a combination of HBM and HES has already been conducted successfully may therefore not be directly transferable to other countries. It is therefore important to include also studies from countries where HBM and/or health studies are generally conducted in different settings (e.g. national funded studies vs. research driven studies funded by grants). This work will build also on the work of the BRIDGE Health project[3] which has been looking for potential synergies between HBM and health surveys.

[3] http://www.bridge-health.eu/

3 Objective

The aim of this evaluation was to identify opportunities and obstacles related to linking HBM, health surveys and administrative data sources, and to create an inventory of the health studies among the 28 countries involved in HBM4EU available which could include an HBM component.

Specific objectives are:

a) To create an inventory of the recently completed, ongoing and planned health studies (some of which could include also dietary surveys) which could be linked to HBM studies;
b) To gather information about existing biological samples collected in the health studies and stored in biobanks for future use;
c) To collect information about whether the ethical approvals for the studies covers the use of the available biological samples for HBM;
d) To assess possible opportunities and obstacles related to combining HBM and health studies.

4 Methods

An electronic online questionnaire for gathering data on recently conducted, ongoing and planned health studies which could be linked to HBM studies was developed by RegionH in collaboration with THL, FIOH, INSA, UBA, ANSP, MOH-L, ISS and HHF. In this questionnaire, information on the obstacles of linking HBM to HES was also collected.

4.1 Identification of ongoing or planned health and cohort studies

Contacts of the principal investigators (PI) of HES or HBM studies were obtained through the National Hub Coordinator (NHC), who has asked the National Hub Contact Points (NHCPs) to identify the studies of interest in the respective countries. Within each participating country ongoing or planned health and cohort studies which could be interested in adding an HBM component were identified (including dietary surveys and occupational studies). Out of the 28 national hubs, information on PIs was obtained from 16 countries with more than one identified PI from several of the included countries.

4.2 Development and distribution of the questionnaire

The content of the questionnaire was developed with stepwise inputs from all involved partners. In light of the questionnaire from WP7, Task 7.1, it was the intention for the questionnaire from WP11, Task 11.1 to keep it simple and clear, and with a minimum overlap with the Task 7.1 questionnaire. A number of initial versions of the questionnaire were drafted and discussed with all involved partners. Secondly, an electronic version was developed in SurveyXact by Rambøll. The electronic version was validated and edited regarding content and design of the questionnaire. Finally, a pilot test was performed and any final changes were incorporated. The final version of the questionnaire can be found in Appendices 1-3. The questionnaire was distributed to the above identified PIs from each of the countries paralleled by a notifying email to all NHCPs (please see Appendices 4 and 5 for email invitations). The PIs of the studies identified were invited to answer the online questionnaire in July 2017. A single reminder mail was sent out two weeks later after which the survey was closed and prepared for data analyses.

To obtain more detailed information from three countries (Germany, France and Israel) that had identified programmes or surveys that specifically have succeeded in combining HBM and HES, a more detailed and targeted questionnaire was developed. The structure of the questionnaire was similar to the electronic questionnaire but the format differed and allowed for more qualitative answers. Like for the electronic questionnaire, the new detailed questionnaire was validated and pilot tested before distribution. PIs from three different health programmes received the detailed questionnaire (Appendix 3) and all three responded.

Results gathered by the online questionnaire as well as the detailed description from Germany, France and Israel are described in the following section.

5 Results

5.1 Analysis of data from the WP11, Task 11.1 questionnaire

5.1.1 Studies reported

Notably, out of 28 EU or EU affiliated countries 30 researchers from 16 countries answered the questionnaire. This means that the results from the questionnaire probably cannot be seen as representative of all 28 countries which is important to have in mind when interpreting the results. In total, 52 different studies were reported as being conducted or planned to be initiated. Initially, the researchers were asked which type of study for which data were reported. All researchers were asked to give a detailed description of the study characteristics in each of the studies but depending on which type of study that was reported a number of targeted questions were also given. Researchers working with HES either targeted or not, occupational surveys, dietary surveys or other types of surveys received the questionnaire in Appendix 1 primarily with focus on the possibility of collecting biological samples, a characterization of biological samples and the possibility to measure chemicals in the samples. Researchers working with HBM surveys received the questionnaire in Appendix 2 and were also asked to give a characterization of biological samples and general study characteristics. Finally, researchers working with combined HES and HBM received the questionnaire in Appendix 3 primarily focusing on possibilities and obstacles combining HES and HBM survey.

5.1.2 Collection of biological samples

One of the specific objectives of Task 11.1 is to evaluate the existing biological samples collected in health studies and stored in biobanks for future use and to make an inventory of this information. Out of the 52 reported studies, 19 studies (37%) had an HBM component (5 HBM surveys and 14 combined HES and HBM surveys), meaning that biological samples were collected and analysed in these studies. From the 33 studies that did not have a HBM component, biological samples were collected in the majority (82%) of these studies. In the 6 studies that did not already collect biological samples, biological samples could be collected in 2 of the studies, but in the other 4 studies collecting biological samples were stated as not a possibility or it was unknown if collecting biological samples were a possibility. The main reason for not collecting biological samples pointed out by researchers from 2 of the studies was lack of funding. Since the aim of this work is to explore obstacles and opportunities for linking HBM and HES, and HBM requires access to biological samples, further data was not collected from the 4 studies. These studies were dietary surveys/HISs and other type of surveys.

In Table 1 is an overview of the studies from which biological samples are or could be collected excluding the 4 studies that did not have this possibility. As seen from table 1 the most frequent type of studies for which data was reported and biological samples available were targeted health studies (31%), Health Examination Surveys (HES) (21%) or combined HBM and HES studies (29%).

Table 1: Type of studies where biological samples are or could be collected

Type of study	Frequency	Percent
A health examination survey (HES)	10	21
A targeted health study (e.g. focusing on specific diseases, age-groups or other population subgroups)	15	31
An occupational health survey	3	6
A dietary survey/health interview survey (HIS)	0	0
A human biomonitoring survey (HBM)	5	10
A combined HES and HBM survey	14*	29
Other	1	2
Total	**48**	**100**

*one study with limited data available.

The obstacles of combining HBM and HES were evaluated for the 14 combined HES and HBM studies reported (Section 5.1.12).

5.1.3 Characterization of the studies with possibility of sampling

The countries of the studies for which data was reported are listed in Table and their geographic distribution across Europe is visualized in Figure 1. The names or short descriptions, acronyms, websites and organizing institutions of the studies for which data was reported are listed in Appendix 7.

Table 2. Countries of the studies for which data was reported

Country	Number of studies	Percent
Cyprus	2	4.2
Czech Republic	4	8.3
Denmark	11	22.9
Finland	1	2.1
France	1	2.1
Greece	3	6.3
Israel	1	2.1
Latvia	3	6.3
Lithuania	1	2.1
Netherlands	1	2.1
Portugal	1	2.1
Slovenia	3	6.3
Slovakia	2	4.2

Country	Number of studies	Percent
Spain	8	16.7
Sweden	5	10.4
Switzerland	1	2.1
Total: 16 countries	**48**	**100.0**

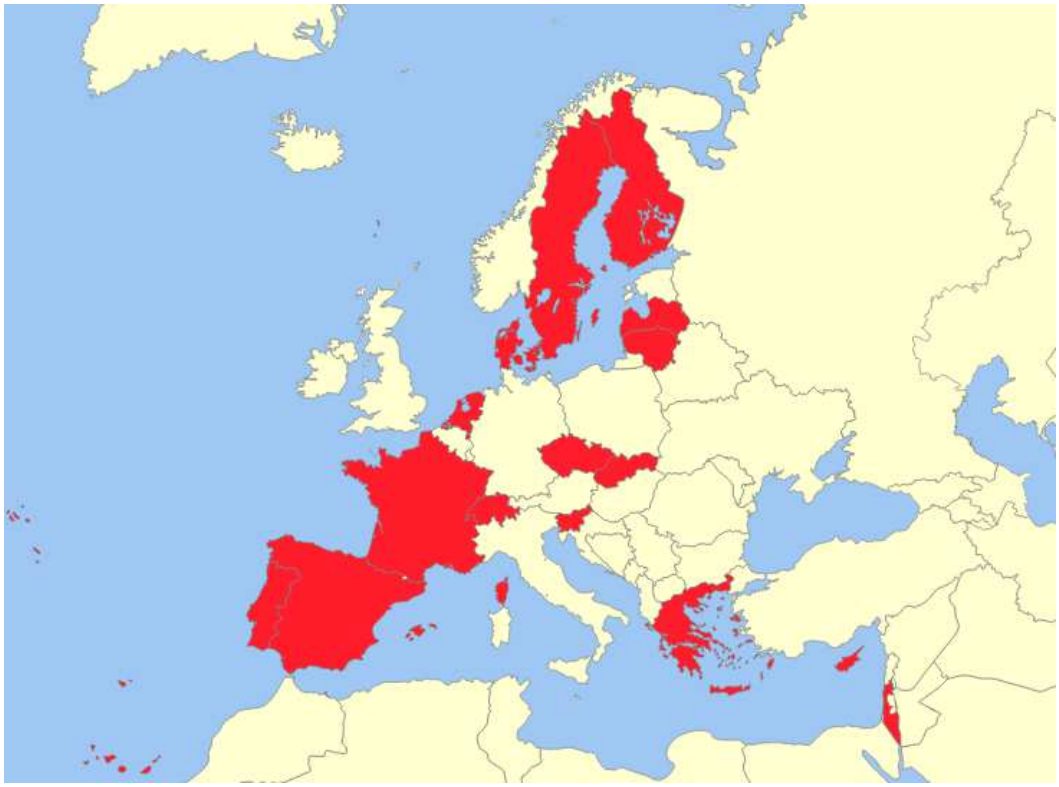
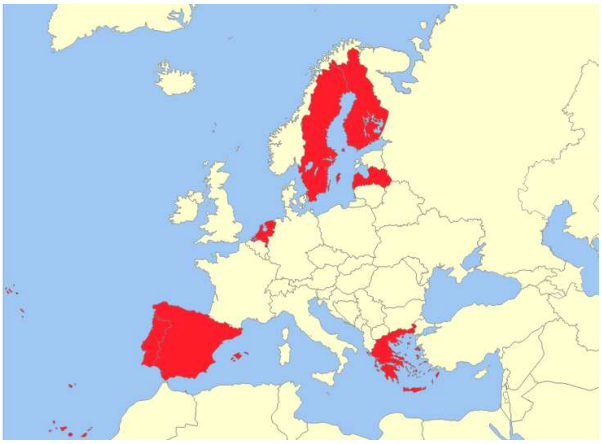
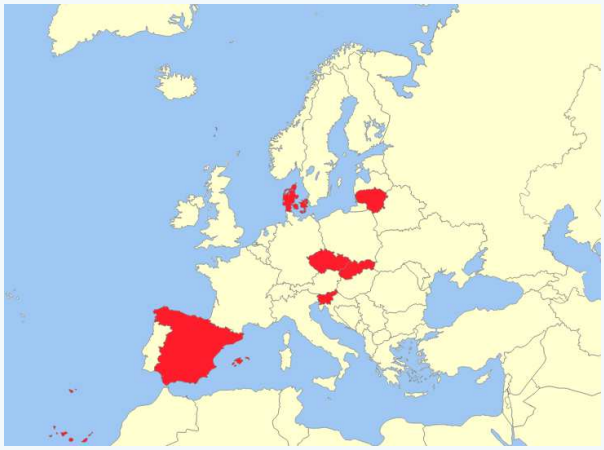
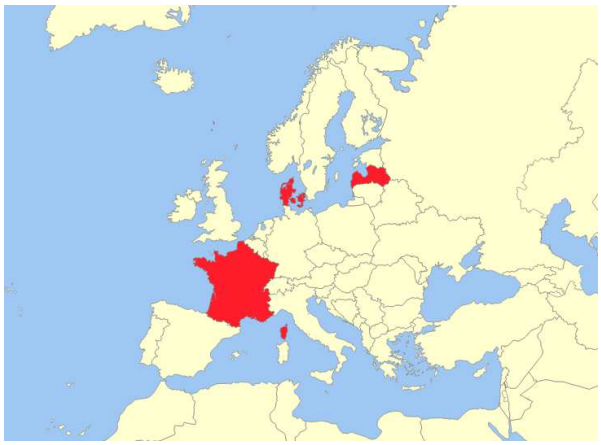
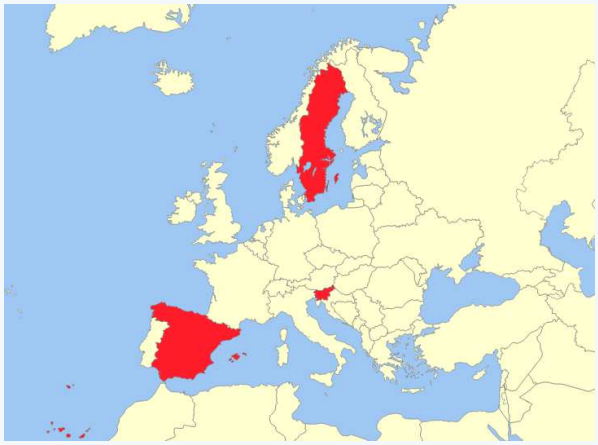
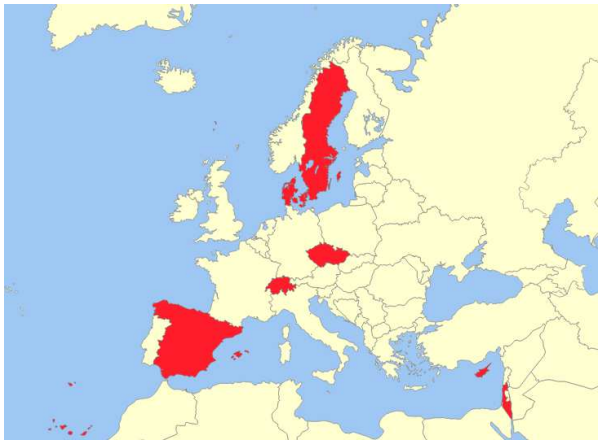


Figure 1. Distribution of the countries of the studies for which data was reported (in red)

In Table 3 is an overview of the 16 countries that responded to the questionnaire stratified according to study type. In general, the different study types were not clustered in certain European regions but were widely distributed between countries. Because only 16 countries out of 28 EU or EU affiliated countries were included it is however, important to have in mind that the 'true' picture most likely will differ from the observed.

Table 3. Type of studies for which data was reported where biological samples are or could be collected by country

Type of study	Countries	Number of studies	Percent
A health examination survey (HES)	Finland	1	10.0
	Greece	3	30.0
	Latvia	2	20.0
	Netherlands	1	10.0
	Portugal	1	10.0
	Spain	1	10.0
	Sweden	1	10.0
Total		**10**	**100.0**
A targeted health study (eg. focusing on specific diseases, age-groups or other population subgroups)	Czech Republic	3	20.0
	Denmark	4	26.7
	Lithuania	1	6.7
	Slovenia	2	13.3
	Slovakia	2	13.3
	Spain	3	20.0
Total		**15**	**100.0**
An occupational health survey	Denmark	1	33.3
	France	1	33.3
	Latvia	1	33.3
Total		**3**	**100.0**

Type of study	Countries	Number of studies	Percent
A human biomonitoring survey (HBM)	Slovenia	1	20.0
	Spain	3	60.0
	Sweden	1	20.0
Total		**5**	**100.0**
A combined HES and HBM survey	Cyprus	2	14.3
	Czech Republic	1	7.1
	Denmark	6	42.9
	Israel	1	7.1
	Spain	1	7.1
	Sweden	2	14.3
	Switzerland	1	7.1
Total		**14**	**100.0**
Other	Sweden	1	100.0
Total		**1**	**100.0**

In total, 12 studies (25%) out of 48 studies were part of multinational collaborations and in most cases with several countries.

Overall, the included studies were initiated or planned to be initiated between 1985 and 2018 with the vast majority being initiated from 2012 (Table 5) and the time span when the studies were planned to be completed ranged from 1999 and 2100 (Table 6). The median length of the studies were planned to be 3 years (min-max: 0-94 years).

Table 4: Year when the study was initiated or planned to be initiated

Year	Number of studies	Cumulative percent
1985	1	2
1987	2	6
1991	2	11
1992	1	13
1994	1	15
1996	2	19
1997	1	21
2006	1	23
2007	2	28
2008	2	32
2009	1	34
2010	2	38
2012	3	45
2013	4	53
2014	1	55
2015	4	64
2016	4	72
2017	8	89
2018	5	100
Total	**47***	**100**

*one study with missing values

Table 5: Year when the study was completed or planned to be completed

Year	Number of studies	Cumulative percent
1999	1	2
2012	1	4
2013	1	6
2014	2	11
2015	2	15
2016	3	21
2017	8	38
2018	4	47
2019	7	62
2020	8	79
2021	1	81
2022	1	83
2028	1	85
2030	2	89
2040	1	92
2100	1	94
Invalid answer	3	100
Total	**47**	**100**

For the studies combining HBM and HES further information was collected only about the obstacles and difficulties of linking HBM and HES.

5.1.4 Storage of biological samples

The vast majority of the studies (excluding combined HES and HBM surveys) (91%) have reported that biological samples were collected and stored for future use. This storage of biological samples poses the possibility to perform chemical analysis on the studies and therefore, to introduce an HBM component. As seen from table 7, the most commonly stored biological samples were blood (as in whole blood) (68%), plasma (65%), DNA (65%), serum (58%), random spot urine (48%) and first morning urine (32%), respectively.

Table 6. Storage of biological samples from the study for future use (total of 31 studies)

Biological sample	Number of studies	Percent
Blood	21	68
Blood erythrocytes	4	13
Plasma	20	65
Serum	18	58
Saliva	5	16
Buccal cells	2	7
Nails	1	3
DNA	20	65
Cell lines	1	3
Urine (24h)	1	3
Urine (spot sample – random)	15	48
Urine (spot sample – first morning)	10	32
Human milk	3	10
Hair (complete locks)	7	23
Semen	1	3
Placenta	1	3
Umbilical cord blood	6	19
Other*	6	19

*Amniotic fluid, Buffy coat (white blood cells), Faeces, Buccal cells were collected and stored. All the other matrices will be collected in the follow-up study starting in January 2018, Specimens of brain tumours.

Although blood samples were stored in the majority of the surveys (68%, see Table 7), only approximately half of the HES surveys (56%) had stored blood samples (Table 8) whereas plasma and serum samples were more frequent (100%, 89% respectively). Also in targeted health studies and HBM studies storage of blood samples was frequent and especially the storage of whole blood samples (73% and 80% respectively).

Table 7: Storage of blood samples (whole blood, plasma and serum) by type of study

Type of study	Blood (whole blood)	Plasma	Serum	Total
	Frequency (%)	Frequency (%)	Frequency (%)	
A health examination survey (HES)	5 (56)	9 (100)	8 (89)	9
A targeted health study (e.g. focusing on specific diseases, age-groups or other population subgroups)	11 (73)	7 (47)	7 (47)	15
An occupational health survey	0 (0)	1 (100)	0 (0)	1
A human biomonitoring survey (HBM)	4 (80)	2 (40)	2 (40)	5
Other	1 (100)	1 (100)	1 (100)	1
Total	**21 (68)**	**20 (65)**	**18 (58)**	**31**

As seen from Table 8, DNA was stored in all HES surveys and by the majority of the targeted health surveys (67%) but this was less frequent in HBM surveys (20%). Both in HBM studies, HES and targeted health studies storage of urine samples were performed in approximately half of the studies and random spot urine samples were most frequent compared to first morning urine samples.

Table 8: Storage of DNA, random and first morning spot urine by type of study

Type of study	DNA	Random spot urine	First morning urine	Total
	Frequency (%)	Frequency (%)	Frequency (%)	
A health examination survey (HES)	9 (100)	3 (33)	1 (11)	9
A targeted health study (e.g. focusing on specific diseases, age-groups or other population subgroups)	10 (67)	8 (53)	7 (47)	15
An occupational health survey	0 (0)	0 (0)	0 (0)	1
A human biomonitoring survey (HBM)	1 (20)	3 (60)	2 (40)	5
Other	0 (0)	1 (100)	0 (0)	1
Total	**20 (65)**	**15 (48)**	**10 (32)**	**21**

5.1.5 Chemicals measured

Out of the 34 studies (excluding combined HES and HBM studies) the majority of the studies (71%) have reported measurement of chemicals. The most frequent chemicals measured were phthalates (63%), cadmium (58%) and bisphenols (54%). In addition, in the majority of the studies (75%), a variety of other chemicals were measured (see footnote in Table 9).

Table 9. Chemicals/chemical groups measured or planned to be measured (total of 24 studies)

Chemicals/chemical groups	Frequency	Percent
Phthalates/DINCH	15	63
Bisphenols	13	54
Per-/polyfluorinated compounds	8	33
Flame retardants	7	29
Cadmium	14	58
Polycyclic aromatic hydrocarbons	6	25
Aniline family: Anilines, MOCA	3	13
Other chemicals*	18	75

BHA, triclosan, difenylfosfat, pesticides, 1-hydroxypyren (PAH). Heavy metals: Cd, Pb, Hg, Cr, Ni, Mn, Co, Al, Se, inorganic As. PCBs, PBDE (BDE-47), DDE, HCB, HCHs, chlordane, PFAS (standard and new substances), Ferritin, Folate, Vitamin D, Mycotoxins, I, Na, organochlorines, Ta, Se, Multi-elemental determinations, POPs, Phenols including benzophenones, other metals including arsenic speciation, other trace elements

Only 5 studies did not include any chemical analysis of collected samples. The main reasons for this was funding in relation to taking additional samples and laboratory analyses of chemicals. Other reasons also pointed out were the lack of relevance for the study, logistical problems, lack of storage space, lack of knowledge on adequate collection and handling methods, and lack of laboratorial capacity.

5.1.6 Description of the studies

In the 34 studies (excluding combined HES and HBM studies), the most frequent sources of funding were public sources (Table 10) either by the government (44%), public grants (44%) and/or EU grants or other international research programmes (41%). Only a small portion of the studies were funded by private grants (18%). Half of the studies had only a single funding source while the other half had several, with the majority of these (41%) having two different funding sources and only a minor portion having three or four different funding sources (6% and 3%, respectively).

Table 10. Funding sources

	Frequency	Percent
Funded by government (e.g. part of a national health programme)	15	44
Funded by public grants (e.g. independent research grants)	15	44
Funded by private grants (e.g. from private foundations)	6	18
Funded by EU grants or other international research programmes	14	41
Other	5	15

*Center on Endocrine Disrupters project, Multiple sources, including Stockholm County Council, National funds, University research funding.

Concerning the frequency of the study, around half of the studies (47%) were conducted only once and the other half (53%) were repeated one or several times. As for study size, in general the studies had a high number of study participants; the majority of the studies had more than 1.000 participants whereas the rest had lower participant numbers but only a minority had below 100 participants (Table 11).

Table 11: Study size

	Frequency	Percent
< 100 participants	2	6
100 - 249 participants	8	24
250 – 999 participants	5	15
1000 or more participants	19	56
Total	**34**	**100**

Concerning the study design around half of the studies were cross-sectional (47%) and the other half longitudinal (44%) (Table 12) and only a small proportion of the studies also reported being case-control studies (12%). Furthermore, 5 studies reported to be a combination of one or more study designs.

Table 12: Study design

	Frequency	Percent
Cross-sectional study	16	47
Longitudinal study (repeated measurements on the same participants)	15	44
Case-control study	4	12
Other*	4	12

**Cross-over study, Different types of recruitment schemes, Prospective cohort, Prospective follow up with adjudicated events from review of health records.*

Among the 16 cross-sectional studies, 6 studies (38%) were reported to be repeated one or more times whereas among the 15 longitudinal studies, 12 (80%) of the studies were repeated and the frequency of the repeated studies varied considerable. For the cross-sectional studies the frequency varied from annually and up to 5 years interval. Also for the longitudinal studies there was a huge variation in frequency ranging from 2 to 10 years interval. Furthermore, 4 out of 12 longitudinal studies were characterized by including a birth cohort either by recruiting pregnant women or infant children whereas the children were followed through childhood and puberty with varying follow-up length.

Furthermore, the researchers were asked to characterize the target group of their study population either as a representative sample of the general population or as a targeted sample (e.g. patient group, occupational setting etc.). As for the target group, 35% of the studies had a representative sample of the general population (Table 13). Furthermore, 44% of the studies had populations classified as targeted populations and a minor proportion reported the studies as other type of target group. However, based on the description of the study groups reported as 'other' (footnote in Table 13) we re-categorized 3 of them as being representative samples and 3 of them as being targeted samples. Thus, approximately half of the studies could be seen as samples from the general population and the other half as different types of targeted samples according to the revised frequency (Table 13).

Table 13: Study group

	Frequency (%)	Frequency revised (%)
Representative sample of the general population	12 (35)	15 (44)
A targeted sample (patients, occupational setting, pregnant women, students, etc.)	15 (44)	18 (53%)
Other*	7 (21)	1 (3%)
Total	**34**	**34**

**Population-based birth cohort study, Representative sample of the Spanish workforce, Representative samples of agricultural workers and self-employed people, several recruitment schemes, Volunteers from all the geographic regions of Greece, approximately representative, Workers, Representative sample of the general children population aged from 3.*

The vast majority of the studies included participants of both sexes (30 studies), although 3 studies included only women and a single study only included men.

Overall, the studies were characterized by participants in a wide age span (Table 14). In total, 6 studies included participants as newborns and in 3 of these cases the maximum age was more than 60 years of age. Half of all studies (n=18) included participants in the age range from 18 to 25 years as minimum and in 13 out of 18 cases the maximum age was more than 60 years. Five studies did not have an upper age limit (data not shown).

Table 14. Minimum age in relation to maximum age of study participants

	Maximum age						
Minimum age	Up to 1 yr	14-17 yrs	19-26 yrs	44-49 yrs	50-59 yrs	>60 yrs	Total (%)
0-3 months	2	0	1	0	0	3	6 (18)
6-10 years	-	1	1	1	1	0	4 (12)
14-17 years	-	1	0	0	0	2	3 (9)
18-25 years	-	-	2	2	1	13	18 (53)
40 years	-	-	-	1	0	1	2 (6)
50-59 years	-	-	-	-	0	1	1 (3)
Total (%)	**2 (6)**	**2 (6)**	**4 (12)**	**4 (12)**	**2 (6)**	**20 (59)**	**34 (100)**

5.1.7 Health and lifestyle parameters

5.1.1.1 Clinical examinations

In the 34 studies (excluding combined HES and HBM studies), the majority of the studies (79%) included clinical examinations. The majority included anthropometric measures and blood pressure measurements but also a number of other clinical examinations were reported characterized by being very diverse and performed infrequently Table 15).

Table 15. Clinical examinations included (total number of studies: 34)

Clinical examinations	Frequency	Percent
Anthropometric measures (e.g. height, weight, waist circumference)	26	77
Blood pressure	19	56
Functional tests (e.g. physical strength, flexibility and reaching, etc.)	11	32
Neurological tests	9	27
Others*	13	38

* Andrologic examination (Ultrasound of testis, sperm parameters), Apgar score, Blood biochemistry, Clinical biochemistry, Cognitive function data and functional testing data, DEXA, food intake, lung function test, allergy testing, sleep quality, Molecular biomarkers, Psychology tests, psycho-motoric tests, physiological parameters.

5.1.1.2 Clinical biomarkers

Out of the 34 studies with biological samples stored, or planned to be stored, clinical biomarkers were analysed in the majority of these (77%). The most frequently analysed clinical biomarkers were metabolic markers and kidney function markers but a variety of other markers were also measured in the different studies (Table 16).

Table 16: Clinical biomarkers included (total of 34 studies)

Clinical biomarkers	Frequency	Percent
Metabolic markers (e.g. lipids, fasting glucose, etc.)	16	47
Reproductive markers	6	18
Liver function markers	8	24
Kidney function markers	12	35
Thyroid function markers	7	21
Others*	10	29

* Bone markers, Cotinine, and many others, CRP and nutrition status (ferritin, folate, Vitamin D), IgE, Insulin-like growth factors I and binding protein 3, Lead metabolism markers, Oxidative stress, metabolomics, epigenetics, genetics, Related to health conditions, Vitamin D on subpopulation, The measured biomarkers depend on recruitment scheme.

5.1.1.3 Questionnaire data

Only a single study (3%) out of 34 studies with biological samples stored, or planned to be stored, did not include collection of questionnaire data.

In general, a number of different types of questionnaire data were included in the studies and almost all the studies collected information about lifestyle, socio-economic characteristics and dietary habits (Table 17).

Table 17: Questionnaire data included (total of 33 studies)

	Frequency	Percent
Medical history	24	73
Self-reported current health	27	82
Lifestyle (e.g. smoking habits, physical activity level, sleep patterns etc.)	32	97
Detailed information on dietary habits (e.g. food frequency questionnaires)	29	88
Occupational information	21	64
Socio-economic information	30	91

5.1.8 Registers

Register data were retrieved for 15 of the 34 studies with biological samples stored, or planned to be stored. The distribution of type of registries is listed in Table 18.

Table 18: Type of registries (total of 15 studies)

Type of registries	Frequency	Percent
Mortality register	9	60
Cancer-specific register	6	40
Register on hospital admissions	9	60
Diabetes register	5	33
Occupational register	5	33
Other*	10	67

*Additional could be available but application is needed, CVDs and fractures register, Electronic Health Recording system, Health care consumption (GP visit, drugs purchase), Pharmacy records, Primary care records, Birth register

Of the 19 studies for which register data were not retrieved , 9 studies (47%) reported that it would be possible to retrieve register data for study participants on an individual level and 10 studies (53 %) denied this possibility.

Of the studies reporting the possibility to retrieve register data for study participants on an individual level, all reported that it would be possible to retrieve data on hospital admissions, and the majority reported that it would be possible to retrieve data on mortality, cancer-specific diagnosis and diabetes (67%, 67% and 56%, respectively).

5.1.9 Health outcomes

Out of the 34 studies with biological samples stored, or planned to be stored, 16 of the studies (47%) reported that they have collected information on health outcomes or health information known or suspected to be associated with exposure to specific chemicals. The recording of the information on the health outcomes, or on health information known or suspected to be associated with exposure to specific chemicals was very diverse in the studies and is presented below:

Overview of specific health outcomes or health information known or suspected to be associated with exposure to specific chemicals
- Birth parameters (ano-genital-distance, birth weight, gestational age)
- Anthropometric parameters
- Obesity markers (incl. diabetes, CVD, oxidative stress)
- Spirometric parameters
- Asthma and allergy
- Medical history and mortality
- Neurodevelopment
- Epigenetics
- Reproductive function and hormone levels
- Fractures and bone density
- Markers of lead poisoning

5.1.10 Ethical approval

Ethical approval covering the measurement of chemicals in collected samples was available in 21 out of the 34 studies with biological samples stored, or planned to be stored. One third of the studies did already have an ethical approval covering the measurements of all chemicals of interest. Specific chemicals that already were covered by ethical approval were metals, especially heavy metals, phthalates and bisphenol A. The matrices that can be used for chemical measurements according to the ethical approval are shown in Table 19.

Table 19. Matrices that can be used for chemical measurements according to the ethical approval

Matrices	Frequency	Percent
Blood	10	56
Blood erythrocytes	1	6
Plasma	10	56
Serum	7	39
Saliva	1	6
Nails	1	6
DNA	3	17
Urine (24h)	2	11
Urine (spot sample – random)	10	56
Urine (spot sample – first morning)	7	39
Human milk	4	22
Hair (chopped/lyophilised sample or complete locks)	4	22
Semen	1	6
Placenta	2	11
Umbilical cord blood	3	17
Other*	4	22

* Amniotic fluid, fetal serum, Brain tumours, Faeces, An individual ethical approval is received for each study, which determines what chemicals and in which matrix we can measure

From the studies which reported that their ethical approval does not cover the measurement of chemicals in the collected samples, the majority (82%) reported that it would be possible to obtain new/extended ethical approval to perform these analyses.

5.1.11 IPChem – the Information Platform for Chemical monitoring

Of the 34 studies with biological samples stored, or planned to be stored, only few studies (9%) reported to be legally allowed to upload chemical data from the study to IPChem (according to ethical and personal data protection directives/regulations) on an individual level and in 68% of the studies it was either unknown or currently not a possibility (Table 20).

Table 20: Legally allowed to upload chemical data from the study to IPChem (according to ethical and personal data protection directives/regulations)

	Number of studies	Percent
Yes, as data on an individual level	3	9
Yes, but only as aggregate data (e.g. distributions, means, etc.)	8	24
Unknown	17	50
Currently no, but it might be possible if specific regulation is taken in future	6	18
Total	**34**	**100**

5.1.12 Obstacles in linking HBM and HES

From the 14 combined HES and HBM surveys, only 3 studies have reported to have experienced any obstacles, shortcomings or difficulties while linking HBM and HES (9 studies reported that they did not experience any obstacles, and 2 studies did not answer this question).

All 3 studies reported obstacles related to legislation issues including issues related to data protection laws. 2 studies experienced logistic issues related to handling of biological samples and related to difficulties in adequately managing samples and data from a large number of studies and individuals with several visits. Other difficulties experienced were financial issues, difficulties in recruitment of participants and lack of flexibility between HES and HBM part.

Finally, 2 studies reported their experiences on how they have overcome the obstacles related to linking HBM and HES and the most relevant point being the importance of an adequate planning that includes both components, HBM and HES, from the beginning. A detailed description of potential obstacles linking HBM and HEs from PIs in Germany, Israel and France is given in Section 5.3.

5.2 Analysis of data from WP7, Task 7.1 questionnaire

From the comprehensive questionnaire developed under WP7, Task 7.1 aimed to identify HBM studies conducted in EU Member States. Among these studies, those which had already included both HBM and health components were selected. Since questionnaires used by WP7 and WP11 had very different aim, it was not possible to combine them at this point for the further analysis but studies identified from WP7 questionnaire could be used in future work of WP11 after additional contacts to them.

The initial WP7 database had in total 124 studies. The following selection criteria were applied:

- At least some biological samples were collected for HBM measurements (question C7 ≠ none) AND some other biomarkers / physiological indicators (question C55 = yes) were collected.

The application of the above mentioned selection criteria resulted in the selection of 57 studies, which are listed in Appendix 8.

It was then decided to further limit the studies to those where at least anthropometric measurements and blood pressure were included. This resulted in the selection of 21 studies (21).

Table 21. Studies selected from the Task 7.1 questionnaire having at least anthropometric measurements and blood pressure included

	Country	Name of the study	Acronym
1	Iceland	The Icelandic Heart Association Reykjavik Longitudinal Study	
2	Israel	Amirim Study on Exposure of Vegetarians to Endocrine Disrupting Chemicals	
3	Switzerland	Swiss Cohort on Air Pollution and Lung And Heart Disease in Adults	SAPALDIA
4	Belgium	ENVIRonmental influence ON AGEing in early life	ENVIROANGE
5	Belgium	STP 2 Hotspot Genk-Zuid	FLEHS II HOTSPOT_GENK
6	Belgium	STP 2 Hotspot Menen	FLEHS II HOTSPOT_MENEN
7	Belgium	STP 3 Reference Adolescents	FLEHS III Ref Ado
8	Belgium	STP 3 Reference Adults	FLEHS III Ref Adult
9	Belgium	STP 2 Reference Adolescents	FLEHS II Ref Ado
10	Belgium	STP 3 Hotspot Gentse Kanaalzone	FLEHS III HOTSPOT_GKZ
11	Belgium	STP 4 Reference Adolescents	FLEHS IV Ref Ado
12	Czech Republic	Health, Alcohol and Psychosocial factors in Eastern Europe	HAPIEE
13	Czech Republic Slovakia, Data form Czech Republic and Slovakia are available through CELSPAC but ELSPAC was/is implemented also in UK (ALSPAC] and other countries.)	(Central) European Longitudinal Study on Parents and Children	(C)ELSPAC
14	Denmark	Odense Child Cohort	OCC
15	Denmark	COPENHAGEN Puberty Study	CPHPUB
16	Denmark	Male Reproductive Health Study	
17	Italy	Ambiente e Biomonitoraggio nell'area di Civitavecchia	ABC
18	Spain	Biomonitoring Study of Environmental Contaminants	BIOAMBIENT.ES
19	Sweden	The Cohort of 60 years old Men and Women	60yo

	Country	Name of the study	Acronym
20	Sweden	Central Sweden Cohort & Biobank	CSC&B, (or SMC and COSM)
21	Sweden	Stockholm Children Allergy and Environmental Prospective Birth Cohort Study	BAMSE

Of the 21 studies selected, three (Israel, (C)ELSPAC in Czech Republic and CPHPUB in Denmark) did not include lipids which are also part of the EHES core measurements, resulting in 18 studies with HBM measures and all the EHES core measurements. All these 18 studies were conducted in the general population and all except Male Reproductive Health Study from Denmark had both men and women. Age range varied considerably between the studies:

- without age limit (Iceland);
- different age groups of children (STP 2 Hotspot Genk-Zuid; STP 2 Hotspot Menen; STP 3 Reference Adolescents; STP 2 Reference Adolescents; STP 3 Hotspot Gentse Kanaalzone; STP 4 Reference Adolescents);
- different age groups of adults (Swiss Cohort on Air Pollution and Lung And Heart Disease in Adults; STP 3 Reference Adults; Health, Alcohol and Psychosocial factors in Eastern Europe; Male Reproductive Health Study; Ambiente e Biomonitoraggio nell'area di Civitavecchia; Central Sweden Cohort & Biobank);
- children and adults (ENVIRonmental influence ON AGEing in early life; Odense Child Cohort);
- no age group provided (Biomonitoring Study of Environmental Contaminants; Stockholm Children Allergy and Environmental Prospective Birth Cohort Study).

These studies also include health related physical measurements and lab analysis (for details about the final selection of studies from WP7, Task 7.1, please see Appendix 9).

5.3 Experiences from Germany, France and Israel

As mentioned in the introduction, there are EU or EU associated countries with health programmes that have succeeded in combining a HBM module with HES, namely Germany, France and Israel. To gather experiences from these countries a detailed questionnaire (Appendix 6) was sent to the PIs of the HBM module from the three countries.

In two of the countries, namely in France and Israel, combined HBM and HES programmes are a rather new phenomena: in France the Esteban Survey ran from 2014 to 2016 and in Israel two combined surveys have been running in 2011 and in 2015 to 2016, respectively. In contrast, Germany has a long tradition for conducting combined HBM and HES: since 1985 five GerES (HBM and ambient monitoring) combined with respective HES-surveys have been conducted with the last one ending in 2017[4,5].

In the following subsections, similarities and differences between the three countries will be highlighted and discussed based on the responses from the three PIs working on the combined programmes.

[4] Schulz, C., Kolossa-Gehring, M., Gies, A., 2017. German Environmental Survey for Children and Adolescents 2014-2017 (GerES V) - the environmental module of Wave 2 of the KiGGS study. Journal of Health Monitoring 2, 45-51.

[5] Schulz, C., Conrad, A., Becker, K., Kolossa-Gehring, M., Seiwert, M., Seifert, B., 2007. Twenty years of the German Environmental Survey (GerES): human biomonitoring--temporal and spatial (West Germany/East Germany) differences in population exposure. Int J Hyg Environ Health 210, 271-297.

5.3.1 Study characteristics

In Israel, a HBM module was added to already ongoing HES. In Germany, the HBM module GerES was developed together with the development of a population-representative HES. In both cases subjects participating in the HBM survey were extracted as a subpopulation from the original HES sample and to a large degree the HES logistical framework was utilized. In contrast, the Esteban Survey in France was initiated as a combined HBM and HES programme from the beginning.

Both similarities and differences exist between the three country-specific programmes. The study populations from the three countries were all random samples from the background population: in France the subjects were recruited to participate in the HBM and HES programme simultaneously, whereas in Israel and Germany subjects for the HBM module were recruited as a subsample from the ongoing HES. Only in Germany incentives were used to recruit subjects to participate.

Notable for all programmes was that the collection of data related to HES and HBM takes place at separate visits. All subjects went through a detailed HES module on the first visit (in France the HES data collection was performed during two visits) and on the second visit – or third in the case of France – the subjects went through the HBM part. The number of questions in each programme varies considerably ranging from 70 questions in one country to more than 600 questions in another. In all cases biological samples were transferred to centralized national biobanks.

5.3.2 Initiation of the combined HES and HBM survey

Common for the three countries was that the combined programmes were initiated and implemented at the governmental level. Thus, the driving forces behind the programmes were primarily under health ministerial direction. Both in Israel and France the programmes were exclusively a programme under the Ministry of Health whereas in Germany, the main drivers are the Federal Ministry of Health for the HES part in combination with the Robert Koch-Instiute, the main public health institute in Germany, and the Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety in collaboration with the German Environment Agency (UBA) for the HBM part. Funding of the programmes were in all three countries secured through ministerial funding primarily from the health and environmental ministries but in the case of Germany individual scientific issues were additionally funded by the Ministry for Education and Research. The fact that these programmes were all initiated and funded at the ministerial level underpins the importance of combined programmes as a national prioritization.

5.3.3 Potential advantages and opportunities

There are several advantages and future opportunities in combining HES and HBM programmes, with the main topics listed below:

Overview of potential opportunities and advantages
- Utilization of existing logistical infrastructure from HES - Reduced cost of the surveys - Sampling size increased - Access to a wide range of detailed nutrition and health-related data - Possibility to investigate links between exposures and health related outcomes - The public awareness and interest in HES issues has a positive influence on the perception of HBM

In Germany and Israel, where the HBM module is conducted as an add-on to the ongoing HES, it is highlighted as an advantage that the initiation of a HBM module is less complicated because of the utilization of the already existing logistical infrastructure from the HES. Furthermore, recruitment of subjects is often time consuming and expensive especially in the case of randomized samples. Thus, another advantage of combined programmes is the reduced costs related to the two surveys and the possibility of increasing the sample size because of a joint effort in the recruitment process. Another stated advantage is the possibility to get access to detailed nutrition and health-related data from the HES part. This leaves the possibility to investigate sources of exposures from e.g. dietary questionnaire data, data on work-related behaviour, lifestyle, etc. In line with this, in contrast to HBM surveys isolated, the combined programme makes it possible to investigate the association between exposures and different health-related outcomes, which is likely to strengthen the research interest in the area. Finally, it is stated that the public awareness and interest in HES issues has a positive influence on the perception of findings from HBM, which could have subsequent positive influence on participation rates and the possibility of receiving more funding.

5.3.4 Potential obstacles

Overview of potential obstacles
- Limitations in the size of questionnaire and other health parameters - Lack of flexibility in data access between databases - Lack of communication between the HES and HBM modules

Because of the combined programme several interests have to be met when constructing the questionnaire. This can lead to a limited number of questions from each partner involved in the study programme which leads to a strict prioritization of questions in the final questionnaire. At the end, if the questions are simplified or too few, the goals for HBM and/or HES each may be difficult to reach.

Especially in countries where the HBM modules are an add-on to an existing HES it can be speculated whether there is limited flexibility in the creation of a HBM study protocol and especially in the construction of the questionnaire because of the different interests in the HES and HBM parts. Thus, it is likely that the study protocol for the add-on part will be created and incorporated in a way where the underlying agenda will be to interfer the least with the already existing programme. Presumably, the overall study protocol for a combined protocol will be a balance between the wish to include as many data as possible but at the same time not straining study participants unnecessarily and jeopardizing the participation rate. Depending on how the data are stored, and if ethical approval is obtained for the combined project or not, lack of flexibility in data access can be a potential logistical issue in comprehensive surveys like combined programmes. Combined ethical approvals were used in France and Israel and primarily also in the German surveys, which probably will ease the transparency and access to data.

Finally, one potential challenge can be the requirements of intense communication between the HES and HBM modules both in the planning of the survey but also during recruitment of participants, data collection and when evaluating the data at the end. It is furthermore stressed that a mutual understanding of the HES part when working with HBM and vice versa is crucial, which is underpinned by one researcher that states that for the sustainability of a combined programme "*a constant and confidential cooperation is inevitable"*.

5.4 Learning from the results of BRIDGE Health

The "BRidging Information and Data Generation for Evidence based Health policy and research" (BRIDGE Health) project is a DG Santé funded research project that was completed in October 2017. The aim of BRIDGE Health was to prepare the transition towards a sustainable and integrated European health information system for both public health and research purposes and one of the means of achieving this was by developing common methods for standardizing the collection of health information. In this Bridge Health deliberately also did preparatory work for HBM4EU in terms of problem identification, gap analysis and the development of blueprint for use of HBM in the field of health information and public health policies. Part of Task 11.1 has been to evaluate how results of the BRIDGE Health project could be integrated in the HBM4EU project. This has been done in the separate deliverable report AD11.1: How can the results from BRIDGE Health be incorporated to the work of HBM4EU?" and we refer to this document for the full evaluation. Here we will only mention the main conclusions related to the HBM4EU WP11, however, the full AD11.1 report includes also information relevant for the other work packages in HBM4EU.

Briefly the main conclusions of BRIDGE Health related to HBM4EU WP11 are:

The value of HES data for research has increased substantially by the possibility to link HES data with administrative registers in many countries and the possibility to link HES data and biobanks with administrative registers has made HES data a part of the Big Data. Experience on the possibilities and obstacles of using registries, based on the lessons learnt in chronic disease registries, is provided.

There are organizational synergies between HBM and HES surveys. The BRIDGE Health results present necessary steps and the potential challenges in combining the two surveillance systems.

Not all of the BRIDGE Health reports were available at the time of preparation of the AD11.1 report and especially the testing of a new data collection protocol to simplify data transmission and improve the quality of its indicators, which was part of BRIDGE Health WP11, needs to be revisited when the report is available.

6 Conclusions

The present work has allowed the gathering of data on health surveys where an HBM component might be added in a cost-effective manner. An inventory with these studies was produced and will be updated in the next years.

The vast majority of the studies for which data were collected include the collection of biological samples and the storage of these samples for future use, posing the opportunity to use them for the analyses of chemicals of interest. The most frequently stored biological samples are blood, plasma, serum and DNA. A little over half of the studies have already reported that the measurement of chemicals was performed or is planned to be performed in the future.

Most of the studies for which data was reported had public funding, either from the government or from public grants (national or European). Half of the studies were longitudinal and present the possibility of introducing a HBM component in the future. The majority of the studies included clinical examinations (79%), clinical biomarkers (77%) and questionnaire data (97%). However, register data were only retrieved for less than half (44%) of the studies. More than half of the studies had ethical approval which allowed measurement of chemicals in the collected samples and the majority of the ones that didn't have ethical approval consider that this approval would be possible to obtain. The vast majority of studies combining HBM and HES did not report any obstacles, shortcomings or difficulties linking HBM and HES. Only a quarter of the studies reported financial, logistic and legislation issues. Experience in overcoming obstacles related to linking HBM and HES points to the importance of an adequate planning that includes both components from the beginning.

In countries with years of experience regarding combined HES and HBM programmes, there are clear benefits in combining the two study designs, however some obstacles can also be identified. It is worth noticing that all country-specific programmes were funded and implemented as national programmes under ministerial direction indicating the importance of combined programmes as a national governmental prioritization. The combined programmes where the HBM part is an add-on to an ongoing HES part have clear benefits in terms of logistical utilization but potential obstacles in terms of prioritization of questions and in general the magnitude of the study protocol for each part of the survey may be compromised due to different interests between HES and HBM.

7 Appendices

7.1 Appendix 1: Questionnaire for researchers working with health examination surveys, occupational surveys and other health interview surveys

health examination surveys,
occupational surveys and
other health interview surveys

General information
The aim of this questionnaire is to evaluate opportunities and obstacles when linking human biomonitoring (HBM) data with health examination surveys (HES) and administrative data sources such as national registers. Furthermore, it is the intention to identify HES which already include or plan to include biological samples which could be used to analyse HBM biomarkers.

If you are responsible for more than one study, please provide information for one study at a time (with a maximum of three studies).

Please note that the questionnaire allows you to save the partially completed form and resume at a later point by using the same link.

Are you currently conducting or planning to initiate one of the following type of studies within the next year?

(please note that if you are conducting/planning to conduct more than one survey you need to fill out the questionnaire for each of the surveys separately)

(1) ❑ A health examination survey (HES)
(2) ❑ A targeted health study (eg. focusing on specific diseases, age-groups or other population subgroups)
(3) ❑ An occupational health survey
(4) ❑ A dietary survey/health interview survey (HIS)
(5) ❑ Other

1.0 Are biological samples collected in the study?

(1) ❑ Yes
(2) ❑ No

If no in 1.0:

1.1 Could biological samples be collected?

(1) ❑ Yes
(2) ❑ No
(3) ❑ Unknown

If yes in 1.1:

1.2 What has been the main reason for not collecting biological samples?

_____

_____

_____

_____

_____

If yes in 1.0 or 1.1:

2.0 Name or short description of the study

_____

_____

2.1 Study acronym

_____

2.2 Website of the study

_____

2.3 Name of the organizing institution

_____

_____

2.4 Country

(1) ❑ Austria
(2) ❑ Belgium
(3) ❑ Croatia
(4) ❑ Cyprus
(5) ❑ Czech Republic
(6) ❑ Denmark
(7) ❑ Finland
(8) ❑ France
(9) ❑ Germany
(10) ❑ Greece
(11) ❑ Iceland
(12) ❑ Ireland
(13) ❑ Israel
(14) ❑ Italy
(15) ❑ Latvia
(16) ❑ Lithuania
(17) ❑ The Netherlands
(18) ❑ Norway
(19) ❑ Poland
(20) ❑ Portugal
(21) ❑ Slovakia
(22) ❑ Slovenia
(23) ❑ Spain
(24) ❑ Sweden
(25) ❑ Switzerland
(26) ❑ United Kingdom

2.4 If the study is part of a multinational collaboration, please state the collaborating countries

_____

2.5 Name and email of contact person(s)

	Name	Email
1:	_____	_____
2:	_____	_____
3:	_____	_____

2.6 Year when the study was initiated or planned to be initiated

_____

2.7 Year when the study was completed or planned to be completed

_____

2.8 Reference to basic report/scientific publications about the study design

_____

_____

_____

_____

_____

3.0 Are biological samples from the study stored or planned to be stored for future use?

(1) ❑ Yes
(2) ❑ No
(3) ❑ Unknown

If yes in 3.0:

3.1 The following biological samples are collected:

(1) ❑ Blood
(2) ❑ Blood erythrocytes
(3) ❑ Plasma
(4) ❑ Serum
(5) ❑ Saliva
(6) ❑ Buccal cells
(7) ❑ Nails
(8) ❑ DNA
(9) ❑ Cell lines

(10) ❑ 12-hours overnight urine
(11) ❑ Urine (24h)
(12) ❑ Urine (spot sample - random)
(13) ❑ Urine (spot sample - first morning)
(14) ❑ Human milk
(15) ❑ Hair (chopped/lyophilised sample)
(16) ❑ Hair (complete locks)
(17) ❑ Fat (adipose tissue)
(19) ❑ Semen
(18) ❑ Placenta
(20) ❑ Umbilical cord blood
(21) ❑ Other, please specify _____

4.0 Are chemicals measured or planned to be measured in collected samples?

(1) ❑ Yes
(2) ❑ No
(3) ❑ Unknown

If yes in 4.0:

4.1 Were any of the following chemicals/chemical groups measured, or planned to be?

(1) ❑ Phthalates/DINCH
(2) ❑ Bisphenols
(3) ❑ Per-/polyfluorinated compounds
(4) ❑ Flame retardants
(5) ❑ Cadmium
(6) ❑ Chromium VI
(7) ❑ Polycyclic aromatic hydrocarbons
(8) ❑ Anilin family: Anilines, MOCA
(9) ❑ Other chemicals, please specify _____

If no in 4.0:

4.2 What are the main reasons for not including measurements of chemicals in collected samples?

(1) ❑ Not considered relevant for the aim of the study
(2) ❑ Lack of knowledge of relevance of measuring chemicals in relation to the aim of the study
(3) ❑ Fear that it would affect recruitment/participation rate
(4) ❑ Lack of funding for additional sample collection for measurement of chemicals
(5) ❑ Lack of funding for laboratory analysis of chemicals
(6) ❑ Collection of additional samples for chemical measurements logistcially not practical
(7) ❑ Lack of storage space of additional samples for chemical measurements

(8) ❑ Lack of knowledge regarding collection and handling of samples for measurement of chemicals

(9) ❑ Lack of capacity available for measurement of chemicals (laboratories, methods etc.)

(10) ❑ Lack of funding for measurement of chemicals

(11) ❑ Other reasons, please state _____

Study 1 - description of the study

The following questions are related to the type of study

5.0 How is the study funded?

(1) ❑ Funded by government (eg. part of a national health programme)

(2) ❑ Funded by public grants (eg. independent research grants)

(3) ❑ Funded by private grants (eg. from private foundations)

(4) ❑ Funded by EU grants or other international research programmes

(5) ❑ Other, please specify _____

5.1 If you chose more than one option above, please specify the main type of funding

_____

5.2 What type of study design characterises the study?

(1) ❑ Cross-sectional study

(2) ❑ Longitudinal study (repeated measurements on the same participants)

(3) ❑ Case-control study

(4) ❑ Other, please specify _____

5.3 Study size

(1) ❑ <100 participants

(2) ❑ 100 - 249 participants

(3) ❑ 250 - 999 participants

(4) ❑ 1000 or more participants

5.4 Frequency of the study

(1) ❑ Repeated (study repeated eg. annually or every 5 year), please specify frequency _____

(2) ❑ Conducted only once

5.5 Which of the following options best describes the study group?

(1) ❑ Representative sample of the general population

(2) ❑ A targeted sample (patients, occupational setting, pregnant women, students etc.)

(3) ❑ Other, please specify _____

5.6 Sex of study participants

(1) ❑ Men

(2) ❑ Women

(3) ❑ Both sexes included

5.7 Age-distribution of study participants

(in case of no lower and/or upper age limit, please state this)

Min age _____

Max age _____

Other details related to age, please specify _____

Study 1 - Health and lifestyle parameters

The following questions are related to what sources of health information and lifestyle are recorded in the study

6.0 Does the study include clinical examinations?

(1) ❑ Yes

(2) ❑ No

If yes in 6.0:

6.1 Which clinical measurements are included?

(1) ❑ Anthropometric measures (eg. height, weight, waist circumference etc)

(2) ❑ Blood pressure

(3) ❑ Functional tests (eg. physical strength, flexibility and reaching etc)

(4) ❑ Neurological tests

(5) ❑ Others, please specify _____

7.0 Does the study include measurement of clinical biomarkers?

(1) ❑ Yes

(2) ❑ No

If yes in 7.0:

7.1 Which clinical biomarkers are included?

(1) ❑ Metabolic markers (eg. lipids, fasting glucose etc)

(2) ❑ Reproductive markers

(3) ❑ Liver function markers

(4) ❑ Kidney function markers

(5) ❑ Thyroid function markers

(5) ❑ Others, please specify _____

8.0 Does the study include questionnaire data?

(1) ❑ Yes

(2) ❑ No

If yes in 8.0:

8.1 Which type of data is included from questionnaires?

(1) ❑ Medical history
(2) ❑ Self-reported current health
(3) ❑ Lifestyle (eg. smoking habits, physical activity level, sleep patterns etc.)
(4) ❑ Detailed information on dietary habits (eg. food frequency questionnaires)
(5) ❑ Occupational information
(6) ❑ Socio-economic information

9.0 Are register data retrieved for the study?

(1) ❑ Yes
(2) ❑ No

If no in 9.0:

9.1 Would it be possible to retrieve register data for study participants on an individual level?

(1) ❑ Yes
(2) ❑ No

If yes in 9.0 or 9.1:

9.2 What kind of registers?

(1) ❑ Mortality register
(2) ❑ Cancer-specific register
(3) ❑ Register on hospital admissions
(4) ❑ Diabetes register
(5) ❑ Occupational register
(6) ❑ Other, please specify _____

10.0 Are health outcomes or health information that are known or suspected to be associated with exposure to specific chemicals recorded in the study?

(1) ❑ Yes, please specify _____
(2) ❑ No
(3) ❑ Unknown

Study 1 - Ethical issues

11.0 Do you have ethical approval for measuring chemicals in collected samples?

(1) ❑ Yes
(2) ❑ No

If no in 11.0:

11.1 Could ethical approval for measuring chemicals in collected samples be obtained?

(1) ❑ Yes
(2) ❑ No
(3) ❑ Unknown

If yes in 11.0:

11.2 Which chemicals/chemical groups are covered by your ethical approval?

_____

_____

_____

_____

_____

_____

If yes in 11.0:

11.3 Which matrices can be used for chemical measurements according to the ethical approval of the study?

(1) ❑ Blood
(2) ❑ Blood erythrocytes
(3) ❑ Plasma
(4) ❑ Serum
(5) ❑ Saliva
(6) ❑ Buccal cells
(7) ❑ Nails
(8) ❑ DNA
(9) ❑ Cell lines
(10) ❑ 12-hours overnight urine
(11) ❑ Urine (24h)
(12) ❑ Urine (spot sample - random)
(13) ❑ Urine (spot sample - first morning)
(14) ❑ Human milk
(15) ❑ Hair (chopped/lyophilised sample)
(16) ❑ Hair (complete locks)
(17) ❑ Fat (adipose tissue)
(19) ❑ Semen
(18) ❑ Placenta
(20) ❑ Umbilical cord blood
(21) ❑ Other, please specify _____

Study 1 - Information platform for data sharing

The EU commission strongly encourage that data on chemical measurements funded through HMB4EU is made available through its Information Platform for Chemical Monitoring - IPChem.

12. Is it legally allowed to upload chemical data from the study to IPChem

(according to ethical and personal data protection directives/regulations)

(1) ❑ Yes, as data on an individual level

(2) ❑ Yes, but only as aggregate data (eg. distributions, means etc.)

(3) ❑ Currently no, but it might be possible if specific regulation is taken in future

(4) ❑ No

(5) ❑ Unknown

Thank you for taking the time to fill out the questionnaire!

7.2 Appendix 2: WP 11.1 Questionnaire for researchers working with human biomonitoring surveys

human biomonitoring surveys

General information
The aim of this questionnaire is to evaluate opportunities and obstacles when linking human biomonitoring (HBM) data with health examination surveys (HES) and administrative data sources such as national registers. Furthermore, it is the intention to identify HES which already include or plan to include biological samples which could be used to analyse HBM biomarkers.

If you are responsible for more than one study, please provide information for one study at a time (with a maximum of three studies).

Please note that the questionnaire allows you to save the partially completed form and resume at a later point by using the same link.

1.0 Name or short description of the study

_____

_____

1.1 Study acronym

_____

1.2 Website of the study

_____

1.3 Name of the organizing institution

_____

1.4 Country

(1) ❑ Austria
(2) ❑ Belgium
(3) ❑ Croatia
(4) ❑ Cyprus
(5) ❑ Czech Republic
(6) ❑ Denmark
(7) ❑ Finland
(8) ❑ France
(9) ❑ Germany
(10) ❑ Greece
(11) ❑ Iceland
(12) ❑ Ireland
(13) ❑ Israel
(14) ❑ Italy
(15) ❑ Latvia
(16) ❑ Lithuania
(17) ❑ The Netherlands
(18) ❑ Norway
(19) ❑ Poland
(20) ❑ Portugal
(21) ❑ Slovakia
(22) ❑ Slovenia
(23) ❑ Spain
(24) ❑ Sweden
(25) ❑ Switzerland
(26) ❑ United Kingdom

1.4 If the study is part of a multinational collaboration, please state the collaborating countries

_____

1.5 Name and email of contact person(s)

	Name	Email
1:	_____	_____
2:	_____	_____
3:	_____	_____

1.6 Year when the study was initiated or planned to be initiated

_____

1.7 Year when the study was completed or planned to be completed

_____

1.8 Reference to basic report/scientific publications about the study design

_____

_____

_____

_____

_____

2.0 Are biological samples from the study stored or planned to be stored for future use?

(1) ❑ Yes
(2) ❑ No
(3) ❑ Unknown

If yes in 2.0:

2.1 The following biological samples are collected:

(1) ❑ Blood
(2) ❑ Blood erythrocytes
(3) ❑ Plasma
(4) ❑ Serum
(5) ❑ Saliva
(6) ❑ Buccal cells
(7) ❑ Nails
(8) ❑ DNA
(9) ❑ Cell lines
(10) ❑ 12-hours overnight urine
(11) ❑ Urine (24h)

(12) ❑ Urine (spot sample - random)
(13) ❑ Urine (spot sample - first morning)
(14) ❑ Human milk
(15) ❑ Hair (chopped/lyophilised sample)
(16) ❑ Hair (complete locks)
(17) ❑ Fat (adipose tissue)
(19) ❑ Semen
(18) ❑ Placenta
(20) ❑ Umbilical cord blood
(21) ❑ Other, please specify _____

3.0 Are chemicals measured or planned to be measured in collected samples?

(1) ❑ Yes
(2) ❑ No
(3) ❑ Unknown

If yes in 3.0:

3.1 Were any of the following chemicals/chemical groups measured, or planned to be?

(1) ❑ Phthalates/DINCH
(2) ❑ Bisphenols
(3) ❑ Per-/polyfluorinated compounds
(4) ❑ Flame retardants
(5) ❑ Cadmium
(6) ❑ Chromium VI
(7) ❑ Polycyclic aromatic hydrocarbons
(8) ❑ Anilin family: Anilines, MOCA
(9) ❑ Other chemicals, please specify _____

If no in 3.0:

3.2 What are the main reasons for not including measurements of chemicals in collected samples?

(1) ❑ Not considered relevant for the aim of the study
(2) ❑ Lack of knowledge of relevance of measuring chemicals in relation to the aim of the study
(3) ❑ Fear that it would affect recruitment/participation rate
(4) ❑ Lack of funding for additional sample collection for measurement of chemicals
(11) ❑ Lack of funding for laboratory analysis of chemicals
(5) ❑ Collection of additional samples for chemical measurements logistcially not practical
(6) ❑ Lack of storage space of additional samples for chemical measurements
(7) ❑ Lack of knowledge regarding collection and handling of samples for measurement of chemicals
(8) ❑ Lack of capacity available for measurement of chemicals (laboratories, methods etc.)
(9) ❑ Lack of funding for measurement of chemicals
(10) ❑ Other reasons, please state _____

Study 1 - description of the study

The following questions are related to the type of study.

4.0 How is the study funded?

(1) ❑ Funded by government (eg. part of a national health programme)

(2) ❑ Funded by public grants (eg. independent research grants)

(3) ❑ Funded by private grants (eg. from private foundations)

(4) ❑ Funded by EU grants or other international research programmes

(5) ❑ Other, please specify _____

4.1 If you chose more than one option above, please specify the main type of funding

_____

4.2 What type of study design characterises the study?

(1) ❑ Cross-sectional study

(2) ❑ Longitudinal study (repeated measurements on the same participants)

(3) ❑ Case-control study

(4) ❑ Other, please specify _____

4.3 Study size

(1) ❑ <100 participants

(2) ❑ 100 - 249 participants

(3) ❑ 250 - 999 participants

(4) ❑ 1000 or more participants

4.4 Frequency of the study

(1) ❑ Repeated (study repeated eg. annually or every 5 year), please specify frequency _____

(2) ❑ Conducted only once

4.5 Which of the following options best describes the study group?

(1) ❑ Representative sample of the general population

(2) ❑ A targeted sample (patients, occupational setting, pregnant women, students etc.)

(3) ❑ Other, please specify _____

4.6 Sex of study participants

(1) ❑ Men

(2) ❑ Women

(3) ❑ Both sexes included

4.7 Age-distribution of study participants

(in case of no lower and/or upper age limit, please state this)

Min age _____

Max age _____

Other details related to age, please specify _____

Study 1 - Health and lifestyle parameters

The following questions are related to what sources of health information and lifestyle are recorded in the study

5.0 Does the study include clinical examinations?

(1) ❑ Yes

(2) ❑ No

If yes in 5.0:

5.1 Which clinical measurements are included?

(1) ❑ Anthropometric measures (eg. height, weight, waist circumference etc)

(2) ❑ Blood pressure

(3) ❑ Functional tests (eg. physical strength, flexibility and reaching etc)

(4) ❑ Neurological tests

(5) ❑ Others, please specify _____

6.0 Does the study include measurement of clinical biomarkers?

(1) ❑ Yes

(2) ❑ No

If yes in 6.0:

6.1 Which clinical biomarkers are included?

(1) ❑ Metabolic markers (eg. lipids, fasting glucose etc)

(2) ❑ Reproductive markers

(3) ❑ Liver function markers

(4) ❑ Kidney function markers

(5) ❑ Thyroid function markers

(6) ❑ Others, please specify _____

7.0 Does the study include questionnaire data?

(1) ❑ Yes

(2) ❑ No

If yes in 7.0:

7.1 Which type of data is included from questionnaires?

(1) ❑ Medical history
(2) ❑ Self-reported current health
(3) ❑ Lifestyle (eg. smoking habits, physical activity level, sleep patterns etc.)
(4) ❑ Detailed information on dietary habits (eg. food frequency questionnaires)
(5) ❑ Occupational information
(6) ❑ Socio-economic information

8.0 Are register data retrieved for the study?

(1) ❑ Yes
(2) ❑ No

If no in 8.0:

8.1 Would it be possible to retrieve register data for study participants on an individual level?

(1) ❑ Yes
(2) ❑ No

If yes in 8.0 or 8.1:

8.2 What kind of registers?

(1) ❑ Mortality register
(2) ❑ Cancer-specific register
(3) ❑ Register on hospital admissions
(4) ❑ Diabetes register
(5) ❑ Occupational register
(6) ❑ Other, please specify _____

10.0 Are health outcomes or health information that are known or suspected to be associated with exposure to specific chemicals recorded in the study?

(1) ❑ Yes, please specify _____
(2) ❑ No
(3) ❑ Unknown

Study 1 - Ethical issues

11.0 Do you have ethical approval for measuring chemicals in collected samples?

(1) ❑ Yes
(2) ❑ No

If no in 11.0:

11.1 Could ethical approval for measuring chemicals in collected samples be obtained?

(1) ❑ Yes
(2) ❑ No
(3) ❑ Unknown

If yes in 11.0:

11.2 Which chemicals/chemical groups are covered by your ethical approval?

_____

_____

_____

_____

_____

_____

If yes in 11.0:

11.3 Which matrices can be used for chemical measurements according to the ethical approval of the study?

(1) ❑ Blood
(2) ❑ Blood erythrocytes
(3) ❑ Plasma
(4) ❑ Serum
(5) ❑ Saliva
(6) ❑ Buccal cells
(7) ❑ Nails
(8) ❑ DNA
(9) ❑ Cell lines
(10) ❑ 12-hours overnight urine
(11) ❑ Urine (24h)
(12) ❑ Urine (spot sample - random)
(13) ❑ Urine (spot sample - first morning)
(14) ❑ Human milk
(15) ❑ Hair (chopped/lyophilised sample)
(16) ❑ Hair (complete locks)
(17) ❑ Fat (adipose tissue)
(19) ❑ Semen
(18) ❑ Placenta
(20) ❑ Umbilical cord blood
(21) ❑ Other, please specify _____

Study 1 - Information platform for data sharing

The EU commission strongly encourage that data on chemical measurements funded through HMB4EU is made available through its Information Platform for Chemical Monitoring - IPChem.

12. Is it legally allowed to upload chemical data from the study to IPChem

(according to ethical and personal data protection directives/regulations)

(1) ❑ Yes, as data on an individual level

(2) ❑ Yes, but only as aggregate data (eg. distributions, means etc.)

(3) ❑ Currently no, but it might be possible if specific regulation is taken in future

(4) ❑ No

(5) ❑ Unknown

Thank you for taking the time to fill out the questionnaire!

7.3 Appendix 3: WP 11.1 Questionnaire for researchers working with combined health examination surveys and human biomonitoring surveys

science and policy
for a healthy future

combined health examination survey
and human biomonitoring survey

General information

The aim of this questionnaire is to evaluate opportunities and obstacles when linking human biomonitoring (HBM) data with health examination surveys (HES) and administrative data sources such as national registers. Furthermore, it is the intention to identify HES which already include or plan to include biological samples which could be used to analyse HBM biomarkers.

If you are responsible for more than one study, please provide information for one study at a time (with a maximum of three studies).

Please note that the questionnaire allows you to save the partially completed form and resume at a later point by using the same link.

1.0 Name or short description of the study

_____

_____

1.1 Study acronym

_____

1.2 Website of the study

_____

1.3 Name of the organizing institution

_____

1.4 Country

(1) ❑ Austria
(2) ❑ Belgium
(3) ❑ Croatia
(4) ❑ Cyprus
(5) ❑ Czech Republic
(6) ❑ Denmark
(7) ❑ Finland
(8) ❑ France
(9) ❑ Germany
(10) ❑ Greece
(11) ❑ Iceland
(12) ❑ Ireland
(13) ❑ Israel
(14) ❑ Italy
(15) ❑ Latvia
(16) ❑ Lithuania
(17) ❑ The Netherlands
(18) ❑ Norway
(19) ❑ Poland
(20) ❑ Portugal
(21) ❑ Slovakia
(22) ❑ Slovenia
(23) ❑ Spain
(24) ❑ Sweden
(25) ❑ Switzerland
(26) ❑ United Kingdom

1.4 If the study is part of a multinational collaboration, please state the collaborating countries

_____

1.5 Name and email of contact person(s)

	Name	Email
1:	_____	_____
2:	_____	_____
3:	_____	_____

1.6 Year when the study was initiated or planned to be initiated

_____

1.7 Year when the study was completed or planned to be completed

_____

1.8 Reference to basic report/scientific publications about the study design

_____

_____

_____

_____

_____

2.0 Did you experience any obstacles, shortcomings or difficulties linking HBM and HES?

(1) ❑ Yes

(2) ❑ No

If yes in 2.0:

2.1 What kind of obstacles did you experience?

(2) ❑ Financial issues, please specify _____

(3) ❑ Logistic issues (eg. laboratory, human resources), please specify _____

(4) ❑ Legislation issues, please specify _____

(5) ❑ Difficulties in recruitment of participants, please specify _____

(6) ❑ Lack of knowledge on HBM or HES issues, please specify _____

(7) ❑ Problems with ethical approval, please specify _____

(8) ❑ Not seen important by policy makers/stakeholders, please specify _____

(9) ❑ Other reasons, please specify _____

If yes in 2.0:

How did you overcome obstacles related to linking HBM and HES?

_____

_____

_____

_____

Thank you for taking the time to fill out the questionnaire!

7.4 Appendix 4: Email invitation - Notifying email to participants

An invitation to respond to the HBM4EU questionnaire: "Opportunities and obstacles in linking human biomonitoring and health studies" has been sent to you in a separate email from SurveyXact with a personal link to the electronic questionnaire. If you have not received that email please let us know by responding to this mail (also maybe check if it got caught in your spam filter). The invitation was sent to you because you have been identified by the HBM4EU national hub contact person in your country as the principal investigator (PI) of an ongoing or planned health study or human biomonitoring (HBM) study – or a combination of both.

There are clear benefits from linking HBM to ongoing or planned health examination surveys (HES) or other health studies; both in terms of sharing the cost and infrastructure for collection and storage of biomaterial (eg. blood or urine) and for the possibility to investigate exposure-health outcome relationships. However, in praxis the opportunities for adding a HBM module to an ongoing/planned health study (and vice versa) is often not exploited. The reasons for this might be multifaceted and may differ from country to country and in different settings.

In the European Joint Project HBM4EU the aim of task 11.1 is to explore obstacles and opportunities for linking HBM with HES/health studies and to learn from the experience of countries/settings where combining both has succeeded. It is for this aim that we invite principal investigators of HES/health studies as well as principal investigators of HBM studies to respond to the 11.1 questionnaire on this topic.

For your information we have also attached here pdf files of the questions so you can see them before entering the electronic questionnaire via the link in the SurveyXact mail. Please note that the electronic questionnaire is built so that it jumps and skips some questions depending on the answers. Furthermore, if you are the PI of a health study you will only be answering questions found in the file HES study if you are the PI of a human biomonitoring study you will be answering the questions found in file HBM study; and finally if you are the PI of a combined human biomonitoring study and health study you will be answering the questions found in file combined HES and HBM study.

Please note that the questionnaire allows you to save the partially completed form and resume at a later time point by using the same link.

If you think that you received the invitation to respond to the questionnaire by mistake please let us know by responding to this mail.

7.5 Appendix 5: Email invitation - Notifying email to NHCP

Today the invitation to respond to the HBM4EU 11.1 questionnaire: **“Opportunities and obstacles in linking human biomonitoring and health studies”** has been emailed to the following Principal investigators in your country :

[Name] [email]

[Name] [email]

7.6 Appendix 6: Questionnaire: Evaluating opportunities and obstacles of combining HBM and health studies: lessons from countries that have ongoing combined programmes

Short description of the national/regional combined health examination survey (HES) and human biomonitoring (HBM) programme/series of surveys

For how long has the programme been running?

Coverage and setting of the programme (geographically, study group), e.g. link to website)

Sampling

What sampling frame was used? If your sample was multistage sample, please list sampling frames used in different stages.

What was the sampling size?

Use of stratification (was HBM possible for the whole sample or only on a subsample?)?

Some specific questions about survey organization

Type of samples/information:

Were all measurements/questionnaires/interviews conducted during one visit?

What was the duration of visit?

Were there specific protocols for collecting HBM/HES data or were all samples collected using the same protocol?

What was the approximately number of questions in the questionnaire?

Were biological samples conducted at one visit?

Were all samples transferred to the same location (lab) from the field or to several locations?

How was the logistics for sample transfer organized?

Initiation of the combined HES and HBM programme

What (who) was the driving force behind the initiation of the combined programme?

Which institution or person was the main driver or initiator of the current study programme?

How was the study programme promoted?

Recruitment of participants

How did recruitment of participants take place?

Did you use incentives and which?

Identified issues important for the success of initiating the combined programme

Please mention any events, requirements, pre requisitions that you consider as having been key for the success of implementing the combined programme?

Which part of the combined programme was initiated first?

Was the HES or the HBM survey initiated first or were the two modules initiated simultaneously?

How was funding to initiate the programme obtained?

Were there problems to obtain funding for a combined survey?

Where/How was the programme implemented?

Which institution is responsible for carrying out the programme and what is the nature of this institution (governmental, university setting, hospital, private institution etc.)?

Has implementation of the programme changed over time? If so, how and why?

Opportunities

What was seen by survey organizers as opportunities when combining the two surveys?

Obstacles

What was seen by survey organizers as obstacles?

How did you overcome any obstacles?

Ethical approval

Were there separate approvals for the HES part and HBM part or was it combined?

Were there separate or combined informed consent?

Were there any problems, additional questions by ethics committee while applying ethical approval?

Sustainability of the combined HES and HBM programme

How is funding for sustainability of the programme secured?

How is the programme currently funded?

For how long time do you have funding for the current programme?

What is the duration of the funding period?

Identified issues important for sustainability of the combined programme

Are there any events, requirements, pre requisitions that you want to emphasise, that has been important for sustaining the combined programme?

Other comments that you want to add

7.7 Appendix 7: Acronyms, names, websites and organizing institutions of the studies where biological samples are collected or could be collected

	Name or short description of the study	Study acronym	Website	Organizing Institution
1	Greek National Health and Nutrition survey	HYDRIA	http://www.hhf-greece.gr/hydria-nhns.gr/index_eng.html	Hellenic Health Foundation (Greece)
2	Greek National Health and Nutrition survey - children up to 10 years old	HYDRIA – Children	http://www.hhf-greece.gr/hydria_children.html	Hellenic Health Foundation (Greece)
3	European Prospective Investigation into Cancer and nutrition	EPIC – Greece	http://epic.iarc.fr/	Hellenic Health Foundation(Greece)
4	Given the influence of environmental factors in cancer development and the links between thyroid nodules and thyroid cancer this scientific collaboration aims to establish and strengthen research efforts in the environmental and public health risks of thyroid nodular disease that is highly prevalent in both Cyprus and Romania	THYROCHEM	http://web.cut.ac.cy/thyroid/	Cyprus International Institute for Environmental and Public Health (Cyprus)
5	Environmental health and urban indicators: an exposome approach	URBANHEAL		Cyprus International Institute for Environmental and Public Health (Cyprus)
6	The Aragon Workers Health Study	AWHS	https://www.ncbi.nlm.nih.gov/pubmed/22712826	Instituto Aragoné de Ciencias de la Salud (Zaragoza, Spain) Instituto de Investigación Sanitaria, Hospital Clinic of Valencia (Spain)
7	The Hortega Follow Up study	Hortega		University Hospital Rio Hortega (UHRH) (Spain) Institute for Biomedical Research, Hospital Clinic of Valencia (Spain)

	Name or short description of the study	Study acronym	Website	Organizing Institution
8	Electronic Health Recording-Based Whole Population Study in Cardiovascular Diseases: The ESCARVAL (Estudio CARdiometabólico VALencia) Prevention Study	ESCARVAL-PREVENTION	http://www.escarval.info/nw/	Conselleria de Sanitat, Generalitat Valenciana (Spain) Institute for Biomedical Research, Hospital Clinic of Valencia (Spain)
9	Biomonitoring Study of Environmental Contaminants	BIOAMBIENT.ES		Instituto de Salud Carlos III / National Health Institute Carlos III (Spain)
10	DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale	DEMOCOPHES-SPAIN	http://democophes.blogs.isciii.es/	Instituto de Salud Carlos III / National Health Institute Carlos III (Spain)
11	BIOMONITORING OF ENVIRONMENTAL POLLUTANTS IN ADOLESCENT POPULATION			Instituto de Salud Carlos III / National Health Institute Carlos III (Spain)
12	Copenhagen minipuberty study		edmarc.net/population-studies.html	Dept. of Growth and Reproduction, Rigshospitalet (Denmark)
13	Biobank of simultaneously obtained maternal urine and blood samples and amniotic fluid collected at the time of amniocentesis			Dept. of Growth and Reproduction, Rigshospitalet (Denmark)
14	Male Reproductive health Study		http://www.edmarc.net/male-reproductive-health-cohort.html	Dept. of Growth and Reproduction, Rigshospitalet (Denmark)
15	New allergy, pollen and air pollution in Danish blood donors	DBDS	http://www.dbds.dk/	Aarhus University Hospital & Aarhus University (Denmark)
16	Workers exposed to styrene and respiratory diseases - 500 workers exposed to epoxy are studied for asthma and eczema and exposure is monitored			Aarhus University Hospital (Denmark)
17	Exposure of children and adolescents to selected chemicals through their habitat environment	SLO-CRP2016		Jozef Stefan Institute (Slovenia)

	Name or short description of the study	Study acronym	Website	Organizing Institution
18	Slovenian birth cohort 2017 (as part of EU HEALS project)	SLO-EXHES		Jozef Stefan Institute (Slovenia)
19	Slovenia Birth Cohort 2008 (as part of EU projects PHIME and CROME LIFE+)	SLO-PHIME-CROME		Jozef Stefan Institute (Slovenia)
20	Biomonitoring and Health survey: Exposure of Inuit women during pregnancy; comparison of mothers exposure level and cord blood level and possible effect on child health	ACCEPT- mother-child health		Aarhus University (Denmark)
21	Pilot study of lead exposure of shooters at a shooting range			Riga Stradins University, Laboratory of Hygiene and Occupational Diseases (Latvia)
22	Investigation of interaction of smoked dietary products with gut microbiome			Latvian Biomedical Research and Study Centre (Latvia)
23	Genome Database of the Latvian Population	LGDB	http://www.biomed.lu.lv/en/about-us/related-organisations/lgdb/	Latvian Biomedical Research and Study Centre (Latvia)
24	Analysis (in 1987) of 225 male welders for exposure to Cr, Ni and other metals by air monitoring and HBM in urine and blood including effect biomarkers of Chromosomal abberrations, Sister Cromatid Exchange and Unscheduled DNA repair. The welders were followed up with Health questionnaire and register data in 1999 and a new follow up is planned			University of Copenhagen, Institute of Public Health (Denmark)
25	Follow-up studies of the Danish DEMOCOPHES study			University of Copenhagen, Institute of Public Health (Denmark)

	Name or short description of the study	Study acronym	Website	Organizing Institution
26	Kardiovize Brno 2030, a population-based prospective study in Central Europe to assess and reduce cardiovascular risk: methods, baseline findings and future directions.	KVBRNO	https://www.fnusa-icrc.org/cz/klinicka-pece/kardiovize-brno-2030.html	International Clinical Research Center (FNUSA-ICRC), St'Anne University Hospital (Czech Republic)
27	Follow up of the previous study - older, parental cohort	KVBRNOold	http://www.fnusa-icrc.org/en/	International Clinical Research Center (FNUSA-ICRC), St'Anne University Hospital (Czech Republic)
28	(Central) European Longitudinal Study on Parents and Children	(C)ELSPAC	www.elspac.cz	Masaryk University (Czech Republic)
29	CELSPAC The Next Generation	CELSPAC TNG	www.celspac.cz	Masaryk University (Czech Republic)
30	Mammographic density and its determinants in premenopausal women (40-49 years old)	DDM-Madrid		Instituto de Salud Carlos III / National Health Institute Carlos III (Spain)
31	Multicase-control study of breast, colorectal, prostate and gastric cancer and chronic lymphocitic leukaemia	MCC-Spain	http://www.mccspain.org/	CIBERESP (Spain)
32	Prenatal environmental exposure to phthalates and bisphenol A associated to children health	PRENATAL		Constantine the Philosopher University in Nitra (Slovakia)
33	Human biomonitoring of endocrine disrupting chemicals in Slovakia - assessment of exposure and the potential health risk for European Human Biomonitoring Initiative			Constantine the Philosopher University in Nitra (Slovakia)
34	The potential health risk for firefighters using protective equipment is studied	BIOBRAND	http://www.arbejdsmiljoforskning.dk/da/projekter/biobrand	National Research Centre for the Working Environment (Denmark)

	Name or short description of the study	Study acronym	Website	Organizing Institution
35	The purpose of the project is to investigate the cardiovascular, respiratory and genotoxic effects of occupational exposure of train conductors to combustion derived particulate matter	BIOTRACK		National Research Centre for the Working Environment (Denmark)
36	The FinHealth Study	FinHealth	www.thl.fi/finterveys	National Institute for Health and Welfare (Finland)
37	BAMSE birth cohort	BAMSE	www.ki.se/bamse	Institute of Environmental Medicine, Karolinska Institutet (Sweden) Stockholm County Council (Sweden)
38	1st Portuguese National Health Examination Survey (1º Inquérito Nacional de Saúde com Exame Físico)	INSEF	www.insef.pt	National Health Institute Doutor Ricardo Jorge (Portugal)
39	Central Sweden Cohort & Biobank	CSC&B, SMC, SMC-C, COSM, COMS-C	http://ki.se/en/imm/swedish-mammography-cohort-clinical-smc-c http://ki.se/en/imm/cohort-of-swedish-men-clinical-cosm-c	Institute of Environmental Medicine, Karolinska Institutet (Sweden)
40	Coset	Coset	http://www.coset.fr/	Santé Publique France (France)
41	The cohort of 60-year-old men and women	60YO		Karolinska Institutet (Sweden)
42	Doetinchem Cohort Study	DCS	http://www.rivm.nl/Onderwerpen/D/Doetinchem_Cohort_Studie (in Dutch)	National Institute for Public Health and the Environment (Netherlands)
43	The Odense Child cohort	OBC	http://subsites.odense.dk/subsites2/odensebornekohorte	Odense University Hospital (Denmark)
44	Northern Sweden Health and Disease Study	NSHDS	http://www.biobank.umu.se/biobank/?languageId=1	Umeå University (Sweden)

	Name or short description of the study	Study acronym	Website	Organizing Institution
45	Riksmaten ungdom	Riksmaten ungdom	https://www.livsmedelsverket.se/Riksmatenungdom	The National Food Agency (Sweden)
46	Swiss study on Air Pollution And Lung Disease in Adults	SAPALDIA	http://www.sapaldia.ch/en/	Swiss TPH (Switzerland)
47	Trace elements and brain tumours			Neuroscience Institute of Lithuanian University of Health Sciences (Lithuania)
48	2015 - 2016 National Health and Nutrition Survey	MABAT	https://www.health.gov.il/English/MinistryUnits/ICDC/mabat/Pages/default.aspx	Israel Center for Disease Control, Ministry of Health (Israel)

7.8 Appendix 8: Studies selected from the Task 7.1 questionnaire

	Country	Name of the study	Acronym
1	Iceland	The Icelandic Heart Association Reykjavik Longitudinal Study	
2	Iceland	Development of a Personalized Nutrition Therapy in Pregnancy	
3	Israel	Israel Biomonitoring Study	IBS
4	Israel	RAV MABAT Biomonitoring Study	
5	Israel	Amirim Study on Exposure of Vegetarians to Endocrine Disrupting Chemicals	
6	Norway	Human Exposure to Toxicants Through the Indoor Environment	NIPH - Indoor Environment Study
7	Norway	HBM Within the Norwegian Mother and Child Cohort Study	NIPH MoBa
8	Switzerland	Swiss Cohort on Air Pollution and Lung And Heart Disease in Adults	SAPALDIA
9	Austria	Environment Agency Austria	EAA
10	Austria	Environment Agency Austria	EAA
11	Austria	Environment Agency Austria	EAA
12	Belgium	ENVIRonmental influence ON AGEing in early life	ENVIROANGE
13	Belgium	STP 2 Reference Newborns	FLEHS II Ref Newborn
14	Belgium	NA	IMPASTRA
15	Belgium	STP 2 Hotspot Genk-Zuid	FLEHS II HOTSPOT_GENK
16	Belgium	STP 2 Hotspot Menen	FLEHS II HOTSPOT_MENEN
17	Belgium	STP 3 Reference Adolescents	FLEHS III Ref Ado
18	Belgium	STP 3 Reference Adults	FLEHS III Ref Adult
19	Belgium	STP 2 Reference Adolescents	FLEHS II Ref Ado
20	Belgium	STP 3 Reference Newborns	FLEHS III Ref Newborn
21	Belgium	3xG Study	3xG
22	Belgium	STP 3 Hotspot Gentse Kanaalzone	FLEHS III HOTSPOT_GKZ
23	Belgium	STP 4 Reference Adolescents	FLEHS IV Ref Ado
24	Belgium	STP 1 Reference Newborn	FLEHS I Ref Newborn
25	Belgium	STP 1 Reference Adults	FLEHS I Ref Adult
26	Cyprus Romania	Bisphenols and Thyroid Function	THYROCHEM

	Country	Name of the study	Acronym
27	Czech Republic	Impact of Environment to Newborns	
28	Czech Republic	Central European Longitudinal Study on Parents and Children - The Next Generation	CELSPAC - TNG
29	Czech Republic	Health, Alcohol and Psychosocial factors in Eastern Europe	HAPIEE
30	Czech Republic Slovakia, Data form Czech Republic and Slovakia are available through CELSPAC but ELSPAC was/is implemented also in UK (ALSPAC) and other countries.	(Central) European Longitudinal Study on Parents and Children	(C)ELSPAC
31	Denmark	Odense Child Cohort	OCC
32	Denmark	A Biomonitering Study of Firefighters and Recruits Under Education as Smoke Divers	BIOBRAND
33	Denmark	Health Effects of Occupational Exposure to Combustion Particles - a Study on Volunteers Performing as Train Conductors	BIOTRACK
34	Denmark	Human Exposure to Novel Flame Retardants - From Materials to Humans	NoFlame
35	Denmark	Polybrominated Diphenyl Ethers (PBDEs) - Fetal and Neonatal Exposure	
36	Denmark	COPENHAGEN Minipuberty Study	CPHMINIPUB
37	Denmark	COPENHAGEN Puberty Study	CPHPUB
38	Denmark	Male Reproductive Health Study	
39	Denmark	Amniocentesis Cohort at dept. of Growth and Reproduction, RegionH	AC_Rigshospitalet
40	France	Etude Longitudinale Depuis l'Enfance	ELFE
41	France	Etude Longitudinale Française depuis l'Enfance	ELFE
42	Germany	German Environmental Specimen Bank	ESB
43	Italy	Programma per il Biomonitoraggio dell'esposizione della Popolazione Italiana	PROBE
44	Italy	Biomonitoring Study on Enviromental Contaminants in Taranto Area	
45	Italy	Impatto Sul Neurosviluppo Cognitivo e Comportamentale Dell'Esposizione Ambientale a Fitosanitari Nell'Area di Trento: Coorte di Madre-Bambino	

	Country	Name of the study	Acronym
46	Italy	Health Surveillance System of the Population Living Near the Waste-to-Energy Plant of Turin, Northern Italy	SPoTT
47	Italy	Ambiente e Biomonitoraggio nell'area di Civitavecchia	ABC
48	Lithuania	Improvement of Infrastructure for Emergency Aid for Injuries and Accidents of External Causes	
49	Lithuania	Breast Cancer Study on Environmental and Lifestyle Risk Factors-2	BCAS-2-LSMU
50	Portugal	Uranium Mines and Their Residues - Effects on the Health of the Population	MinUrar
51	Slovakia	NA	PCB cohort
52	Slovenia	National HBM Survey	SLO_HBM
53	Spain	Biomonitoring Study of Environmental Contaminants	BIOAMBIENT.ES
54	Sweden	The Cohort of 60 years old Men and Women	60yo
55	Sweden	Health Related Environmental Monitoring – Children	HÄMI - Children
56	Sweden	Central Sweden Cohort & Biobank	CSC&B (or SMC and COSM)
57	Sweden	Stockholm Children Children Allergy and Environmental Prospective Birth Cohort Study	BAMSE

7.9 Appendix 9: Final selection of studies from the Task 7.1 questionnaire, biological samples collected and measurements performed

Country	Name of the study	Biological samples	Lung-function test	Height	Weight	Waist	Hip	BIA	DXA	Others	Measurements
Iceland	The Icelandic Heart Association Reykjavik Longitudinal Study	Blood, Plasma, Serum, Saliva, DNA, Urine (spot sample-random)	Yes	Y	Y	Y	Y	N	Y	N	YES, Blood pressure, Heart rate, Status of the thyroid gland, Glucose tolerance, Fasting glycaemia, HDL cholesterol, LDL cholesterol, Total cholesterol, Serum triglycerides, Bone density, Iron status, Vitamin levels, Haematocrit, Haemoglobin, Growth factors, Hearing assessment, Visual accuracy, Clinical assessment
Switzerland	Swiss Cohort on Air Pollution and Lung And Heart Disease in Adults	Blood, Plasma, Serum, DNA	Yes	Y	Y	Y	Y	Y	N	N	YES, Blood pressure, Heart rate, Glycated haemoglobin, HDL cholesterol, LDL cholesterol, Total cholesterol, Serum triglycerides
Belgium	ENVIRonmental influence ON AGEing in early life	Blood, Blood erythrocytes, Plasma, Buccal cells, Nails, DNA, Urine (spot sample-random), Placenta, Umbilical cord blood		Y	Y	Y	N	N	N	N	YES, Oxidative damage, Blood pressure, Heart rate, Glucose tolerance, HDL cholesterol, LDL cholesterol, Total cholesterol, Bone density, Iron status, Vitamin levels
Belgium	STP 2 Hotspot Genk-	Blood, Plasma, Serum, Urine (spot sample-		Y	Y	N	N	N	N	N	YES, Blood pressure, Status of the thyroid gland, HDL

Country	Name of the study	Biological samples	Lung-function test	Height	Weight	Waist	Hip	BIA	DXA	Others	Measurements
	Zuid	first morning), Hair (complete locks)									cholesterol, LDL cholesterol, Total cholesterol, Serum triglycerides, Iron status
Belgium	STP 2 Hotspot Menen	Blood, Plasma, Serum, Urine (spot sample-first morning), Hair (complete locks)		Y	Y	N	N	N	N	N	YES, Oxidative damage, Blood pressure, HDL cholesterol, LDL cholesterol, Total cholesterol, Serum triglycerides, Iron status
Belgium	STP 3 Reference Adolescents	Blood, Urine (spot sample-random), Exhaled breath condensate		Y	Y	N	N	N	N	N	YES, Blood pressure, Total cholesterol, Serum triglycerides, Iron status
Belgium	STP 3 Reference Adults	Blood, Urine (spot sample-random)		Y	Y	N	N	N	N	N	YES, Blood pressure, Heart rate, Total cholesterol, Serum triglycerides, Iron status
Belgium	STP 2 Reference Adolescents	Blood, Plasma, Serum, Urine (spot sample-first morning), Hair (complete locks)		Y	Y	N	N	N	N	N	YES, Oxidative damage, Blood pressure, Status of the thyroid gland, HDL cholesterol, LDL cholesterol, Total cholesterol, Serum triglycerides, Iron status, Specific metabolising genes
Belgium	STP 3 Hotspot Gentse Kanaalzone	Blood, Urine (spot sample-random), Exhaled breath condensate		Y	Y	N	N	N	N	N	YES, Blood pressure, Total cholesterol, Serum triglycerides, Iron status
Belgium	STP 4 Reference Adolescents	Blood, Plasma, Serum, Urine (spot sample-		Y	Y	N	N	N	N	N	YES, Oxidative damage, Blood pressure, HDL cholesterol, LDL

Country	Name of the study	Biological samples	Lung-function test	Height	Weight	Waist	Hip	BIA	DXA	Others	Measurements
		first morning), Hair (complete locks)									cholesterol, Total cholesterol, Serum triglycerides, Iron status, Vitamin levels, Haemoglobin
Czech Republic	Health, Alcohol and Psychosocial factors in Eastern Europe	Blood, Plasma, Serum, DNA	Yes	Y	Y	Y	Y	N	N	N	YES, Oxidative damage, Blood pressure, Heart rate, Fasting glycaemia, HDL cholesterol, LDL cholesterol, Total cholesterol, Serum triglycerides, Vitamin levels
Denmark	Odense Child Cohort	Blood, Plasma, Serum, DNA, Urine (24h), Urine (spot sample-first morning), Human milk, Hair (complete locks), Umbilical cord blood		Y	Y	Y	Y	N	N	N	YES, Blood pressure, Heart rate, HDL cholesterol, LDL cholesterol, Total cholesterol, Haemoglobin
Denmark	Male Reproductive Health Study	Serum, DNA, Urine (spot sample-random), Hair (complete locks), Semen		Y	Y	Y	Y	N	Y	N	YES, Blood pressure, HDL cholesterol, LDL cholesterol, Bone density, Haemoglobin, Reproductive hormones
Italy	Ambiente e Biomonitoraggio nell'area di Civitavecchia	Blood, Serum, Nails, Urine (spot sample-first morning), Hair (complete locks)	Yes	Y	Y	N	N	N	N	N	YES, Blood pressure, Status of the thyroid gland, Glucose tolerance, Glycated haemoglobin, HDL cholesterol, Total cholesterol, Haematocrit, Haemoglobin, Creatinine, uric acid, GOT, GPT, GGT, FT4,

Country	Name of the study	Biological samples	Lung-function test	Height	Weight	Waist	Hip	BIA	DXA	Others	Measurements
											TSH
Spain	Biomonitoring Study of Environmental Contaminants	Blood, Serum, Urine (spot sample-first morning), Hair (complete locks), Blood clots	Yes	Y	Y	N	N	N	N	N	YES, Blood pressure, Heart rate, HDL cholesterol, LDL cholesterol, Total cholesterol, Haematocrit, Haemoglobin, Hearing assessment, Visual accuracy
Sweden	The Cohort of 60 years old Men and Women	Blood, Plasma, Serum, DNA		Y	Y	Y	Y	N	N	Sagittal diameter	YES, Blood pressure, Heart rate, Fasting glycaemia, HDL cholesterol, LDL cholesterol, Total cholesterol, Serum triglycerides, Haemoglobin
Sweden	Central Sweden Cohort & Biobank	Blood, Blood erythrocytes, Plasma, Serum, Saliva, DNA, 12-hours overnight urine, Urine (spot sample-first morning), Fat/adipose tissue		Y	Y	Y	Y	N	N	N	YES, Blood pressure, Fasting glycaemia, HDL cholesterol, LDL cholesterol, Total cholesterol, Serum triglycerides, Bone density, Iron status, Haemoglobin
Sweden	Stockholm Children Children Allergy and Environmental Prospective Birth Cohort Study	Blood, Saliva, DNA, Urine (spot sample-random)	Yes	Y	Y	Y	Y	Y	N	N	YES, Blood pressure, HDL cholesterol, LDL cholesterol

Part B - Availability of administrative registers and possibilities for their use in HBM studies

1 Authors and Acknowledgements

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

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2 Background

Administrative registers, such as registers of in- and out-patient hospitalizations and mortality registers provide often nationally representative data on morbidity and mortality in a country. In many countries such registers are nationally representative or several regional registers exists covering the majority of a country. In principle, if register information is recorded using personal identification or other type of identification which would be available also in HBM studies, a record linkage could be conducted if allowed by national data protection regulation. This type of record linkage would provide a cost-effective data source for morbidity and mortality follow-up, and for obtaining baseline health information.

The aim of this evaluation was to identify administrative registers in different EU Member States and learn about their contents and how they could be linked to the HBM studies.

3 Methods

3.1 Preparation of the questionnaire

An electronic questionnaire was prepared to obtain information about existing health related administrative registers in the EU Member States. The content of the questionnaire was prepared in collaboration, through several rounds of iteration by all involved partners (NIPH, THL, MUW, WIV-ISP, IHIS, SDU, KI, UMU). NIPH prepared an electronic version from the questionnaire using QuestBack by Digium. The web questionnaire was pilot tested with task partners and final adjustments were made based on received feedback.

3.2 Identification of administrative registers

The HBM4EU National Hub Coordinator (NHC) Ovnair Sepai was asked to contact the National Hub Contact Points (NHCP) asking for contact information for a person/persons who know about national /regional health related administrative registers and legislation related to data linkage between survey data and register information. The person providing this information did not have to be the register owner, he/she could (preferably) also be a researcher/ICT administrator/etc. working with data linkage. In this questionnaire, administrative registers were limited to health based registers such as cancer registers, hospitalization registers, causes of death register and other possible registers related to health outcomes, uses of health services, health insurance, medication reimbursements, etc. Also, information about registers covering socio-economic information and possibly also GIS codes/related information were of interest. This e-mail request was sent out on 4th April 2017.

By 4th July 2017, 11 countries still had not answered the request for contact person(s), therefore Ovnair Sepai was asked to send a reminder. By the end of September, a complete list of possible contact persons was obtained, however not all provided by the NHCPs.

A web-questionnaire (Appendix 1) was sent to the national contact points identified by the NHCPs (or others) on 2nd October 2017. Reminders were sent out on 30th October 2017.

By 8th November 2017, 19 countries (Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Iceland, Ireland, Israel, Lithuania, Norway, Poland, Portugal, Slovenia, Sweden and Switzerland) had provided answers to the questionnaire. At that point, responses from seven countries were still lacking. One of these, UK, provided links to specific registries after this date, but it was not possible to start going through these to obtain structured information for the questionnaire.

4 Results

Results presented here are based on replies to the questionnaire by different register owners/users. Since all EU Member States (MS) are not represented and number of registers also varies considerably between those MS which have replied, there may be some bias on representativeness of the results within and between MSs.

4.1 Health related administrative registers

Respondents to the questionnaire reported altogether 103 registers (Appendix 2) from 19 countries. Most of the reported registers were classified as 'Other type of register' (34%). From specified register, most common were the disease specific registers (23%), while birth registers and causes of death registers both constituted 10%. Smaller proportion of the registers covered in-patient hospitalizations (8%) and out-patient consultations (5%), prescriptions of medications (5%) and malformations (5%). (Figure 1)

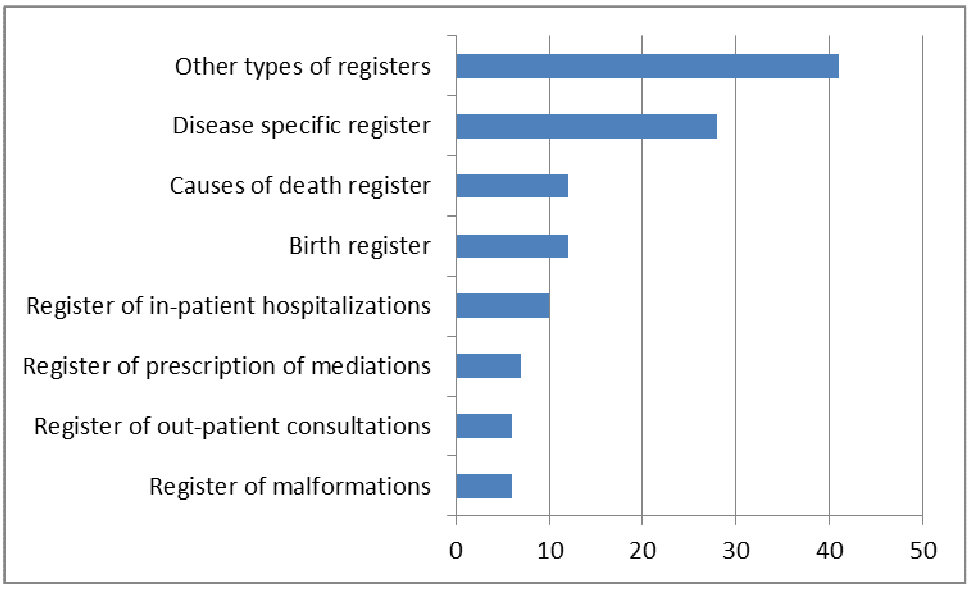

Figure 1: Number of reported registers by type of register

Among the disease-specific registers, 50% were cancer registries, 11% coronary heart disease registers and 7% diabetes registers. Remaining 32% included registers for multiple sclerosis, AIDS, occupational diseases, childhood diseases, rare diseases, stroke and infectious diseases.

In the other types of registers, majority of reported registers were morbidity registers (80%). All of these were French registers. Most of the reported French registers were regional or type specific cancer registers. Additional to this, several cardiovascular disease registers were included under morbidity registers from France. Also individual registers of blood donors, abortions, vaccinations, hospital infections and antibiotic use and medical records for recruits and serving personnel were reported under this category.

4.2 Types of personal identifiers used in different registers

Most of the EU Member States have some personal identifier (PIC) to identify individuals[6] as listed in Table 1.

[6] https://en.wikipedia.org/wiki/National_identification_number#Europe

Table 1: Type(s) of identifier(s) used in different countries

Country		Type of identifier
Austria	AT	Sector-specific personal identifier
Belgium	BE	National register number
Bulgaria	BG	Uniform civil number
Croatia	HR	Personal identification number
Cyprus	CY	no information available
Czech Republic	CZ	Birth number
Denmark	DK	Personal identification number
Estonia	EE	Personal identification code
Finland	FI	Personal identity code
France	FR	INSEE code
Germany	DE	No national identification number. Taxpayer identification number and economy identification number but used only for taxation purposes
Greece	EL	National identification numbers. ID card number is not unique and changes if the person gets a new identity card.
Hungary	HU	No national identification number. ID card identification number, social security number, tax identification number, passport identification number, driving license number exists.
Iceland	IS	National identification number
Ireland	IE	Personal public service number
Italy	IT	Italian fiscal code
Latvia	LV	Personal code
Lithuania	LT	Personal code
Luxembourg	LU	No information available
Malta	MT	No information available
Netherlands	NL	Citizen service number (personal number)
Norway	NO	Birth number
Poland	PL	Public electronic census system number
Portugal	PT	Not one national number but several different identification numbers: civil identification number, tax identification number, social security number, healthcare user number, voter's number, driver's license number.
Romania	RO	Personal numerical code
Slovakia	SK	Two national identification numbers: birth number and citizen's identification card number
Slovenia	SI	Unique master citizen number

Country		Type of identifier
Spain	ES	National identity document after age of 14 years
Sweden	SE	Personal identity number
Switzerland	CH	Social security number (most persons)
United Kingdom	UK	National insurance number

Obviously having a personal identification number in a country doesn't automatically mean that it is systematically used in registers. In the reported registers, national level personal identifier was used in 50% of the registers, other identifiers which possibly would allow register linkage in 14% of the registers and in 3% registers did not include any identifier allowing the register linkage. It should be noted from 33% of registers (all reported French registers) information about availability of the identifier was missing. (Table 2)

Table 2: Registers according to the type of identifier

Type of identifier	Number of registers	% of all reported registers
Individual identification code (national level personal identifier)	52	50%
Register-specific individual identification (with possibilities to link to other (national) registries for research purposes)	7	7%
Non-person identification (possibility for e.g. probability linkage)	7	7%
Stored with pseudonym	1	1%
No identification at all	2	2%
Unknown	34	33%
TOTAL	**103**	100%

Out of 19 countries, 14 (AT, BE, HR, CY, CZ, DK, FI, IS, IL, LT, NO, SI, SE, CH) include PIC in some of their registries and 8 in all of their registers. In six countries also registries with a different type of personal identifier (CY, DK, IL, LT, NO and CH) were reported. Register-specific individual identification (with possibilities to link to other registries for research purposes) was reported for the National Registry of Congenital Anomalies in Portugal. Non-person identification (with a possibility for, e.g., probability linkage) was reported for General Hospital Morbidity Study in Poland. German Centre for Cancer Registry Data stores data with pseudonym. Ireland reported register-specific individual identification for cancer registry and non-person identification for infectious disease reporting. (Table 3)

Table 3: Countries according to the type of unique identifier in reported registers

Type of identifier	Countries	Number of countries	% of all countries
Individual identification code (national level personal identifier)	AT, BE, HR, CZ, FI, IS, SI, SE	8	42%
Varies between registers but at least some registers have national level personal identifier	CY, DK, IL, LT, NO, CH	6	32%
Register-specific individual identification (with possibilities to link to other (national) registries for research purposes)	PT	1	5%
Non-person identification (possibility for e.g. probability linkage)	PL	1	5%
Stored with pseudonym	DE	1	5%
Varies between registers and none has national level personal identifier but possibility link (e.g. probability linkage etc.)	IE	1	5%
Unknown	FR	1	5%

The identifiers used in different reported registers are well in line with general availability of PIC in different countries. There are few register specific exceptions in six countries (CY, DK, IL, LT, NO, CH) which have PIC and this is usually due to sensitive nature of the specific register. For example, in Cyprus the HIV/AIDS register and in Norway the Registry of Pregnancy Terminations doesn't have personal identification; in Denmark the Occupations Birth Register, in Israel the National Cancer Registry and in Norway the Prescription Database and the Surveillance System for Infections in Hospitals have only register specific identifier; and in Lithuania the Injury and Accident Monitoring and in Switzerland the Rare Disease Registry doesn't have any identifiers.

Although Ireland uses Personal public service number, its use is limited and has not been reported in disease registries. Similarly Polish citizens have their PESEL number but its use was not reported in the Polish hospital morbidity study.

4.3 Information covered by the registers

4.3.1 Main purposes of the registers

The purpose of the register is often defined by the type of the register:

- **Birth registers** are designed to collect information about pregnancies and births. In Denmark, a special Occupational Birth Register exists which is designed to provide information about parental work on pregnancies and child development. Birth registers will provide statistics on pregnancies and births.
- **Causes of death register** are designed to collect information about causes of death for statistical purposes.
- **In-patient hospitalization registers** vary between countries in design and purpose. Generally these cover hospitalized patients and their diagnoses for monitoring purposes. In Lithuania, the Injury and Accident Monitoring was also classified as in-patient

hospitalization register and its main purpose is to collect data on injuries and accidents for statistical purposes. Some of the in-patient registers like the Danish Occupational Hospital Register are focused on issues related to occupational health.

- **Out-patient consultations** generally collect data health care usage, prevention and treatment of diseases outside hospitals. Collected data is used for statistics and monitoring.
- **Registers for prescriptions of medications** are designed to monitor the patterns of medication prescriptions and use, to evaluate the costs and in some countries such as Finland where some medication are reimbursed, the reimbursements. In Sweden the register is used to increase patent security. Registers also provide information for statistics.
- **Registers for malformations** are designed to provide surveillance and statistical information about congenital anomalies. In Czech Republic, the National Register of Reproductive Health is merged with the National Registry of Mothers at Childbirths, the National Registry of Newborns, the National Registry of Congenital Malformations, the National Registry of Abortions and the Nationals Registry of Assisted Reproduction into a unified system providing better monitoring of reproductive health.
- **Disease specific registers**, which were mainly cancer registers are designed to provide statistics and epidemiological overview of cancer incidence and prevalence in a country. Similarly for other reported disease specific registers, purpose is on evaluation and monitoring.
- **Multi-purpose registers** are available in some countries. For example, Belgium reported their www.healthdata.be which is not a register but a technical platform and service provided consolidating all patient registers in Belgium. Other examples are Danish Occupational Hospital Register and Finnish Care Register for Health Care which have both in-patient hospitalizations and out-patient consultations.

The basic purpose of national health registers is the documentation of health data. They are used for monitoring, trend analyses and sometimes also for the examination of spatial variation.

4.3.2 Availability of registers electronically and updating frequency

The availability of registers in electronic format, and year from which they are available vary considerably between the countries and type of register. A summary is presented in Table 4. Causes of death registers go back to mid-1930's (Finland) and in most of the countries they are available electronically at least from 1980's. Also other registers are available for decades in many countries. Registers tend to be updated regularly.

Among specific disease specific registers, 14 were specified as cancer registers. Also 22 out of 34 registers reported by France under 'Other types of registers' could be identified as cancer register based on the name of the register. Therefore, cancer registers were added to the Table 4 as separate line.

Table 4: Year of electronic availability and last update for different types of registers.

Type of register	Number of registers	Year of availability in electronic format min-max	Year of last update (N of registers)	Updating frequency (N of registers)
Birth register	12	1967-2007	2015 (2) 2016(2) 2017(6) Unknown (2)	Irregularly (1) Annually (5) Periodically (0) Continuously (5) Unknown (1)
Causes of Death register	12	1936-2010	2015 (4) 2016 (4) 2017(3) Unknown (1)	Irregularly (1) Annually (6) Periodically (1) Continuously (4) Unknown (0)
In-patient hospitalizations	10	1969-2016	2010 (1) 2015 (1) 2016 (4) 2017 (2) Unknown (2)	Irregularly (1) Annually (3) Periodically (1) Continuously (4) Unknown (1)
Out-patient consultations	6	1969-2008	2010 (1) 2015 (1) 2016 (1) 2017 (2) Unknown (1)	Irregularly (1) Annually (0) Periodically (1) Continuously (4) Unknown (0)
Register for prescriptions of medications	7	1968-2005	2015 (2) 2016 (1) 2017 (3) Unknown (1)	Irregularly (1) Annually (1) Periodically/semi-annually (2) Continuously (3) Unknown (0)
Register of malformation	6	1963-1997	2015 (2) 2016 (2) 2017 (1) Unknown (1)	Irregularly (1) Annually (4) Periodically (0) Continuously (1) Unknown (0)
Disease specific	28	1950-2016	2012 (1) 2014 (6) 2015 (3) 2016 (3) 2017 (10) Unknown (5)	Irregularly (1) Annually (8) Periodically/Semi-annually (4) Continuously (12) Unknown (3)
Other types	41	1975-2017	2016 (2) 2017 (6)	Irregularly (0) Annually (1) Periodically (1)

Type of register	Number of registers	Year of availability in electronic format min-max	Year of last update (N of registers)	Updating frequency (N of registers)
			Unknown (33)	Continuously (7) Unknown (32)
Cancer registers	36	1950-2014	2012 (1) 2014 (6) 2015 (1) 2016 (1) 2017(4) Unknown (23)	Irregularly (0) Annually (6) Periodically (1) Continuously (6) Unknown (23)

4.3.3 Size of the registers

The size of the register is dependent on the time that past since the start of registration and on the proportion of the population covered by the register. Table 5 provides a general overview of the sizes of the reported registers by country. In some countries registers are national covering all the cases in the country while in others they are more limited.

Table 5: Size of the registers in different countries

Country	Number of cases in different registers (range)
Austria	About 80,000 per year
Belgium	Varies between registers up-to millions per register
Croatia	About 450,000
Cyprus	Varies between registers from 1,116 to 64,473
Czech Republic	Varies between registers from about 2 million to 54 million cases
Denmark	Some registers are national, covering all cases in the country and others cover about 2M cases
Finland	All registers are national, covering all cases in the country
France	Unknown
Germany	About 8.5 million cases
Iceland	Varies between the registers from 80,000 cases to 3.5 million cases per year
Ireland	Varies between the registers from 31,941 to 139,526
Israel	Varies between the registers from 53,000 to 800,000
Lithuania	Varies between the registers but annually between 400 and 350,000
Norway	Most registers are national, covering all cases in the country. Some registers are more limited with 30,000 to 140,000 cases per year
Poland	8 million
Portugal	22,728

Country	Number of cases in different registers (range)
Slovenia	Varies between the registers, some being national and covering all cases in the country while others are more limited with 18,000 to 107,000 per year
Sweden	Most registers are national, covering all cases in the country. Some registers are more limited with 5 to 12 million cases
Switzerland	20,000 to 2.8 million

In general all major registers are relatively large in size (Table 6) and in most cases also have national coverage.

Table 6: Size of the major registers

Type of register	Number of countries	Number of cases (range)	Countries with total population coverage
Birth registers including registers of malformations	11	23,000 – total population	>5
Causes of death registers	9	Generally very large	Probably all nine countries
In-patient hospitalizations and out-patient consultations	7	8 million – total population	>4
Registers for prescriptions of medications	5	Generally very large	Probably all 5 countries
Cancer registers	12	50,000 – total population	>3

For prospective studies, where incident diseases are ascertained through register linkage during follow-up, the completeness/population coverage is a major issue to avoid bias.

4.3.4 Coverage of registers including problems with representativeness

From reported 103 registers, 61% were classified as national registers, 3% reported to be regional and for remaining 36% coverage was not reported. Most of the registers without know coverage were from France. Yet, based on the names of the registers (e.g. ‘Somme Cancer Registry’, ‘Registry of general cancers in Gironde’), it can be presumed that some – not all - of them have a limited spatial coverage.

Even though majority of the registers were reported to have a national coverage, this does not imply that all registers are complete or representative. For some registers, specific exclusion criteria are applied: e.g. in the Swedish ‘Prescribed Drug Register’, medications given to patients at the hospitals are not included, in the Danish ‘Occupational Hospital Register’ no information can be found on employees in companies with less than 10 employees, etc. Yet, in overall terms, the registers currently identified in the database have mostly a national coverage and are representative at population level.

4.3.5 Contents of the registers

In the questionnaire about administrative registers, some basic information about the type of information included to the registers was asked. Figure 2 summarizes the key elements included to the registers excluding 34 registers reported from France for which this information was not provided. In 81% of the registers included sex and date or year of birth for the subject. In 75% of registers also date of registration of condition and in 70% of registers, the residence (e.g. rural or urban) was recorded. Since most of the registers were health related, 67% of them used ICD-codes to register events.

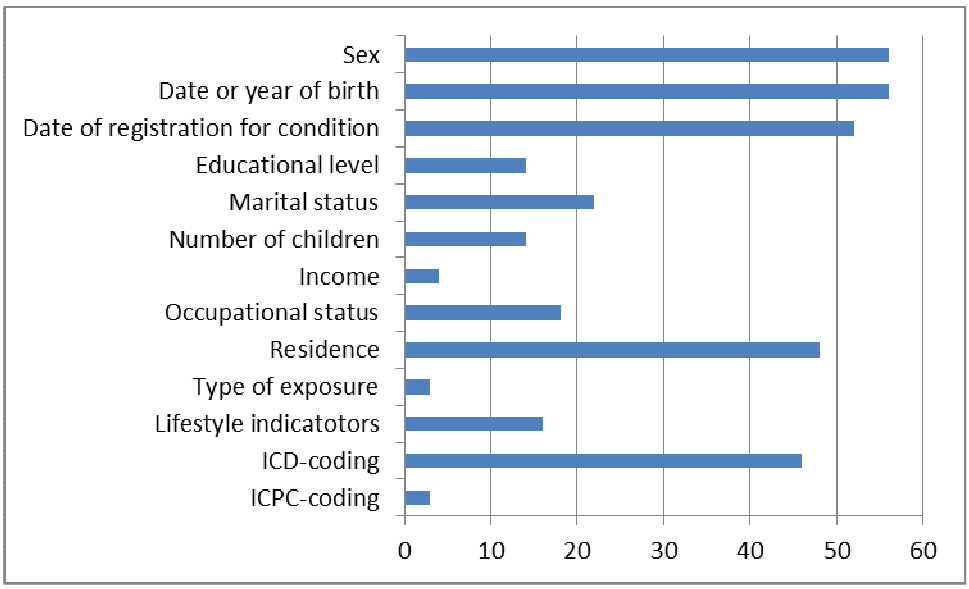

Figure 2: Key elements included to the registers

4.4 Problems related to linking of registers to other registers

Even when PIC is available in the register and commonly used in the country, there may be problems in register linkage. Even more complicated register linkage may be if common identifier is missing and linkage has to be done based on other available information. Table 7 provides information about reported, identified problems for record linkage in different countries.

Table 7: Identified problems related to record linkage

Country	Personal identification code used in registers	Identified problems
Austria	Yes	All registers don't include the PIC
Belgium	Yes	None identified
Croatia	Yes	None identified
Cyprus	Yes for death and cancer registers, register specific PIC for birth register, no PIC for some HIV/AIDS registers	If national identification code is missing.
Czech Republic	Yes	Linkage between registers under National Health Information System is allowed. The linkage with other data sources is very restricted.
Denmark	Yes except occupational birth	None if the application is approved by all register

Country	Personal identification code used in registers	Identified problems
	register has a register specific PIC	authorities in question. For occupational birth register, the use would need to be within those of a birth register (mainly to investigate the influence of parent's occupation on child health)
Finland	Yes	None if the application is approved by all register authorities
France	Not defined in the questionnaire	Not defined in the questionnaire
Germany	No. Data stored in pseudonym format	Not defined in the questionnaire
Iceland	Yes	Authorization by the Icelandic Data Protection Authority required and when used for scientific research also permission by the Icelandic Ethical Committee required.
Ireland	Register specific PIC	Not currently possible.
Israel	Yes	Not defined in the questionnaire.
Lithuania	Yes, except for register on injuries and accident monitoring has none	No technical problems identified but some legal problems for linkage due to personal data protection may exist.
Norway	Yes	None identified in general. For Norwegian Surveillance System for Communicable Diseases for some endpoints there is not enough information about patient to do the linkage. For Norwegian Surveillance System for Infections in Hospital data type in not suited.
Poland	No	Not defined in the questionnaire.
Portugal	Register specific PIC	No problems identified in general. However, the change in laws and regulations related to the data protection, final authorization is still pending.
Slovenia	Yes	None identified for those who are entitled to do the linkage by law.
Sweden	Yes	None identified.
Switzerland	Yes	Record linkage is heavily regulated by legislation and data linkage with other data sources and final data file must be fully anonymised. For some registers it might be possible to obtain permission from the register owner and Ethics Committee for data linkage, but again, final data file must be fully anonymised.

In countries where the PIC is systematically used throughout the registers, no technical problems were identified for register linkage. Also in most of the countries with register specific PIC, register linkage seemed possible. Several countries stated that national legislation/regulations on personal data protection may have some impact on feasibility of the register linkage. Also for some specific registers (with very sensitive data), register linkage was not possible even when PIC was existing.

4.5 Access to register data

The rules of access to the register data varies between countries and often also between registers within country. When register data is accessed for the purpose of register linkage to the HBM or other survey data, usually several levels of authorization are required. First of all, the ethical approval and data protection approval has to be obtained for the record linkage and in most cases also informed consent of the study participant is required. Obviously also register owner has to approve the record linkage. The question in our questionnaire may have been somewhat misleading on this as we asked 'What are the conditions for access to data?' which may have led some respondents to think access to register data in general, not in relation to record linkage to survey data. Therefore, our results have to be considered with some level of reservation. They may better represent the general rules of access for register data for example in case of register based studies.

Only 26% of the registers reported that informed consent of the participant would be required. Most commonly required approvals were the approval by local ethics committee and register owner. (Figure 3) For example in Finland and Sweden, when register data is linked to survey data, this has to be approved by ethics committee and informed consent from survey participants is required.

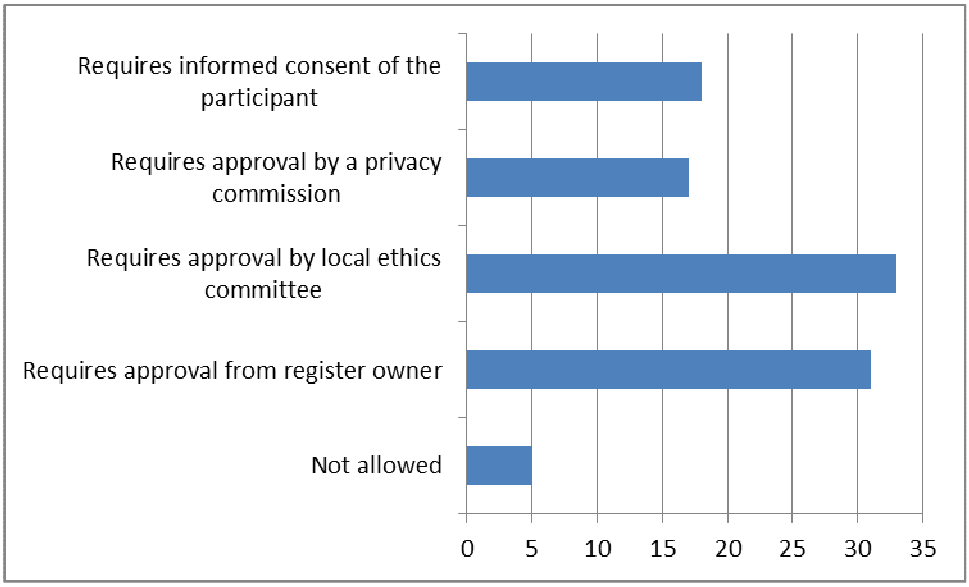

Figure 3: Required approvals before access to the register data

In many cases access to the register data is free of charge (55% of reported registers) but some registers also charge fees from data access (45%). Costs vary from standard fees (10%) to hourly rates for time used for data retrieval (70%), and their combinations (20%).

In most cases (77%), register data can be delivered within 3 months, in 3% it may take over one year and for remaining 20% required time for obtaining data from the registers is unknown. Many registers restrict the access to the data only in anonymous or at the aggregated level.

5 Conclusions

When analysing the responses available, it becomes apparent that a lot of data are missing, both on how many registers there are within the countries and details about the specific register. France has for instance listed the name of 32 registers, but neglected most of the other questions. Therefore, further contacts with countries would be required in coming years to update and complement missing information. This means new contacts with NHCP in countries which have not already provided information about contact points for register or from which no replies were received from provided contact points. Also feasibility to obtain more information through literature/web search needs to be evaluated. Web sites for national registers most likely exists but if they are not available in English or other languages spoken by involved partners it may be difficult to obtain further information from them. Since this report is planned to be updated as Deliverables D11.3 (due M28) and D11.4 (due M52), work will continue.

Current report provides a general overview on availability of health related administrative registers in countries. Countries tend to have several different types of health registers and most of them have national coverage. This provides good bases for morbidity and mortality monitoring and statistics. The circulated questionnaire was aimed at health-related registers; therefore other registers (e.g., pension registers, etc.) that might provide additional information on health-related questions were not reported. Extending request in coming years to other administrative registers should be considered.

In three quarters of the reporting countries, use of national level personal identifiers was reported for one or more registers. Vast majority of the registries report some unique identifier making the linkage to other data theoretically possible. There is several probability based record linkage methods which could be used when direct personal identifier is missing. These include for example deterministic record linkage[7] and probabilistic record linkage[8].

In most of the countries, it is possible to link data between registers. From the replies to this questionnaire, it is still unclear how many countries could link HBM/health survey data to registers to obtain mortality and morbidity follow-up. From the questionnaire administered with Task 11.1 to obtain information about health studies, 47% of studies reported that study participants could be linked to register data on individual level (Part A., Section 5.1.8).

Easy access to register data to determine baseline health profiles, and mortality and morbidity follow-up could provide relatively well coverage of data and cost-effective way to obtain this. Currently biggest limitations are lack of personal identification is some registers within countries and in some countries in general. Also when personal identification exists, national data protection regulations may prevent the use of register data to support survey based studies. Nordic countries have long traditions for register-linkage within registers but also to survey data.[9]

[7] Roos LL, Wadja A. Record linkage strategies. Part I: Estimating information and evaluating approaches. Methods of Information in Medicine 1991;30(2):117-123

[8] Blakely T, Salmond C. Probabilistic record linkage and a method to calculate the positive predictive value. International Journal of Epidemiology 2002;31(6):1246-1252

[9] United National Economic Commission for Europe. Register-based statistics in the Nordic countries. Review of best practices with focus on population and social statistics. 2007. United National.

6 Appendices

6.1 Appendix 1: HBM4EU Questionnaire about type and availability of health register

This questionnaire is part of the HBM4EU Project (https://www.hbm4eu.eu/). The main aim of the project is to coordinate and advance human biomonitoring in Europe to provide evidence for chemical policy making. One of many tasks is to get an overview of health registers in Europe. Thank you for answering the questions now coming up.

If you are providing information about more than one register, please fill in one questionnaire per register.

If you have questions, please contact Helle Margrete Meltzer, email HelleMargrete.Meltzer@fhi.no or phone +47 21 07 63 37. Please answer within deadline Friday October 20th, 2017.

2) *Country

❑ Austria

❑ Belgium

❑ Croatia

❑ Cyprus

❑ Czech Republic

❑ Denmark

❑ Finland

❑ France

❑ Germany

❑ Greece

❑ Iceland

❑ Ireland

❑ Israel

❑ Italy

❑ Latvia

❑ Lithuania

❑ Netherlands

❑ Norway

❑ Poland

❑ Portugal

❑ Slovakia

❑ Slovenia

❑ Spain

❑ Sweden

❑ Switzerland

❑ UK

3) Official name of the register

4) Type of register (please use one questionnaire per register)

❑ Birth register

❑ Cause of death

❑ In-patient hospitalizations

❑ Out-patient consultations

❑ Prescription of medications

❑ Register of malformations

❑ Disease specific register

❑ Other type of register

5) What other type of register?

❑ Pension

❑ Occupation

❑Education

❑ Other, please specify

6) What kind of disease-specific registry?

❑ Cancer

❑ Diabetes

❑ Coronary heart disease

❑ Other, please specify

7) Type of unique identifier

❑ Individual identification code (national level personal identifier)

❑ Register-specific individual identification (with possibilities to link to other (national) registries for research purposes)

❑ Non-person identification (possibility for e.g. probability linkage)

❑ Stored with pseudonym

❑ No identification at all

❑ Other, please specify

8) Are there any problems regarding linkage of this register to other registers?

9) What are the conditions for access to data? (Answer alternative Access/use requires informed consent of the participants of the HBM/health surveys/studies / Access/use requires approval by a privacy commission / Access/use requires approval by local ethical committee / Access/use requires approval from register owner / Access/use not allowed / Other)

❑ Researcher gets her own copy of the data file

❑ Researcher gets access to the data on the server of the provider

❑ Researcher gets the data ready analysed (the analyses are done by provider)

❑ Other (use text box or specify in e-mail)

10) What is the coverage of the register?

Possible alternatives are National, Regional (please specify), Other (please specify)

11) Are there any known problems with representativeness?

❑No

❑ Yes

12) Please specify the problems

13) What is the main purpose of the register?

14) Year from which data are available in electronic format (YYYY)

15) Year last update

16) Updating frequency of the register

❑ Annually

❑ Semi-annually

❑ Continuously

❑ Periodically

❑ Irregularly

17) Periodic updates: please indicate frequency

18) How many cases are included in the register?

19) What type of information does the register contain?

❑ Sex

❑ Date or year of birth

❑ Date or registration for condition

❑ Educational level

❑ Marriage status

❑ Number of children

❑ Income

❑ Occupational status

❑ Residence (e.g. rural vs urban)

❑ Type of exposure (e.g. industrial, in the home)

❑ Lifestyle indicators (e.g. smoking, diet)

❑ ICD-coding (International Classification of Diseases)

❑ ICPC-coding (International Classification of Primary Care)

❑ Other

20) Name of institution with responsibility for technical management of data

21) Name of institution with administrative management of data (may be different from institution with responsibility for technical management)

22) Are there costs for obtaining data?

❑ No

❑Yes

23) Please specify costs and, if possible, how costs are estimated

24) How long does it take on average to obtain data (after complete and satisfactory documentation has been submitted)?

❑ Less than 3 months

❑3-6 months

❑6-9 months

❑ 9-12 months

❑ More than 1 year

25) Are there issues or final comments you would like to share with us?

6.2 Appendix 2: Reported administrative registers

Country	Official name of the register
Austria	Causes of Death statistics
	Birth Statistics
	Austrian National Cancer Registry
Belgium	healthdata.be (is not a register but technical platform and service provider that will consolidate all patient registries in Belgium)
Croatia	Croatian National Cancer Registry
Cyprus	Causes of Death Registry
	Birth Registry
	HIV/AIDS Registry
	Cancer Register
Czech Republic	Czech National Cancer Registry
	National Register of Reproduction Health
	National Register of Hospitalised Patients
	Information system Deaths
Denmark	Danish Occupational Hospital Register
	Occupational Birth Register
Finland	Finnish Cancer Registry
	Care Register for Health Care
	Archive of death certificates
	Statistics on reimbursements for prescription medicines
	Medical Birth Register
	Register of Congenital malformations
France	Aquitaine Registry on Interventional Cardiology (ACIRA)
	Digestive cancers registry of Burgundy
	Côte d'Or registry of hematological malignancies (RHEMCO)
	French registry of pleural mesothelioma cases (MESONAT)
	Gironde register of primitive tumors of the central nervous system (Certified Registry 2012-2015)
	Registry on Breast Cancer Patients from The Antoine Lacassagne Centre (SEINON)
	Severe Obesity outcome Network (SOON)
	National cohort on the vascular Ehlers-Danlos syndrome (SEDv)
	Dijon Stroke Registry
	Registry of Congenital Malformations in Alsace (Certified Registry) (REMACA)
	Cancer Registry of French Guiana (certified cancer registry) (RCG)
	Registry of general cancers in Gironde
	Tarn Cancer Registry (Certified Registry 2010-2013) (RCT)
	General Registry on Cancer in the Poitou-Charentes Region (Certified 2013-2015 Registry)
	Somme Cancer Registry (Certified Registry 2013-2016)
	Registre Régional des Hémopathies Malignes de Basse Normandie (Certified register) (RRHMBN)
	ISERE CANCER REGISTER
	Doubs and Territoire de Belfort primitive malignant tumors register
	Cancer Registry of the Manche (certified registry)
	Bas-Rhin Cancer Registry (Certified Registry)
	Bas Rhin Ischaemic Heart Disease Register (Certified Register 2013-2016)
	Doubs and Côte d'Or viral hepatitis register
	Registry of general cancers in Lille and its periphery
	Hérault Cancer Registry (Certified Registry 2010-2013)
	Gironde register of hematologic malignancies
	Finistère Registry for Digestive Tumours (Certified Registry 2013-2016)
	Ile de la Réunion Congenital anomalies register
	The Côte d'Or registry for breast cancer and gynecological cancers (Certified Registry)
	The Brest REgistry of STroke (BREST) (certified register 2011-2017)
	Midi-PYRENEÉS CYTOPENIA REGISTRY (CARMEN)
	Limousin Region General Cancer Registry (CERTIFIED REGISTRY 2015-2020)
	Aquitaine Registry on Interventional Cardiology (ACIRA)
	Registry on Amyotrophic Lateral Sclerosis (ALS) in Limousin (FRALim)

Country	Official name of the register
Germany	Centre for Cancer Registry Data (Zentrum für Krebsregisterdaten)
Iceland	Icelandic Birth Register
	Icelandic Causes of Death Register
	Prescription drugs database
Ireland	National Cancer Registry of Ireland (NCRI)
	Computerised Infectious Disease Reporting
Israel	Cancer
	The Israeli National Cancer Registry
	National diabetes registry
	National stroke registry
Lithuania	Lithuanian Cancer Register
	Occupational Disease Register
	Register of blood donor
	Causes of Death Register
	Children health monitoring system
	Injury and Accident Monitoring
Norway	Medical Birth Registry of Norway
	Norwegian Registry of Pregnancy Termination
	Norwegian Cardiovascular Disease Registry
	Norwegian Cause of Death Registry
	Norwegian Prescription Database (NorPD)
	Norwegian Immunisation Registry SYSVAK
	Norwegian Surveillance System for Communicable Diseases (MSIS)
	Norwegian Surveillance System for Infections in Hospitals (NOIS)
	Norwegian Patient Registry
	Cancer Registry of Norway
	Registry of the Norwegian Armed Forces Medical Services
Poland	General Hospital Morbidity Study
Portugal	National Registry of Congenital Anomalies
Slovenia	Register raka Slovenije
	birth register
	Register umrlih
	Register hospitaliziranih
	Baza zdravil
Sweden	Cause of death register
	Register of prescription of medications
	Longitudinal integration database for health Insurance and occupational studies (LISA)
	The Swedish Medical Birth Register
	the National Patient Register
	The Swedish Cancer Registry
Switzerland	Enquête suisse sur la santé
	Swiss Multiple Sclerosis Registry
	National Institiute for Cancer Epidemiology and Registration (NICER)
	Swiss Neborn Screening
	Swiss Diabetes Registry - SwissDiab Study (SwissDiab)
	AMIS Plus (Acute Myocardial Infarction in Switzerland)
	Swiss Rare Disease Registry (SRDR)
	Causes of death statistic

Part C - Criteria for the use of existing biological samples from health studies for HBM analysis

1 Authors and Acknowledgements

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2 Background

In health surveys, especially in health examination surveys (HES), biological samples are commonly collected and often also stored for future use. This provides a possibility to extend the health surveys also to HBM if underlying criteria for the sample collection and supporting information is met.

This document will provide a short overview of what is known about availability of stored samples in national HESs in Europe, what are the key criteria for samples when analysing the HBM4EU 1st priority chemicals, and what are the criteria for the use of stored biological samples from health studies for HBM analysis.

2.1 Stored biological samples from national HESs

In 2007-2017, a national HES was conducted in 14 EU Member States.[10] In all these surveys, blood samples (Figure 1[33]) were collected and all except one country also stored sample for future use (Figure 3[33]). Urine samples were collected in nine countries (Figure 2[33]). Two collected 24 hour urine and eight spot urine samples. In four countries also urine samples were stored for future use (Figure 3[33]).

Figure 1: Blood sample collection

Figure 2: Urine sample collection

[10] Tolonen H, Paalanen L, Sääksjärvi K et al. Inequalities in availability of health information from national health examination surveys in EU Member States. October 2017. Available at: http://www.ehes.info/publications/Report_inequalities_health_information.pdf

Figure 3: Samples stored for future use

Additional to these national HESs, several smaller regional and disease specific surveys have been conducted in most of the EU Member States. Many of these have also collected biological samples and stored them for future use.

2.2 Sample collection and handling in health studies

Sample collection and handling procedures vary between health studies. In EHES, basic guidelines for blood and urine sample collection were provided.[11] These are guidelines for procedures and don't provide any specification for types of sample collection and storage materials such as tubes. Obviously each individual national HES may have their own variations from these and they have used sample collection material available for them. Therefore, these guidelines provide only indicative procedures on how sample collection in health studies could go.

In principle, EHES recommendations to collect blood samples also allows for long term storage to be used in the future. Since in EHES, collection of urine (preferably 24 hour) is optional, collection of urine samples is voluntary but recommended whenever possible.

[11] Tolonen H (Ed.) EHES Manual. Part B. Section 6. Collection of biological samples. 2nd 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

3 Requirements for 1st priority chemicals

Some chemicals are more prone for contamination during the sample collection, handling and storage than others. Table 1 provides a short overview of the key points to take into account during the sample collection and storage for HBM4EU 1st priority chemicals. Table 1 also provides sample type (preferred in bold) on which the chemical can be measured and minimum amount of sample needed.

Table 1: Sample type, amount of sample needed, storage and other special requirements for the HBM4EU 1st priority chemicals

Chemical	Sample	Amount of sample	Storage	Accepted materials	Special requirements
Phthalates/DINCH	**urine**/ spot or 24-h	0.25-0.50 ml	at least -20°C	PP- and PE-plastic	Phthalate-containing materials must be avoided
Bisphenols	**urine**/ spot or 24-h	0.25-0.50 ml	at least -20°C	PP- and PE-plastic	
Per-/Poly-fluorinated compounds	**serum**	0.25-0.50 ml	at least -20°C	PP- and PE-plastic	No special requirement, except fluorinated materials must be avoided
Flame Retardants	**urine**/ spot or 24-h, serum	5-10 ml urine, 1-2 ml serum	at least -20°C	PP- and PE-plastic	Potential target compound contamination by sampling devices should be explored before sampling if possible
Cd, Cr **Cd**	urine/spot blood	20 ml urine 5 ml whole blood	at least -20°C at least -20°C	PP- and PE-plastic A heparinized vacuum tube (e.g. Vanosafe®, Vacuette ® trace element)	Special-washed containers have to be used, and no preservatives may be added. Specimen is prone to contamination. Specimen is prone to contamination.
PAHs and air pollutants	**urine**/ spot or 24-h	5-10 ml	at least -20°C	PP- and PE-plastic	
Anilin family: Aniline, 4.4'-MDA, MOCA	urine/spot	20 ml	at least -20°C	PP- and PE-plastic	Specimens (Aniline, 4.4'-MDA and MOCA) are prone to contamination. Aniline: no preservative 4.4'-MDA: sulfamic acid added as

Chemical	Sample	Amount of sample	Storage	Accepted materials	Special requirements
					preservative MOCA: no preervative
Chemical mixtures	**urine**/ spot or 24-h, serum	5-10 ml urine, 1-2 ml serum	at least -20ºC	PP- and PE-plastic	Potential target compound contamination by sampling devices should be explored before sampling if possible
Emerging chemicals	**urine**/ spot or 24-h, serum	5-10 ml urine, 1-2 ml serum	at least -20ºC	PP- and PE-plastic	Potential target compound contamination by sampling devices should be explored before sampling if possible

4 Criteria

Since in many health studies biological samples, mainly blood and sometimes also urine, are collected and stored for future use, these provide a potential also for further analysis of HBM biomarkers. To be able to use stored samples from health studies for HBM analysis, following key points has to be checked and clarified:

Ethics	***Does the ethical approval and informed consent used for original data collection cover the secondary use of stored samples for HBM analysis?*** Depending on national guidelines and practices, samples collected in health studies may be used broadly for any public health purposes, for studies on specific diseases etc. If original ethical approval and informed consent doesn't allow the use of stored samples for HBM analysis, it may be possible to obtain new ethical approval for this secondary use of samples.
Study population	***Does the target population of the health study correspond to one needed for HBM analysis?*** When samples and data are used for the secondary purposes, we cannot change the definition and selection of the target population anymore. Therefore, it has to be assessed if the target population for the health survey is adequate for the needs of the HBM analysis.
Information collected by questionnaire(s)/health measurements	***What kind of information has been collected by questionnaire(s) about background, lifestyles and possible exposures in health studies, and are there any relevant health measurements included?*** Health surveys always have questionnaire(s) and health measurements to support and amend the results obtained from biological samples. Questionnaire(s) tend to have socio-demographic background information, information about diagnosed diseases and general health and also some lifestyle topics such as smoking, alcohol use and diet. Extent of the questionnaire(s) varies considerably between the surveys. Since similar information is also needed to support interpretation of the HBM analysis, it should be checked that all the relevant information is available and if not, does that limit the use of biological samples for HBM analysis.
Type of available samples	***What type of samples is available for the secondary analysis?*** In most of the health studies, blood (serum and/or plasma) is stored for future use. Collection of urine, especially 24 hour urine samples, is rarer in health studies. Therefore, availability of the samples may already set limitations for what could be measured.

Amount of available samples	***How much of the samples are available for the secondary analysis?*** Since each of the HBM analysis has a minimum requirement for the amount of sample needed, it should be checked how much of the sample(s) is available for the secondary analysis and is that enough for the planned HBM analysis.
Sample collection materials	***What type of materials was used for sample collection?*** If possible and information is available, it should be checked what kind of materials were used for sample collection to avoid possible contamination by the target compounds. In health studies, field blanks recommended for HBM studies are not usually used.
Sample handling procedures	***How samples were handled and processed on the field?*** Survey protocols should include details about sample handling and processing in the field. These should be checked to ensure that samples are handled the way that it does not result in problems for HBM analysis, including possible contamination with target compounds after collection of the samples.
Sample storage	***On what type of tubes and on which temperature samples were stored?*** Sample storage environment is essential for preservation of the biological samples and for what they can be used for in the future. Therefore, before making the decision about the use of stored samples, it should be checked on which type of tubes they are stored, on which temperature, have the samples been thawed and re-frozen, and does that affect the usability of samples for HBM analysis.
Access to the samples	***How one can get access to the sample and does that cost something?*** Usually every study has their own protocol and rules on how and for which types of analysis they provide access to the stored samples. When samples of interest have been identified, the conditions for access have to be agreed with the principle investigator or management board of that specific health study. It varies between countries and studies whether samples can be accessed without cost or whether the interested party has to pay for accessing the samples.

Part D - Guidelines for linking HBM and health studies

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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[12], experience from COPHES/DEMOCOPHES[13,14,15,16,17,18,19] and HBM protocols/recommendations[20] For HESs the guidelines and SOPs are taken from the EHES[21,22]. 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.

[12] 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[23] and Rao 2000[24].

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

[23] Porta M (Ed.) A Dictionary of Epidemiology. 5th edition. 2008. Oxford University Press
[24] 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 population register.	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 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[25].

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, 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.

[25] 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

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
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[26] 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.

[26] 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	-
		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

	HBM	HES
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 (20-25ºC) 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 (20-25ºC) 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 -	• Long term storage: Samples

	HBM	HES
	20°C but preferably -70°C or less	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})
	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[27] 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
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

[27] 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

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
Anthropmetrics	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.[28] 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 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.

[28] 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

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

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

Type of health measurements	EHES[29]		Esteban (France)[30,31]	GerES IV (Germany)[32,33]	CHMS (Canada)[34]	NHANES (USA)[35]	KNHANES (Korea)[36]
	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

[29] 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

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

[31] 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

[32] 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

[33] 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

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

[35] 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)

[36] 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	

4.2 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[37]; • OrganophosphorusFRs and PhosphateFRs has been measured in urine samples, respectively in a Swedish and Californian population[38],[39].	• PBDEs and HBCDs have potential neurotoxic, endocrine, and carcinogenic effects • Evidence of Firemaster 550 as an endocrine disrupting compound and obesogen

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

[38] 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

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
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	–

[39] 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

Overall conclusions

Human biomonitoring uses similar methods for data collection than health monitoring in general, i.e. both collect data through surveys. Regardless of the aim of the survey, there are several common elements on planning and organizations. During the planning, the target population has to be defined, sampling frame and scheme decided and actual sample selected. Organization includes the recruitment of survey participants and in most surveys also administration of questionnaires. Additional to these general issues, HBM and health studies both collect biological samples and do some health measurements such as anthropometric measurements.

Due to these common components, in many occasions it could be possible to combine HBM and health studies into one study using common survey logistics and personnel. This would provide wider aim for the survey but also save money by removing duplication of planning and fieldwork organization and management.

In Europe, we have a lot of nationally representative health studies which could be used also for HBM studies. It was evaluated what type of obstacles survey organizers would see for combining HBM and health studies. Most common obstacles were related to financial resources, difficulties in logistics due to large sample size and legislative issues. For potentials following the combination of HBM and health studies, utilization of existing infrastructure from health surveys, reduced costs, increase of sample size, access to wide range of details on nutrition and health were mentioned.

Addition to the combined HBM and health studies, possibility to link survey data to administrative health registers such as hospitalizations, cancers, and mortality would provide a cost effective way to collect baseline health profiles, and morbidity and mortality follow-up information. Even though many countries have national registers and personal identifiers which could be used for record linkage, national data protection regulations may prevent this.

We also provided general guidelines for combining HBM and health studies. Guidelines cover such issues sampling, ethics and data protection, requirement for personnel, survey contents (questionnaires, collection of biological samples and health measurements and analysis of biomarkers), and requirement of participants. These are general principles how combination could be done since final solutions may vary between countries due to level of previous experience on HBM or health studies, existing infrastructure, funding, national legislation etc.

Since most of the health studies conducted in Europe have also collected and stored biological samples for future use, it was investigated what would be a minimum criteria for their use in HBM analysis. This provides bases for use of biobanked samples from health studies and also sets ground for further collaboration between HBM and health entities in countries.

This deliverable will be updated in coming years as Deliverables D11.3 (due M28) and D11.4 (due M52). These updates will evaluate new health studies and biological samples from health studies which could potentially be combined with HBM studies, and obtain more information about administrative registers in Europe. Detailed standardized operating procedures for recommended health measurements which would be needed for combined HBM and health studies based on research questions relevant for 1st and 2nd priority chemicals will be prepared, excluding those already included in the EHES Manual.