HBM4EU science and policy for a healthy future

HORIZON2020 Programme
Contract No. 733032 HBM4EU

Description of the national programs

A strategy to collect EU wide HBM data

Deliverable Report

D 8.1

WP - 7 Strategies for recruitment and sampling &

WP 8 - Targeted field work surveys and alignment at EU level

Revision: February 2018

Upload by Coordinator: dd/mm/yyyy

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2 Abstract

The Deliverable 8.1 presents the strategy of HBM4EU to collect HBM data EU wide in a harmonised way to get comparable HBM data all over Europe.

We started from a theoretical approach on how to organise recruitment and sampling to obtain representative data for chemical exposure of the European population. The document addresses sample size and variability in the population. It provides strategies for assessing actual exposure of EU population, assess differences between EU countries, monitor time trends and evaluate policies.

Based on this strategy we have designed a sampling frame for assessing current chemical exposure in Europe to the HBM4EU priority compounds of the first round. A proposal was made for implementing it. The strategy considers to include countries from different European regions, and focuses on three age groups: children from 6 to 11 years old, adolescents between 12 and 19 years old and adults between 20 and 39 years of age. The implementation plan builds on the alignment of ongoing and planned studies.

As a first step we have made an inventory of national HBM studies that collected samples between 2014 until 2019 and that have the potential for participating in the first round HBM4EU human biomonitoring program. After a reality check with the responsible study centres we revised the plan to end up with a definitive proposal.

3 Introduction and background

One of the goals of HBM4EU is to obtain HBM data on the distribution of internal exposure to prioritised chemicals in the EU population, and to calculate reference values[1] for prioritised compounds. A coherent and representative dataset of HBM data is needed to statistically describe the internal exposure of the EU population and differences between EU countries, to evaluate time trends and the efficacy of policies over time. This information will also allow to calculate the proportion of citizens in a region or country that exceeds the EU reference value (based on the 95th percentile) of HBM values for a specific exposure biomarker or the proportion of the population that exceeds safe levels or health based guidance values[2] for specific exposure markers. This information will feed into chemical's risk assessment.

To address specific data requirements, partners of WP7 under task 7.2 have developed strategies for recruitment and sampling in order to attain European representativeness regarding age, sex, geographical distribution and socioeconomic status (SES) of participants. This document is inserted in this deliverable under section 3.

To obtain a EU wide coherent and comparable dataset from current exposures of the general EU population to the first set of priority substances (phthalates and DINCH, bisphenols (A, S, F), short chain per-fluorinated compounds, new generation flame retardants, cadmium, chromium VI, PAHs and anilines) WP8 partners have developed an approach to collect current HBM samples and data with EU wide coverage from existing, ongoing or planned national studies. Current was hereby defined as samples taken between 2014 and 2018. Although in some EU countries national programs exist that collect population representative values[3], within the EU no overarching strategy exists and studies are not harmonised and aligned to common goals. Such an overarching sampling strategy is presented under section 4. The implementation of the strategy is presented under section 5.

Section 6 lists ongoing and planned studies within the partner countries. This list has been compiled based on input of the partners of Task 8.1, the information from the inventory that was made under Task 7.1 and input that has been received from consortium partners after the presentation of the approach to align studies at the EU level at the consortium meeting in September 2017.

Based on a reality check and validation of the specific study information by bilateral contacts with the study directors, we have proposed to deviate from the original sampling strategy. Requirements regarding national wide coverage and covering 5 age groups cannot be met based on the ongoing and planned studies in Europe and taken into account budget requirements to set up completely new studies. An adapted proposal to incorporate studies that may contribute to the EU sampling frame in order to get harmonised HBM data with EU wide coverage is presented in section 7. The proposed list of studies is presented in Table 13. This proposal will be further elaborated in 2018. Included studies have to fulfil a set of criteria on ethics, privacy issues, sampling strategy, willingness to post harmonise their information and share single measurement data through the EU repository and IPCHEM[4]. Samples need to comply with control measures for

[1]Reference values are statistically derived values that indicate the upper margin of background exposure to a given pollutant in a given population at a given time. They may be used to assess the exposure of individuals or population groups in relation to the ubiquitous background exposure (Schulz, C., et al. (2007). "The German Human Biomonitoring Commission." International Journal of Hygiene and Environmental Health 210(3–4): 373-382.

[2] HBM values derived on the basis of toxicological and epidemiological studies. Angerer, J., et al (2011). "Human biomonitoring assessment values: Approaches and data requirements." International Journal of Hygiene and Environmental Health 214(5): 348-360.

[3] Choi, J., et al. (2015). "Major national human biomonitoring programs in chemical exposure assessment." AIMS Environmental Science 2(3): 782-802

[4] Willingness to post-harmonize their information and share single measurement data through the EU repository to answer HBM4EU research questions. The data shall be accessible to EU policy makers upon request (during and after the project); request for environment and health research purposes can not be refused.

influencing factors that may interfere with the analysis of the target parameters and analytical labs have to successfully complete the QA/QC scheme to perform the analytical determinations.

4 Strategies for recruitment and sampling to attain EU representativeness

The content of this section has been delivered already on August 14, 2017 under Task 7.2 of HBM4EU. The document has been integrated in the new deliverable D8.1.

4.1 Background on sampling

As specified in task 10.3, one of the aims of HBM4EU is to develop 'reference values[5]' of exposure biomarkers that are representative for the exposure variability in Europe. Due to logistic and financial constraints we can only include a 'sample' of the European population in our studies. However, representativeness means that this sample reflects the composition of the European population and the sampling strategy should be developed as such that, if we would re-do the sampling, we would obtain - within a predefined precision - the same values for the biomarkers. A sample reflects specific characteristics of the population from which it is drawn.

Sampling methods are classified as either probabilistic or non-probabilistic. A representative study population can only be achieved by the use of a probability sampling method. Probability methods include random sampling, systematic sampling, and stratified sampling. Stratified sampling is most commonly used in human biomonitoring (HBM) studies. By using a multistage probability sampling method, relevant strata can be set up for sampling. Typically primary sampling units (PSUs) should be identified, and in a next step even secondary sampling units (SSUs). For each PSU/SSU sample size should be determined. Typically this sampling can be done with probability of being selected proportionate to size (PPS sampling). It should be decided for each selection step if this PPS sampling will be applied. In this document we will propose **sampling approaches that will lead to representativeness** and we will elaborate on the sample size needed. A strategy for the calculation of the "reference values" is elaborated under task 10.3 and can be found in D10.2.

Representative sampling of the European population has been elaborated already by EUROSTAT and has been applied e.g. for the European Health Interview Surveys (EHIS) (European Commission and Eurostat 2013) and European Health Examination Surveys (EHES) (Tolonen 2016). These are good starting points. However, human biomonitoring has specific requirements and constraints that relate to logistics and to specificities of uptake of chemicals in the human body across populations and age groups. For example, in the US (Johnson et al. 2014), Canada (Giroux 2007; Statistics Canada 2011, 2012, 2015), Germany (Kurth et al. 2008; Schulz, Conrad, et al. 2007), France (Dereumeaux et al. 2017), Spain (Perez-Gomez et al, 2013) and Flanders (Belgium) (Baeyens et al. 2014; De Craemer et al. 2016; Den Hond et al. 2009) procedures are in place for representative sampling in HBM studies (See Appendix I) Sample Design Approaches for Representative Studies.

Europe

German Environmental Surveys GerES IV (2003-06) **and V** (2015-17): a two-stage design was used i.e. after drawing 167 communities (PSUs) according to degree of urbanization in Germany; participants were selected randomly from population registers according to birth year and sex. GerES IV and V consist of children of the age 3-14 and children/adolescents aged 3-17, respectively.

French national biomonitoring program: consists of two main surveys: (i) the perinatal component of the birth cohort **ELFE** (Etude Longitudinale Française depuis l'Enfance or 'French longitudinal study of children') implemented on a subsample of 4,145 pregnant women. Women were recruited in one of the 211 maternity unit (PSU) participating in the biological data collection. These PSUs have been chosen in order to guarantee the regional coverage expected to have

[5] Reference values are statistically derived values that indicate the upper margin of background exposure to a given pollutant in a given population at a given time (Schulz, Angerer, et al. 2007).

a representative sample of the pregnant women having given birth in continental France in 2011. Three waves of height days of recruitment were defined to take into account the seasonal variability of exposure. (ii) the **Esteban** study (Etude de SanTé sur l'Environnement, la Biosurveillance, l'Activité physique et la Nutrition or 'Health study on the environment, bio-monitoring, physical activity and nutrition') in which recruitment was based on a three stages probability sampling method. The PSU were towns or groups of towns for which probability of selection was proportionate to the number of dwellings. Stratification was operated on two variables: area (8 mains areas) and urbanization level (5 levels). The household was the secondary sampling unit. Two samples of households were built by random selection, one regarding households with at least one child between 6 and 17 years and another with only adults between 18 and 74 years. Phone numbers were randomly generated using the regional codification. At last, one only individual was randomly selected in each household including a total of 2,503 adults and 1,104 children.

Flemish Environment and Health Survey (**FLEHS III**) (2012-2015) (Schoeters et al. 2017): the 3th survey was performed in three age groups: mother-newborn pairs, adolescents of 14-15 years and adults between 50 and 65 years. Between 200 and 300 study participants per age group were recruited from the five provinces of Flanders. The number of participants per province was proportional to the number of inhabitants of that province. A stratified clustered multi-stage design was used to select participants within randomly selected PSUs: maternities for newborns, schools for adolescents and general practitioners groups for 50-65 years adults. Within each PSU, individuals were randomly selected. To account for seasonal variation, recruitment was spread over one year.

USA and Canada

In the National Health and Nutrition Examination Survey (**NHANES**) (2011-2014) (Johnson et al. 2014), a national representative US study, a four-stage sample design was used. In the first stage PSUs were selected from a list of all US counties. These PSUs were selected with probabilities proportionate to a measure of size. In the second stage a sample of area segments were selected. In the third stage dwelling units were selected, and in the fourth stage persons were selected. All eligible members within a household were listed, and a subsample of individuals was selected based on sex, age, ethnic origin, and income. From the 2846 PSUs, 15 sampling locations were selected, in which in total 5000 persons were recruited. They ended up with 87 subdomains of sex-age groups for different subgroups regarding ethnicity and income. They split up all ages from birth in a maximum of 12 age groups.

The Canadian Health Measures Survey (**CHMS**) uses a stratified three-stage sample design. The sampling unit at the first stage is a collection site, i.e. a geographical unit. At the first stage, collection sites are stratified in the 5 Canadian regions. Within each region, sites were sorted according to the size of the population. 16 sites were randomly selected using a systematic sampling method with probability proportional to size. The second stage sampling unit is the dwelling and at the third stage the person. The target sample size for cycle 3 was 5,700 respondents, so approximately 356 respondents per collection site. The sample was allocated amongst 6 age groups and by sex.

Some key elements are important to generate representative HBM descriptive values of environmental exposures in different subdomains of the European population.

Target population

The population segment in which the study will be performed or the so-called target population may depend on the pollutants under focus and in the context of HBM4EU, on the policy questions set out for each of the substances. Typical target population groups set out for HBM studies are: age group(s) (e.g. children, adolescents, adults, newborns, etc.), sex, risk-exposure groups (e.g. occupational), and income groups. Additionally, in case of HBM4EU, which is building on already running HBM studies, the gap analysis of task 7.1, will reveal lacking HBM data. Differentiation between the pollutants is needed depending on the age of susceptibility or differences in exposure.

Geographical coverage

Reference values should be obtained that are representative for the exposure variability in Europe. To obtain European representativeness, data from Northern, Western, Eastern and Southern-Europe should be included. Not all EU countries will be included and for some of the substances it may not be needed, in case the exposure is not so much geographically/lifestyle determined. Countries need to aim for a representative sample within that country. Representativeness per country can be reached without or with disaggregation i.e. sampling randomly according to population numbers or disaggregated according to sex, age, SES.

Longitudinal coverage

Depending on the characteristics of the pollutant different time points are needed to evaluate the changes in exposure over time in the EU population. One should consider the biological half-life of the pollutant, but also trends in chemical production volume, market and use in the population, or

restrictions, legislations. For each pollutant one should determine the frequency of sampling over time (every year, 5y, 10y, …). Depending on the available data from existing HBM studies, it can be determined for each pollutant what is already available and how frequent it has been measured so far. In a given sampling site, and over time, the sample should be as homogeneous as possible with respect to e.g. age, sex, SES, for focusing on the influence of "time". To evaluate whether exposures changes with time are consistent over Europe, some geographical coverage should be achieved as explained in the paragraph above.

Prevalence of detection of chemical in population

In case a substance is not measurable in some part of the population, the sample size needs to be larger. For each pollutant the percentage of people with levels below the limit of detection/quantification (LOD/LOQ) should be listed to have an indication about the prevalence of pollutant levels at or above LOD/LOQ in that specific target population.

Variance in measurements

The higher the variability (e.g. standard error, coefficient of variation (CV)), in the biomarker concentrations among individuals, the larger study population is needed to get a representative sample of the population. For each of the selected pollutants, the variability is different. Based on previous information theoretical sample size calculations are performed.

Sampling frame

The sampling frame is the list of the target population units from which the sample is drawn. The frame should be so that you get a representative population composition of that subgroup. As such the sampling frame depends a lot on the chosen target population, e.g. general population by population registers, school children by schools, working population by companies, newborn-mother pairs by maternities/hospitals.

All sampling strategies are compromises; ideally one should go for random sampling and attempt to include proportional representation of age groups and sex but also proportional representation of other variables that are considered important such as SES, occupational groups, residential degree of urbanization, ethnicity, patient groups etc. We will have to build a solid and realistic approach and decide which important domains we need to include and how this can be brought into practice.

4.2 Representative sampling in Europe

4.2.1 Primary sampling unit (PSU) and sampling within PSU (Table 1)

To set up a multistage probability sampling method in EU, we should decide on the PSU. In our view the most obvious is that **each participating country in HBM4EU is a possible PSU**. One reason is that the project reports already country-based results to WHO, OECD, EEA. Another reason is that HBM4EU builds on national programs and that national governments as program owners contribute 30% to the HBM4EU project. If a country however does not have a national program, it will be a substantial effort to set up a new national representative sample within HBM4EU. An alternative, which we don't support for the reasons mentioned above, could be the use of the NUTS classification (Nomenclature of territorial units for statistics) that is a hierarchical system for dividing up the economic territory of the EU for the purpose of the collection, development and harmonization of EU regional statistics, socioeconomic analyses of the regions, and framing of EU regional policies.

To attain an entire European coverage within HBM4EU, a European maximal scenario will be sampling in each of the 27[6] participating EU countries (PSUs). To ensure sampling feasibility and due to financial constraints, one may reduce the number of PSUs to about 12 to 15 European countries (cf. NHANES, CHMS (Appendix I)). These countries need to be distributed over all geographical regions in Europe. **Four geographical regions (clusters)** are defined according to the United Nations geoscheme for Europe (Figure 1): Northern Europe, Eastern Europe, Southern Europe and Western Europe. Another approach could be to pick by random sampling a set of countries, independent of geographical location. However, there is a chance that the selected countries do not represent properly the different geographical regions.

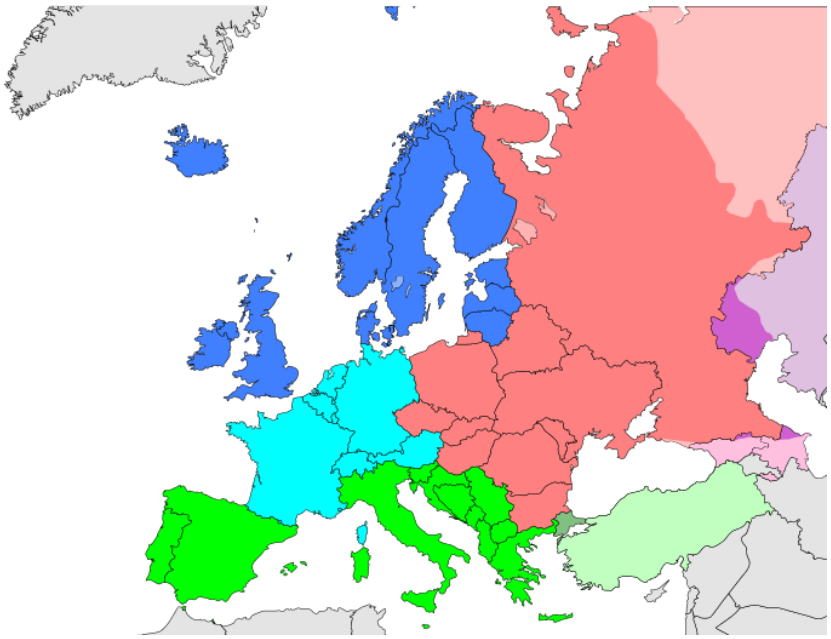

Figure 1: United Nations geoscheme subregions of Europe (*Armenia, Azerbaijan, Cyprus, Georgia, Kazakhstan, and Turkey are classified as being in Asia.*) Northern Europe Western Europe Eastern Europe Southern Europe (source: https://en.wikipedia.org/wiki/United_Nations_geoscheme_for_Europe)

Within HBM4EU the participating countries are attributed to the four different geographical regions as follows: ***Northern Europe***: Denmark, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, United Kingdom; ***Eastern Europe***: Czech Republic, Hungary, Poland, Slovakia; ***Southern Europe***: Croatia, Cyprus[7], Greece, Italy, Portugal, Slovenia, Spain; ***Western Europe***: Austria, Belgium, France, Germany, Luxembourg, The Netherlands, Switzerland. The number of countries per geographical region could be selected according to **population density (PPS)** or it could be decided that in each region the same number of PSUs will be selected. When using PPS, a better representation of the mean EU citizen will be attained, when selecting an equal number of countries per region, probably a better geographical representation is obtained.

To obtain a **representative sample in each country** (PSU), a different approach could be handled depending on the size of the country and the previous experience in national HBM studies. Within a country, sampling could be done in national geographical entities (e.g. provinces, communities, municipalities) with selection probability proportional to population size. Another approach could be random selection from population registers. Both choices have obviously different implications for organizing the fieldwork.

[6] Israel is not a European country
[7] Cyprus was allocated to Southern Europe

Table 1: Sample design approaches for HBM4EU, and the proposed 'first choice' for: clustering of the PSU, selection of the PSU, and sampling within the PSU (PSU: primary sampling unit, PPS: population size proportional sampling)

Sample design		HBM4EU	PRO	CONTRA
PSU	Proposal	Country	country-based reporting; national programs/governments	country has no national program
	Alternative	NUTS		
Clustering of PSU	Proposal	Geographical region	Geographical EU coverage	
	Alternative	No cluster – random sampling of country		No/less geographical coverage
Selection of PSU	Proposal	Proportional to population size (PPS)	Mean EU citizen	Less geographical representation
	Alternative	Equal number in each region	Better geographical representation	Only 3 participating countries from Eastern Europe
Sampling design in PSU	Proposal	PPS in geographical entity	Fieldwork can be organized easier	
	Alternative	From registers		Fieldwork

4.2.2 Sampling domains

The sampling domains for which at least specified reliability is desired in Europe (cf. NHANES, CHMS) are sex and age groups. Other stratifying factors could be socio-economic groups representing different SES or groups related to community size.

To cover the prevalence of 10% of specific SES in each sex-age domain, approximately 150 individuals[8] are needed per domain. The six age groups that could be targeted within the HBM4EU surveys are: 3-5y, 6-11y, 12-19y, 20-39y, 40-59y, 60-79y. This is comparable to the Canadian approach (Appendix I). The reasons for not selecting younger and older age groups are both increasing the logistic feasibility of the field work and to lower noise as e.g. physiology may differ more within those age groups. To cover SES variation, sampling could be done over different educational or income levels. For the educational classification, the International Standard Classification of Education (ISCED) can be used. ISCED is the reference international classification for organizing education programs and related qualifications by levels and fields. ISCED was developed by UNESCO in the mid-1970s and first revised in 1997. ISCED 1997 which had 7 levels of education was also implemented in (DEMO)COPHES. A further review led to ISCED 2011 with 9 levels of education. Eurostat's online tables on or by educational attainment level present data for three aggregated groups representing low – medium – high level of education. With lower educational level representing individuals with no to lower secondary education (ISCED 0-2), medium level of education individuals with upper secondary to post-secondary non-tertiary education (ISCED 3-4), and high level of education individuals with tertiary education and higher (ISCED ≥5). At this level of aggregation data are comparable over time for all

[8] Calculated according to the following formula:

$$N = \frac{Z^2 * (p) * (1-p)}{c^2}$$

where Z = Z value (i.e. 1.96 for 95% confidence interval), p = prevalence expressed as a decimal (i.e. 0.1) and c = confidence interval (=margin of error) expressed as decimal (i.e. 0.05).

participating EU countries except Austria where the reclassification of one education program from ISCED level 4 to level 5 caused the increase of tertiary educational attainment.

4.2.3 Adjustment of sample size according to biomarker variability

When calculating the sampling numbers for the different domains, we aim for representative sampling within Europe taking into account feasibility and practical aspects. However, these numbers will not take into account the **variability in the biomarker concentrations among individuals**. If the latter is high (high standard error, coefficient of variation (CV)), a larger study population is needed. In case the variation is known or can be predicted, the sample size formula for comparing two group means using a *t*-test for independent samples can be used to estimate the needed sample size for the comparison of pollutant concentrations in specific groups. The numbers assuring representativeness among Europe, might not allow statistical significance when comparing groups.

The following formula can be used to compare two groups: $n = Deff * \frac{2 f(\alpha, P)\sigma^2}{(\mu_1 - \mu_2)^2}$,

where n = number per group; f(α, P) = 7.9 for α = 0.05 and a power of 80% (β = 0.20); σ = standard deviation; (μ_1-μ_2) = difference to be detected; *Deff* captures the effect of not using a simple random sampling. The formula will be applied to the ln-transformed pollutant data because of the skewed distribution. So the mean and standard deviation in the formula refers to the ln-transformed data. By working on the ln-transformed data, the analysis is equivalent to comparing the geometric means of the pollutant (i.e. the untransformed data) between two groups. As an example, sample size calculations based on published DEMOCOPHES data for urinary BPA (Covaci et al. 2015), indicate that for BPA between roughly N=100 and N=300 individuals are needed to observe a 20% difference at the ln-transformed level among the participating European countries. Another important issue regarding the exposure levels in human samples is the **quantification possibility**. In case a substance is not quantifiable in some part of the population, the sample size needs to be larger.

4.3 Representative sampling within HBM4EU, tailored to specific objectives

In the HBM4EU project, for each of the prioritized chemicals several objectives are described in the scoping documents. Depending on the objective, different sampling approaches should be followed (Table 2). To achieve those objectives (new or modified) biomonitoring surveys can be set up, but it is also possible to use data available from past/ongoing biomonitoring surveys, which are (if needed) completed with newly recruited individuals up to the numbers presented in Table 2. IMPORTANT NOTE: **As earlier mentioned, the sample size for representative sampling as given in Table 2, needs to be adjusted according to the samples sizes needed for the specific chemical group because of expected population variability of the biomarker.**

4.3.1 Objective: Assessing actual exposure of EU population or differences between EU countries

For assessment of the actual exposure of the EU population, and as such obtain reference values representative for EU, over all six age groups (3-5y, 6-11y, 12-19y, 20-39y, 40-59y, 60-79y), respectively N=48,600 or N=21,600 participants would be needed in case of sampling in all countries (=complete scenario), or in 12 selected countries (=reduced scenario) of the four geographical EU regions. The number of individuals can be further reduced, in case only one

specific age group is selected to measure the actual European-wide exposure (N=3,600) (Table 2). For assessment of differences between countries, the same approach can be followed.

4.3.2 Objective: Monitoring time trends in exposure

The assessment of time trends of exposure should be done in a selected, as far as possible homogeneous age group, therefore reducing the number of individuals to N=3,600. Time trends can also be studied in one PSU or SSU per geographical region, which makes N=1,200 (Table 2), as there is no European representativeness aimed for in this setting. The only condition is that at least three time points of exposure data within this specific area are needed to assess a time trend, as such two previous time points should be available already.

4.3.3 Objective: Assessing impact of policy

The impact of policy measures (e.g. effect of regulation at EU level, differences in national regulations) can be studied over e.g. three (groups of) countries that clearly have a different policy, i.e. no regulation, phasing out, and complete restriction of a substance. In this scenario, N=900 individuals will need to be included to allow representative evaluation of the regulation (Table 2). Another possibility is to study the impact in one country (or more), before and after a legislation, allowing to compare the impact of changing legislation within the same 'background' of life style conditions in the country.

Table 2: Possible sampling schemes for HBM4EU surveys, tailored to specific objectives. The strategy which we recommend, is indicated with an asterisk (*). (SSU: secondary sampling unit)

Scenario	N° of countries	Sex	N° of age groups	N° per subgroup	Total number
Objective: Actual exposure in Europe or difference between countries/regions					
Actual EU-wide exposure in all age groups (complete scenario)	27	2	6	150	48,600
Actual EU-wide exposure in all age groups (reduced scenario)	12	2	6	150	21,600
Actual EU-wide exposure in specific age group (*)	12	2	1	150	3,600
Objective: Time trends follow-up					
Time trends follow-up in Europe	12[a]	2	1	150	3,600
Regional time trends follow-up (*)	4 SSU[a]	2	1	150	1,200
Objective: Impact of policy					
Impact of policy within a country (*)	1 (before & after)	2	1	150	600
Impact of policy differences among countries (*)	3 (no, median, strict policy)	2	1	150	900

[a] *with the precondition that for the selected country/SSU at least two previous time points of exposure data are already available.*

5 HBM4EU strategy to assess the internal exposure in EU citizens

Objective: sampling frame to assess current internal exposure in Europe

Sampling the entire EU population is not possible. Work package 7.2 partners propose here a strategy for sampling a subset of the EU population that can be considered as representative of the entire population. This strategy shall ensure that, if we would re-do the sampling, we would obtain - within a predefined precision - the same values for the biomarkers. Logistic and financial feasibility were considered important input to design the strategy.

The following population characteristics were identified as key factors for which considerable differences in internal exposure levels are expected: **geographical region, age, and sex.** For these factors we aim to establish representativeness of the EU population. It is likely that internal exposure levels from inhabitants from one country differ from internal exposure levels from inhabitants from another country; and that levels measured in younger versus older citizens and in males and females are different. This may be explained by e.g. different food habits, different regulation of substances between countries, different external exposure levels, different genetics, etc.

As age has a high resolution, we propose to further stratify into subsets to organise sampling. Age can be stratified into typical age group(s): newborns, younger children, children, adolescents, adults, and elderly.

- **Selection of a particular age group for sampling and analysis:** Ideally one should get exposure data from each age group, however if budget is restricted one may consider **to select a particular age group for sampling and analysis** which can then be considered a sentinel for exposure to the chemical, e.g. exposure levels are considered to be higher in that particular age group and/or the impact of exposure may be higher. We propose to distinguish the following age groups which are comparable to the approach used by Health Canada[9]. We also propose to select a particular age group for sampling and analysis depending on the chemical of interest. The reasons for not including younger as well as older age groups are two-fold: increasing the logistic feasibility of the field work and to lower the variability, for example physiology may differ more within those age groups. Although very young age (newborns and first years of life) is a very vulnerable and important age group, we did not include them here since there is already a lot of information on early life stressors, including environmental chemicals, that has been collected in newborns in the EU.

Table 3: Age groups considered in HBM4EU

Age groups considered in HBM4EU
Younger children (3-5 yrs)
Children (6-11y)
Adolescents (12-19 y)
Adults (20- 39y)

- **Collection of data in minimally 3 countries for each geographical unit:** To attain an entire European coverage within HBM4EU, a European maximal scenario will be sampling in each of the 27 participating EU countries. To lower the resolution, Europe can be stratified into four

[9]Giroux, S. 2007. 'Canadian Health Measures Survey: sampling strategy overview', *Health Rep*, 18 Suppl: 31-6

clusters, according to the United Nations geoscheme for Europe: Northern Europe, Eastern Europe, Southern Europe and Western Europe. We propose **to collect data in minimally 3 countries for each geographical unit** to establish European coverage (for each age group).

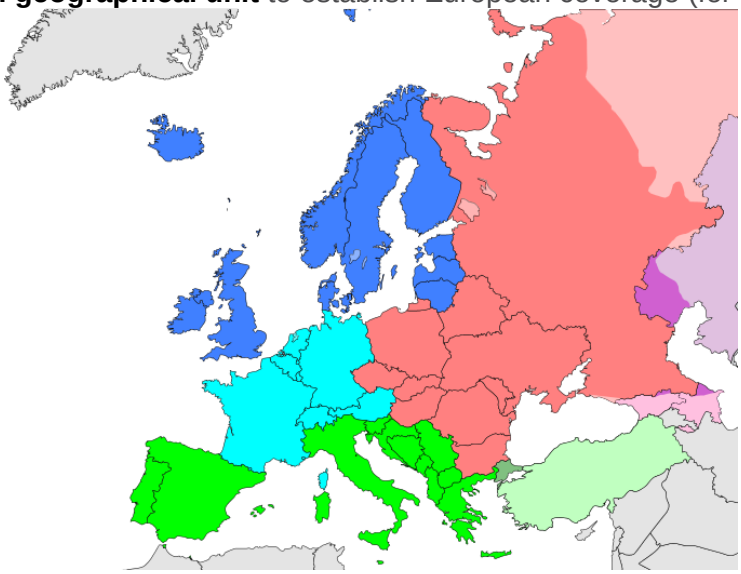

Figure 2: United Nations geoscheme sub-regions of Europe (Armenia, Azerbaijan, Cyprus, Georgia, Kazakhstan, and Turkey are classified as being in Asia.) Northern Europe Western Europe Eastern Europe Southern Europe (source: https://en.wikipedia.org/wiki/United_Nations_geoscheme_for_Europe)

In each participating country, and for each of the selected age groups we propose **to include 150 male and 150 female participants**. The sample size was chosen to ensure also inclusion of participants from different socioeconomic strata and from different community sizes (see 3.2). The sample size is indicative and may need further adjustment for the specific chemical group because of expected population variability of the biomarker.

In summary: to calculate EU reference values we propose to collect samples and data in minimally 12 countries, with 3 countries per geographical region. We propose at least one age group to provide information of a selected chemical. We propose to include per country and per age group 150 males and 150 females. This results in minimally 3600 EU participants that will contribute (see Table 4).

Objective: Monitoring time trends in exposure

The assessment of time trends of exposure should be done in a selected, as far as possible homogeneous age group. Time trends can be derived from a country representative population sample or from a subpopulation recruited in a geographical sub-region of a country(city, province, municipality). We propose to include at least one country or sub-region from each EU region (North, East, South, West) to achieve EU wide coverage. Another condition is that at least three time points of exposure data within the selected age group and area are needed to assess a time trend, as such two previous time points should be available already. **This results in minimally 1200 EU participants per time point (see Table 4).**

Objective: Assessing impact of policy measures

The impact of policy measures (e.g. effect of regulation at EU level, differences in national regulations) can be studied over e.g. three (groups of) countries that clearly have a different policy, i.e. no regulation, phasing out, and complete restriction of a substance. In this scenario, N=900 individuals will need to be included to allow representative evaluation of the regulation (Table 4). Another possibility is to study the impact in one country (or more), before and after a legislation, allowing to compare the impact of changing legislation within the same 'background' of life style conditions in the country. In each case the age group that will be selected depends on the chemical to be studied and the policy measure that has been taken.

Table 4: Possible sampling schemes for HBM4EU surveys, tailored to specific objectives. The strategy which we recommend, is indicated in red with an asterisk (*). (SSU: secondary sampling unit i.e. province, city, municipality,..)

Scenario	N° of countries	Sex	N° of age groups	N° per subgroup	Total number of participants
Objective: sampling frame to assess exposure in Europe or difference between countries/regions					
Actual EU-wide exposure in all age groups (complete scenario)	27	2	6	150	48,600
Actual EU-wide exposure in all age groups (reduced scenario)	12	2	6	150	21,600
Actual EU-wide exposure in specific age group (*)	12	2	1	150	3,600
Objective: Time trends follow-up					
Time trends follow-up in Europe	12[a]	2	1	150	3,600
Regional time trends follow-up (*)	4 SSU[a]	2	1	150	1,200
Objective: Impact of policy					
Impact of policy within a country	1 (before & after)	2	1	150	600
Impact of policy differences among countries (*)	3 (no, median, strict policy)	2	1	150	900

[a] *with the precondition that for the selected country/SSU at least two previous time points of exposure data are already available.*

(*)*the sample size for representative sampling as given in Table 4, needs to be adjusted according to the samples sizes needed for the specific chemical group because of expected population variability of the biomarker.*

6 Implementation plan for assessing current internal exposure levels of prioritised substances in EU citizens

The AWP2018 aims to collect HBM samples and data from national studies to derive EU representative current internal exposure data for the first group of priority compounds according to the agreed strategies for obtaining spatial and time trend HBM data for the EU (Objective 17).

The AWP2018 aims to analyse collected samples for filling the knowledge gaps identified for the first priority substances (Objective 18).

- We propose to consider samples taken during the last 5 years (2014-2015-2016-2017-2018) suitable for assessing “current” exposure
- According to the strategy developed under 3.1 we aim for contributions of representative data from at least three countries per geographical region and per age group of interest
- The data should be made available at the individual participant level including the accessory data on age, sex, SES, smoking behaviour, weight, height, BMI, sampling matrix, sampling time during the day, spot/repeated sampling, information on time of sampling in the year (season)
- Not all chemicals will be measured in all age groups but in the age group which is most of interest for exposure assessment- see proposal in Table 5
- The countries can contribute with:

    1. **Data**, provided that they fulfil minimal requirements for comparability
    2. **Existing samples,** that are obtained based on minimal requirements for comparability (WP7) and that will be analysed based on HBM4EU QA/QC program (WP9)
    3. **Organizing a new study,** following the HBM4EU protocols for regions and age groups where gaps are identified (WP8).

HBM4EU Task 7.1 has established a database with additional information on recent and ongoing HBM studies based on input from the national hubs. The database contains information on study design, target age group, available data, available samples, etc. The database still needs further exploration. Several HBM studies are representative at national level (for a particular age group). If permission obtained, these will provide the opportunity to build on the existing data and samples to compile the fundamentals of an EU representative dataset. Datasets and samples, being representative at national level, including at least 150 males and 150 females, and sampling within the time frame 2014-2018 will be used as selection criteria. As a starting point, we propose to select a particular age group for each of the prioritised chemicals, i.e. new generation flame retardants and phthalates in children (6-11y); per-fluorinated compounds and phthalates in adolescents (12-19y), bisphenols and occupational exposures in adults (20-39y) (see Table 5).

If not enough data are available, we propose to initiate new studies to fill the remaining data gaps for the set of prioritised substances. Data from all the age groups are welcomed, we propose to focus for new studies on new generation flame retardants and phthalates in children (6-11y); per-fluorinated compounds and phthalates in adolescents (12-19y), bisphenols and occupational exposures in adults (20-39y).

HBM data of Cat A substances[10] may be available for some EU regions, but we anticipate that there is a lack of Cat B and Cat C data for most, if not all of the EU regions.

Table 5: Overview of proposed sampling scheme

Geographical region of Europe **% of European population**	**North** **21%**	**West** **40%**	**South** **28%**	**East** **11%**	**Substances**
	Denmark Finland Iceland Ireland Latvia Lithuania Norway Sweden UK	**Austria Belgium France Germany Luxembourg The Netherlands Switzerland**	**Croatia Cyprus Greece Italy Portugal Slovenia Spain**	**Czech Republic Poland Slovakia Hungary**	
Representative samples					
Younger children (3-5y)	X,X,X	X,X,X	X,X,X	X,X,X	phthalates
Children (6-11y)	DK,X,X	FR*, DE,X	X,X,X	CZ,X,X	flame retardants, phthalates
Adolescents (12-19y)	SE,X,X	BE,DE,FR	ES,X,X	X,X,X	phthalates, per-fluorinated compounds
Adults (20- 39y)	DK,X,X	FR,X,X	X,X,X	CZ,X,X	bisphenols, occupational: Cr-VI, Cd, anilines, PAH
Elderly (60-79y)	X,X,X	X,X,X	X,X,X	X,X,X	
Time Trend analysis					
Age groups may differ	SE,DK	DE,BE	SI,X	CZ,X	phthalates, bisphenols, per-fluorinated compounds

X: country to be named

*From some countries we have preliminary information that they have HBM data or samples from the specific age group. In this case the country is named, but in depth research is further needed to investigate the possibility to share individual data and samples and whether they fit the requirements of HBM4EU.

[10] Cat A compounds, many studies were recently conducted. Data may be sufficient to provide an overall picture across Europe, interpretation of health risks is possible and we expect to answer important policy-related research questions within the first two years of the project., Cat B substances, spatial gaps have been identified. Cat C substances, very little or no data or toxicological/health effect information is available.

This schedule offers at least 36 slots for countries to participate in the framework of representative sampling. National hubs will be asked to express their preferences for the age group to which they want to contribute. If the age group of (60-79y) is included, this may offer 48 slots in total. Pregnant mothers were indicated to be a special interest group. They are included in the age category 20-39y – women of child bearing age. It is expected that women in this age group represent exposure levels that are also representative for the body burden of pregnant women. The presented frame acts also as a base line for targeted analysis of specific sub groups (e.g. occupational groups, hot spot areas, pregnant mothers – if desired). Also, younger children (age 3-5y) are an interest group e.g. for phthalates. Since there is not much experience with this age group we may postpone to include this in EU wide studies. Targeted studies in one or two countries may provide information for this specific age groups. For assessing occupational exposures, we will oversample the specific interest groups and will use the data collected in the general framework as control (background data) from the general population.

To investigate **time trends** a similar approach is proposed, with no need for country representative sampling, but with the requirement to follow time trends in the same age group, with the same personal characteristic in selected countries (regions, sub-regions). To attain EU coverage we need at least one country from each EU region (North, East, South, West). Additionally, we need information if participants take part at only one or more time points, and if it is a longitudinal/cohort study or if participants change over the years.

7 Inventory of national HBM studies potentially participating in the first HBM4EU human biomonitoring program

An inventory was made of the performed and planned studies in the period 2014-2018 based on the HBM4EU Task 7.1 database (on recent and ongoing HBM studies; input collected via the National Hubs), and information provided by partners of the current Task 8.1 (highlighted in green in the tables below). The goal of this inventory was to have a first rough picture of HBM studies in Europe and to assess where alignment is possible for further work in WP7 (field work protocols, questionnaires) and WP8 (practical organization). Data will be used according the objectives of HBM4EU and according the data management plan as developed in HBM4EU.

From the tables below (Table 6, Table 7, Table 8, Table 9) it can be deduced, that in each of the European geographical areas (North, East, South and West[11]), in at least two different countries, HBM samples were/are collected/running/planned on children and/or adults in the period of 2014-2018.

The type and number of HBM4EU priority substances measured (phthalates/DINCH, bisphenols, per- and poly-fluorinated substances, flame retardants, cadmium/chromium VI, polycyclic aromatic hydrocarbons and anilines) are varying considerably from study to study. There will be a need of analysing additional priority substance in existing samples, to fulfil the sample number requirements for each geographical area (set out in section 3). However, all studies have a HBM component and address exposure to environmental chemicals. We can build on these studies since they have samples available that can be used for additional analyses. As a next step, the study coordinators of the potentially interesting studies, were contacted bilaterally for validating the information and to check whether additional priority substance analysis is needed (aside from what is collected in the completed/running studies). This work has been carried out in fall 2017, in cooperation with WP7 and the National Hub Coordinator.

[11] United Nations geoscheme sub-regions of Europe - source: https://en.wikipedia.org/wiki/United_Nations_geoscheme_for_Europe

Table 6: Running and after 31/12/13 completed studies in Eastern European countries (in green highlighted are the inventorized studies of the partners in Task 8.1, dd: fall2017)

country	EU region	child (age)	N	adol. (age)	N	mother child (age)	N	adult (age)	N	elderly (age)	N	study	status study (1=completed, 2=ongoing, 3=planned)	start sampling	end sampling	population representative	which level?	Phthal. DINCH	Bisph.	PFCs	Flame retardants	Cd	Cr	PAH	anilin
Czech Repu	**E**	**0-11**	**7500**	**15-19**	**4000**		**5000**	**25-**	**1000**			**(C)ELSPAC:follow-up**	**2**	**01/04/1991**	**31/12/2030**	**1**	**Regional level (Brno)**	**1**	**1**	**1**	**1**	**0**	**0**	**1**	**0**
Czech Repu	**E**	**0-19**	**10000**				**10000**					**CELSPAC-TNG**	**2**	**01/04/2015**	**31/12/2030**	**1**	**Regional level (Brno)**	**1**	**1**	**1**	**1**	**0**	**0**	**1**	**0**
Czech Repu	**E**							**25-64**	**2160**			**Kardiovize Brno 2030, 1-2-3 (comp**	**1**	**2013**	**2018**	**1**	**Regional level (Brno)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Czech Repu	**E**									**65-79**	**550**	**Kardiovize Brno 2030, 1-2-3 (comp**	**2**	**2013**	**2018**	**1**	**Regional level (Brno)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Czech Repu	E	0-5	400			18-40	400					Impact of Environment to Newborr	2	01/07/2016	31/12/2021	1	Districts: exposed (Most	0	0	0	0	0	0	1	0
Czech Repu	E	5-11	350			18-45		18-65	300	61-100	197	CZ-HBM (NIPH)	2	04/02/2009	30/12/2016	1	4 regions (sub)urban	1	0	1	1	1	0	0	0
Czech Repu	E							20-29	95			Students study (CU+NIPH)	2	in time frame of CZ-HBM		0	2 urban areas	1	1	0	0	0	0	1	0
Czech Repu	E									55-	7000	HAPIEE Ageing cohort	2	2014	2015	1	8 towns	1	1	1	1	1	1	1	0
Czech Repu	E									55-	7000	HAPIEE Ageing cohort	2	2017	2018	1	8 towns	1	1	1	1	1	1	1	0
Hungary	E	9-10	250									InAirQ project	2	2017	2018	0		1	1	0	0	0	0	1	0
Hungary	E	6-10	240									Lead study	2	2018	2019	1	National level	0	0	0	0	0	0	0	0
Poland	E									55-	10000	HAPIEE Ageing cohort	2	2002	every 2-3y	0	1 town (Krakau)	0	0	0	0	0	0	0	0
Slovakia	E					mothers						PCB cohort	2	03/03/2002	10/04/2017	0		1	0	1	0	1	0	0	0
Slovakia	E	-3	290			18-	640					PRENATAL cohort	1	12/03/2010	30/11/2015	1	Regional level	0	0	1	1	1	0	0	0
Slovakia	E					15-30	166	15-30	83			BDEINTAKE	1	09/07/2013	30/06/2016	1	National level	0	0	0	1	0	0	0	0
Slovakia	E	1-12	572			19-42	51					UKF	2	01/01/2012	01/02/2017	0		1	0	0	0	0	0	0	0

Legend: EU region: E=Eastern Europe; population representative: 0=no, 1=yes

Table 7: Running and after 31/12/13 completed studies in Northern European countries (in green highlighted are the inventorized studies of the partners in Task 8.1, dd: fall2017)

country	EU region	child (age)	N	adol. (age)	N	mother child (age)	N	adult (age)	N	elderly (age)	N	study	status study (1=completed, 2=ongoing, 3=planned)	start sampling	end sampling	population representative	which level?	Phthal. DINCH	Bisph.	PFCs	Flame retardants	Cd	Cr	PAH	anilin
Denmark	N	0-1	200			20-40	200	20-60	200			CPHMINIPUB	2	17/05/2017	01/03/2019	1	Regional level	1	1	1	1	0	0	0	0
Denmark	N	0-7	2500			18-39	2500					OCC	2	01/01/2010	31/12/2028	1	National level	1	1	1	0	0	0	0	0
Denmark	N	5-20	46 ('14)									CPHPUB	1		01/01/2014	1	Regional level (capital re	1	1	1	0	0	0	0	0
Denmark	N					21-44	155					AC_Rigshospitalet	1	01/09/2012	30/08/2014	0		0	0	0	0	0	0	0	0
Denmark	N							18-59	75			BIOBRAND (firefighters)	2	04/06/2015	07/12/2016	0		0	0	0	0	0	0	1	0
Denmark	N							adults				BIOTRACK (train conductors	2	16/05/2017	23/11/2017	0		0	0	0	0	0	0	1	0
Denmark	**N**							**18-20 (M)**	**2100**			**Reproductive Health (RH) study**	**1**	**2006**	**2013**	**0**	**Wide Cophenhagen area**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
Denmark	**N**							**18-20 (M)**	**1200**			**Reproductive Health (RH) study**	**2**	**2014**	**2017**	**0**	**Wide Cophenhagen area**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
Iceland	N							17-45	3000			Development of a Personalized Nut	2	01/10/2015	01/10/2018	1	Regional level (the metro	1	1	1	0	1	0	0	0
Iceland	N							45-75	18000	67-102	5600	Icelandic Heart Association Reykjav	2	01/01/1967	01/01/2020	1	Regional level (Reykjavik	0	0	0	0	0	0	0	0
Lithuania	N							adults				Improvement of Infrastructure for E	3	01/01/2018	31/12/2019	0	intoxicated patients	0	0	0	0	0	0	0	0
Lithuania	N									55-	7500	HAPIEE Ageing cohort	2	2005	every 2-3y	0	1 town (Kaunas)	0	0	0	0	0	0	0	0
Sweden	N	9-10	106 ('15)									HÄMI-child (time series)	1	1986	2015	0		0	0	0	0	1	0	0	0
Sweden	N	4	113 ('15)									HÄMI-child (time series)	1	1996	2015	1	regional level Stockholm	1	1	0	1	0	0	1	0
Sweden	N	4,8,12	231									HÄMI-child (time series)	1	2008	2015	0		0	0	1	0	0	0	0	0
Sweden	**N**	**, 14-15, 17-18 yrs**			**1200**							**HÄMI-Riksmaten**	**2**	**2017**	**2018**	**1**	**National**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**
Sweden	N							20-29 (F)	60			HÄMI-adult (time series)	1	2014	2015	0		0	0	0	0	1	0	0	0
Sweden	N							50-59 (F)	54			HÄMI-adult (time series)	1	2014	2015			0	0	0	0	1	0	0	0
Sweden	N							20-29 (F)	100			HÄMI-adult (time series)	2	2017	2018	1	regional level Stockholm	0	0	0	0	1	0	0	0
Sweden	N							50-59 (F)	100			HÄMI-adult (time series)	2	2017	2018	1	regional level Stockholm	0	0	0	0	1	0	0	0
Sweden	N							20-92	660			HÄMI-adult	1	2014	2016	1	regional level Kalmar cou	0	0	0	0	1	0	0	0
Sweden	N							25-60	333 (2014)			HÄMI-adult (time series)	1	1990	2014	1	regional level Västerbott	1	1	0	0	1	0	1	0
Sweden	N							30 (F)	20 (2015)			HÄMI-adult (time series)	1	1972	2015	0		0	0	1	1	0	0	0	0
Sweden	N							20-38 (F)	30 (2014)			HÄMI-adult (time series)	1	1996	2014	0		0	0	0	1	0	0	0	0
Sweden	N							20-41 (F)	30/year			HÄMI-adult (time series)	1	2009	2014	0		1	1	0	1	0	0	1	0
Sweden	N							20-38 (F)	30/year			HÄMI-adult (time series)	1	2012	2014	0		0	0	1	0	0	0	0	0
Sweden	N							26-60	228 (2014)			HÄMI-adult (time series)	1	2009	2014	1	regional level Västerbott	0	0	0	0	0	0	0	0
Sweden	N							22-24	2000			BAMSE	2	2016	2018	1	Regional level	0	0	0	0	0	0	0	0
Sweden	N							40-73	110000			CSC&B, (or SMC and COSM)	2	01/09/1987		1	Regional sample but sho	0	0	0	0	1	0	0	0
Sweden	N							60-60	4232			60yo	2	01/01/1998		1	Regional level (Stockholr	0	0	0	0	0	0	0	0
UK	N							45-69	8856			HAPIEE	2	01/10/2002	31/12/2020	1	Town level but broadly fi	0	0	0	0	0	0	0	0

Legend: EU region: N=Northern Europe; population representative: 0=no, 1=yes

Table 8: Running and after 31/12/13 completed studies in Southern European countries (in green highlighted are the inventorized studies of the partners in Task 8.1, dd: fall2017)

country	EU region	child (age)	N	adol. (age)	N	mother child (age)	N	adult (age)	N	elderly (age)	N	study	status study (1=completed, 2=ongoing, 3=planned)	start sampling	end sampling	population representative	which level?	Phthal. DINCH	Bisph.	PFCs	Flame retardants	Cd	Cr	PAH	anilin
Croatia	S	0-0	50			-						CERRM	3	01/12/2017	01/03/2019	0		0	0	0	0	0	0	0	0
Croatia	S					19-43	290					CIPH	1	09/01/2015	03/01/2016	1	National level. In a cond	0	0	0	0	0	0	0	0
Cyprus	S	0-0				-		30-60	230			THYROCHEM	1	08/12/2014	13/10/2015	1	Regional level	0	1	0	0	0	0	0	0
Greece	S	0-4	2100			18-55	2100					HERACLES / EXHES Study	2	01/05/2017	31/05/2019	1	The study covers the two	1	1	0	1	1	0	1	0
Greece	S	7-8	179			-		30-51	179			CROME	1	16/05/2016	19/11/2016	1	Regional level (central Sl	0	0	0	0	1	0	0	0
Greece	S					25-45	10	21-50	50			HERACLES / Pilot Sensors	1	01/07/2015	31/12/2015	1	Representative adult wo	0	0	0	1	0	0	0	0
Greece	S	6-12	40					25-45	20			HERACLES / Aspropyrgos study	1	06/06/2015	10/06/2015	1	Regional level (Aspropyr	0	0	1	0	0	0	0	0
Greece	S							36-60	10	60-	81	HERACLES / Asopos	1	01/09/2015	31/12/2016	1	This is a typical populatic	0	0	0	0	1	1	0	0
Italy	**S**	**6-12**	**400**					**-**				**Apple-PAT-H**	**3**	**01/01/2018**	**31/12/2021**	**1**	**Regional level**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
Italy	**S**							**60-70**	**500**			**Apple-PAT-H**	**3**	**01/01/2018**	**31/12/2023**	**1**	**Regional level**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
Italy	**S**					**20-32wk, 18m**	**200**	**-**				**Apple-PAT-H**	**3**	**01/01/2018**	**31/12/2023**	**1**	**Regional level**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
Italy	**S**							**20-50**	**629**			**Veneto: Biomonitoraggio di Sostar**	**2**	**21/04/2015**	**31/12/2017**	**1**	**Regional level (it's a rep**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**
Italy	**S**							**35-69**	**392**			**SPoTT**	**2**	**23/04/2013**	**31/12/2018**	**1**	**The sample is represent**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**
Italy	**S**							**20-40**	**120**			**Taranto: Studi di Biomonitoraggio**	**2**	**01/10/2015**	**01/03/2016**	**1**	**Regional level**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**
Italy	**S**							**35-69**	**1177**			**ABC**	**1**	**01/04/2013**	**01/04/2015**	**1**	**Regional level**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**
Italy	**S**	**7-7**	**200**					**-**				**NAC II**	**1**	**01/04/2013**	**31/12/2016**	**1**	**Regional level**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
Italy	**S**	**7-7**	**280**					**-**				**NAC II**	**2**	**01/01/2016**	**31/12/2018**	**1**	**Regional level**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
Italy	**S**	**6-12**	**299**					**-**				**Taranto: Studi di Biomonitoraggio**	**1**	**01/03/2014**	**01/03/2016**	**1**	**Regional level**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
Italy	**S**							**25-35**	**80**			**Brescia**	**3?**	**01/11/2015**	**31/10/2017**		**Subnational**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Portugal	S	0-0						18-70	200			MycoPrev	2	24/04/2017	29/10/2020	1	National and occupation	0	0	0	0	0	0	0	0
Portugal	S	-						45-64	600			MinUrar	1	01/07/2002	24/04/2017	0		0	0	0	0	0	0	0	0
Portugal	S	0-17	935					18-64	3262	65-84	871	IAN-AF	1	08/04/2015	31/12/2016	1	Regional Level, NUTS II	0	0	0	0	0	0	0	0
Slovenia	S	2-4	849									Remediation Program of the Upper	2	01/01/2004	31/12/2022	1	Regional level (Upper Me	0	0	0	0	0	0	0	0
Slovenia	S	-						20-45	1000			SLO_HBM	1	01/06/2008	30/04/2014	1	National level	0	0	0	0	1	0	0	0
Slovenia	S	3-5	72									Refined Risk Assessment for Childre	1	20/04/2016	04/11/2016	0		0	0	0	0	0	0	0	0
Slovenia	S	6-9	150	12-15	150							SLOCRP2016	2	01/11/2017	01/03/2018	1	Regional level (North-ea	1	1	0	1	1	1	0	0
Spain	S							25-85	4000			MCC-SPAIN	2	01/01/2015		0		0	0	0	0	1	0	0	0
Spain	S							18-65	40	66-99		MODELBIS	2	01/09/2017	01/02/2018	1	Regional level	0	1	0	0	0	0	0	0
Spain	S							>16y				Andalusian Biomonitoring in Andalu	2	01/10/2013	31/12/2015	1	Regional level	0	0	0	0	1	0	0	0
Spain	S					mothers+						HEALS	2	04/04/2016	31/12/2018	1	European level	1	1	0	0	0	0	0	0
Spain	S											Study of Cadmium in Human Tissues	2	01/01/2007	31/12/2017	1	Regional level	0	0	0	0	1	0	0	0
Spain	**S**			**14-15**	**500**							**BEA study**	**3**	**01/09/2017**		**1**	**National coverage**	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**0**

Legend: EU region: S=Southern Europe; population representative: 0=no, 1=yes

Table 9: Running and after 31/12/13 completed studies in Western European countries (in green highlighted are the inventorized studies of the partners in Task 8.1, dd: fall2017)

country	EU region	child (age)	N	adol. (age)	N	mother child (age)	N	adult (age)	N	elderly (age)	N	study	status study (1=completed, 2=ongoing, 3=planned)	start sampling	end sampling	population representative	which level?	Phthal. DINCH	Bisph.	PFCs	Flame retardants	Cd	Cr	PAH	anilin
Austria	W							25-46	11			EAA (PFAS study)	1	01/08/2016	30/08/2016	0		0	0	1	0	0	0	0	0
Belgium	W	0-0						25-65	50			IMPASTRA	2	03/07/2016	28/04/2017	0		0	0	0	0	0	0	1	0
Belgium	W	9-12	259									EXPOPESTEN	2	15/04/2016	07/06/2016	0		0	0	0	0	0	0	0	0
Belgium	W	0-7	1400			18-42	1400					ENVIRONAGE	2	09/04/2012	31/12/2019	1	National level	0	0	0	0	1	0	1	0
Belgium	W							18-80	200			BIOPEST	3	01/10/2018	01/01/2019	1	Regional level	0	0	0	0	0	0	0	0
Belgium	W						150	-				3xG	2	01/01/2011	31/05/2015	1	Population of communit	1	1	1	0	1	0	1	0
Belgium	**W**			**14-15**	**600**			**-**				**FLEHS IV Ref Ado**	**3**	**01/07/2017**	**31/08/2018**	**1**	**Regional level (Flanders**	**0**	**1**	**0**	**1**	**1**	**0**	**1**	**0**
Belgium	W							18-76	252			Endocrine disruptors in a Belgian Ad	1	01/02/2015	01/05/2015	1	General population (wor	1	0	0	0	1	0	0	0
Belgium	W			14-16	208			-				FLEHS III Ref Ado	1	12/03/2013	03/12/2013	1	Regional level (Flanders)	1	0	0	0	1	0	1	0
Belgium	W							50-66	209			FLEHS III Ref Adult	1	26/05/2014	18/11/2014	1	Regional level (Flanders)	0	1	1	0	1	0	0	0
France	W	0-6	3421	12-13	600	18-44	3421					PELAGIE Mother-Child Cohort	2	01/04/2002	10/04/2017	0		1	0	1	1	0	0	0	0
France	W					18-	100					NEWPLAST	1	11/06/2014	16/09/2015	0		0	1	0	0	0	0	0	0
France	W	0-5	18000			18-49	18000					ELFE	2	01/04/2011	31/12/2017	1	National level (only Met	1	1	1	1	1	1	0	0
France	W	0-5	3000			18-49	3000					ELFE	2	01/04/2011	31/08/2017	1	Mainland national	1	1	1	1	1	1	0	0
France	W	0-5	470			18-50	470					SEPAGES	2	01/07/2014	30/09/2017	0		1	1	1	0	0	0	0	0
France	**W**	**6-12**	**709**	**13-17**	**397**			**18-65**	**2115**	**65-74**	**389**	**Esteban (by ANSP)**	**1**	**14/04/2014**	**31/03/2016**	**1**	**National level**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**
Germany	W							20-29				ESB	2	12/12/2016	07/05/2017	0		1	1	1	1	1	0	0	0
Germany	**W**	**3-14**	**1800**	**15-17**	**450**							**GerES V**	**2**	**04/01/2015**	**31/08/2017**	**1**	**National level and East/**	**1**	**1**	**1**	**0**	**1**	**0**	**1**	**0**
Germany	W	18-79	4000	18-79	4000							GerES VI	3	01/01/2018	31/12/2020	1	National level and East/\	1	1	1	0	0	0	0	0
Germany	W	0-17		18-28								KiGGS	2	01/09/2014	31/08/2017	1	National level	0	0	0	0	0	0	0	0
Switzerland	W							18-60	6000			SAPALDIA	2	28/04/2017		1	8 different communities	0	0	0	0	0	0	0	0
NL	W											Doetichem cohort	2	2018		0	village Doetichem	0	0	0	0	1	0	0	0
NL	W	0-6	3000	0-6	3000							Dutch YOUTH cohort	2	2015	~2025	1	National	0	0	0	0	0	0	0	0

Legend: EU region: W=Western Europe; population representative: 0=no, 1=yes

8 Adapted strategy to collect HBM data with EU wide coverage

In order to achieve EU wide coverage adaptations of the strategy will be necessary. First we provide some background on the adjustments that are needed. Then the proposed adaptations are further explained.

8.1 Background for the adaptation

We analysed the information from the questionnaire provided by Task 7.1. The information was complemented with information from bilateral contacts with consortium partners of Task 8.1 from BE, IT, DK, SL, FR, DE, ES, SE and consortium partners who explicitly expressed their interest to start studies that are aligned at EU level (CH, LT, NL) .

Although we extracted information from Q7.1 we realised that all the information needs to be consolidated. There were doubts about several studies that indicated that they have national representative samples. It is not clear whether the biomarker analysis that are mentioned were already performed. It is often not clear whether a randomised sampling strategy is used or whether subgroups of the population are targeted.

8.1.1 National representativity

Few national representative studies were identified that are ongoing or planned. Only the following countries have data/samples from national representative studies: FR, DE, SE while national representative studies are planned in Spain, Slovenia. There were concerns that within the time frame of HBM4EU it will be difficult to organise new national representative studies although it is desired.

There are several countries that report regional studies, these studies often take samples of the general population but only in a specific region of the country.

8.1.2 Number of countries to be included per EU region:

We proposed to include at least 3 countries per EU region. If we consider the available studies (ongoing/ planned- regional and national), in all regions we lack studies, the gaps are most noticed in the North and East.

8.1.3 Age categories

Upon analysis of the questionnaires we realised that the age groups with relevant samples/information are scattered among different age groups. We proposed to consider the following age categories : 0-2 y, 3-5y, 6-11y, 12-19y, 20-39y, 40-59y, 60-79y . The data of all age categories are welcomed in HBM4EU. A lot of regional studies seemed to exist with samples/data of 0-2y, 3-5y, and mothers. Available data from these age groups are collected, and it was proposed not to initiate new birth cohort studies in 2018-2019. We proposed to focus in 2018-2019 on collecting harmonised data and samples of the age categories: 6-11y, 12-19 y, 20-39 y.

8.2 Adaptations of the strategy

8.2.1 National representativity

Although national representativity should be kept as the golden standard (see protocol 7.2), it may not be feasible to initiate a large number of national representative studies within the frame of HBM4EU. Reasons are that the time frame to initiate and complete these studies will be beyond HBM4EU. Any additional study needs 50% co-funding from the partners of the consortium, it is doubtful that a lot of countries (partners) will be able to generate this co-funding. It was proposed to

include also regional studies provided that they sample the general population, both sexes and were not targeted to occupational subgroups, residents of hotspots near industrialised sites or patient populations.

Table 10: Alternatives for including only national representative studies

Alternatives	Pros	Cons
National	General population Can be used for comparisons between countries	Only few countries Few consortium partners are responsible for carrying out national studies
Regional	General population More study centres can be involved Aggregation per EU region is still possible	No comparison possible between countries

No financial consequences: We will strengthen regional studies, this may delay the onset of national representative studies?

8.2.2 Number of countries to be included per European region

The number of countries that, according to the scheme, are included in the North, West, South and East EU region, are respectively DK, FI, SE, IS, NO, LV, LT, EE, IE, UK for the North representing 21% of the EU inhabitants, BE, NL, FR, DE, CH, LU for the West representing 41%, HR, CY, EL, IT, PT, SL, ES for the South representing 28% and CZ, PL, SK, HU representing 11% of the EU inhabitants. Our initial proposal was to include 3 countries per EU region, but from the inventory information it can be seen that this is hard to attain in some regions.

Table 11: Alternatives for including 3 countries per EU region

Alternatives	Pros	Cons
3 countries /EU region	12 of the 27 countries that will contribute with data for a specific age group	In the East and North we have not enough countries with available studies in the selected age groups
N° of countries proportional to inhabitants of the region: 2 countries for the North 1 country for the East 3 countries for the South 3-4 countries for the West	Feasibility, proportional to the capacity in the region	In the East and North, strong country-specific contribution

8.2.3 Age categories

Data from all the age groups were collected however, the focus for new studies is on children (6-11y), adolescents (12-19y) and adults (20-39y).

Table 12: Specific age groups to consider

Alternatives	Pros	Cons
6-11y 12-19y 20-40y	Homogeneous adult age group, with a more similar health status Adult group of reproductive age is considered separately	Age group 40-60 is lacking No older age group (60+)
6-11y 12-19y 20-60y 60+	Easier to fit in adult datasets (no problem of overlap of data with 2 age categories) If this group serves as a base line for occupational exposure groups (T8.3), a wider age range is needed Older age group is present in several studies and may be vulnerable	More heterogeneous age groups will be less suitable for linkage to health data and effect markers No specific emphasis on reproductive age group (20-40y)

The HBM4EU management board decided:

- ✓ To include regional studies in order to obtain EU wide coverage of HBM data
- ✓ To keep the number of countries included proportional to the number of inhabitants of the EU region
- ✓ To restrict the inclusion of adults to the age group between 20 and 39 years old for which we want to recruit 300 samples.

9 Revised inventory of national HBM studies potentially participating in the first HBM4EU human biomonitoring program

The inventory was refined based on the bilateral contacts with the coordinators of the potentially interesting studies and the National Hub consultation.

Table 13: Overview of selected studies that fit the sampling frame to obtain EU wide coverage with recent (2014-2018) HBM exposure data

Geographical region of Europe	North		West		South		East	
% of European population	21%		40%		28%		11%	
Minimal number of countries to be included per age	2 countries		3 countries		3 countries		1 country	
Participating EU Countries and number of inhabitants (millions): Countries with relevant samples and data sets Countries who have no relevant samples and data sets or planned HBM activities	DK	*5.75*	AT	*8.77*	HR	*4.15*	CZ	*10.57*
	FI	*5.50*	BE	*11.36*	CY	*0.854*	PL	*37.98*
	SE	*9.96*	NL	*17.08*	EL	*10.75*	SK	*5.44*
	IS	*0.338*	FR	*67.02*	IT	*60.59*	HU	*9.8*
	NO	*5.26*	DE	*82.8*	PT	*10.3*		
	LV	*1.95*	CH	*8.42*	SL	*2.06*		
	LT	*2.85*	LU	*0.590*	ES	*46.52*		
	IE	*4.77*						
	UK	*65.64*						
Children (6-11y)	Norway_ NEBII Denmark_OCC		France_ESTEBAN Germany_GerEsV Netherlands_Dutch Youth cohort		Slovenia_SLOCRP Greece_CROME Italy_NACII		Hungary_InAirQ Slovakia_PCB cohorte Poland_Arsenic study	
Adolescents (12-19y)	Sweden_Riksmaten Norway_NEBII		France_ESTEBAN Belgium_FLEHS IV Germany_GerEsV Netherlands_PYJAMA		Slovenia_SLOCRP Greece _CROME Spain_BEA		Poland_Arsenic study	
Adults (20-40y)	Denmark_CPHMINIPUB (parents) Iceland_Nutrition survey Finland_FinHealth		France_ESTEBAN Switserland_New Study Belgium_ Adult cohort (Liège)		Croatia_CIPH Portugal_INSEF or IAN-AF		Poland_Arsenic study	

Table 14: Selected studies that fit the sampling frame to obtain EU wide coverage with recent (2014-2018) HBM exposure data within age category 6-11, (dd January 2018).

Age groups	EU region	Country	Study	N° samples	Matrix	Specific age	M/F	Status study (C: collected, O: ongoing, P: planned)	National/Regional
6 - 11 years	North	Norway	NEBII	>300	Whole blood, serum, plasma, spot urine	6 to 11	M/F	C: 2016-...	National
		Denmark	OCC	300	Whole blood, serum, urine	7	M/F	O: 2017-...	Regional (Fyn region)
	East	Hungary	InAirQ	±240-300	Urine	9, 10	M/F	O: Nov 2017- March 2018	National
		Slovakia	PCB cohort	300	Urine	10, 11	M/F	C: 2014-2017	National
		Poland	Arsenic study	>300	Urine	7 to 11	M/F	O: 2017-...	Regional (Głogów)
	South	Slovenia	SLOCRP	±150	Urine, blood, saliva, hair	6,7,8,9	M/F	P: 2018	National
		Greece	CROME (extension)	±150	Urine, blood, hair, (exhaled breath)	6 to 11	M/F	P: 2019	National
		Italy	NACII	300	urine	7	M/F	O: 2016-2018	Regional (Trieste)
	West	France	ESTEBAN	300	Urine, whole blood, serum, plasma, hair	6 to 11	M/F	C: 14/04/2014 - 31/03/201	National
		Germany	GerESV	300	Urine, (blood)		M/F	C: 2015 - 2017	National
		The Netherlands	Dutch Youth cohort	300	N.A.	N.A.	M/F	N.A.	N.A.

Table 15: Selected studies that fit the sampling frame to obtain EU wide coverage with recent (2014-2018) HBM exposure data within age category 12-19, (dd January 2018).

Age groups	EU region	Country	Study	N° samples	Matrix	Specific age	M/F	Status study (C: collected, O: ongoing, P: planned)	National/Regional
12 - 19 years	North	Sweden	Riksmaten	>300	Urine, serum, whole blood	12, 16, 19	M/F	P: 2017-2018	National
		Norway	NEBII	>300	Whole blood, serum, plasma, spot urine	12 to 19	M/F	C: 2016-...	National
	East	Poland	Arsenic study	>300	Urine	12 to 19	M/F	O: 2017-...	Regional (Głogów)
		Czech Republic	Pilot study school children	300	Urine, (blood)	12 tot 15	M/F	P: 2018	Regional
	South	Slovenia	SLOCRP	±150	Urine, blood, saliva, hair	12,13,14,15	M/F	P: 2018	National
		Greece	CROME (extension)	±150	Urine, blood, hair, (exhaled breath)	12 to 19	M/F	P: 2018	National
		Spain	BEA	>300	Urine, blood, hair	14, 15, 16	M/F	O: 1/09/2017-31/01/2018	National
	West	France	ESTEBAN	>300	Urine, whole blood, serum, plasma, hair	12 to 19	M/F	C: 14/04/2014 - 31/03/201	National
		Belgium	FLEHS IV	±300	Urine	14, 15	M/F	P: 2018	Regional (Flanders)
		Germany	GerESV	>300	Urine, (blood)	12 to 17	M/F	C: 2015 - 2017	National
		The Netherlands	PYJAMA	300	N.A.	N.A.	M/F	N.A.	N.A.

Table 16: Selected studies that fit the sampling frame to obtain EU wide coverage with recent (2014-2018) HBM exposure data within age category 20-40, (dd January 2018).

Age groups	EU region	Country	Study	N° samples	Matrix	Specific age	M/F	Status study (C: collected, O: ongoing, P: planned)	National/Regional
20 - 40 years	North	Denmark	CPHMINIPUB (parents)	>200	Urine, whole blood, serum, plasma, hair	N.A.	M/F	P: 2018	Regional
		Iceland	Nutrition Survey	±200	Urine, whole blood, plasma	N.A.	M/F	P: 2018	National
		Finland	FinHealth	>300	Urine, blood	N.A.	M/F	C: Jan-July/2017	National
	East	Poland	Arsenic study	>300	Urine	N.A.	M/F	O: 2017-...	Regional (Głogów)
		Czech Republic	ELSPAC	300	N.A.	N.A.	M/F	P: 2018	Regional
	South	Croatia	CIPH (extension) New study	±300	Urine, blood	N.A.	M/F	P: 2018	National
		Cyprus			N.A.	N.A.	M/F	N.A.	N.A.
		Portugal	INSEF	>300	Whole blood, serum, plasma, DNA	25 - ...	M/F	C: 2015	
		Portugal	IAN-AF	±50	Urine	N.A.	M/F	C: 2015	National
	West	France	ESTEBAN	>300	Urine, whole blood, serum, plasma, hair	N.A.	M/F	C: 14/04/2014 - 31/03/201	National
		Switserland	New Study	±300	N.A.	N.A.	M/F	P: 2018	N.A.
		Austria		±150	N.A.	N.A.	M/F	N.A.	N.A.
		Belgium	Adult cohort (Liège)	200	Urine	N.A.	M/F	C: 2015	Regional (Wallonia)

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Appendix I. Sampling Design approaches for Population Representative Studies

STUDY	Population	Population size	Primary Sampling Units (PSUs)	Number of selected sampling locations	Primary Sampling Design	Total number or individuals	Sampling domains	Number of groups in each domain
NHANES 2011-2014	US	321.4 million (2015)	2846 counties (smaller counties taken together)	60 (15 per year)		5000/year (ca. 333/location)	age	12 (<1, 1-2, 3-5, 6-11, 12-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, >=80y)
							sex	2
							etnicity/income	5
CHMS	Canada	35.85 million (2015)			chance to be selected proportional to population size			
Cycle 1 (2007-2009)			257 collection sites	15		5000	age	5 (6-11, 12-19, 20-39, 40-59, 60-79y)
							sex	2
Cycle 2 (2009-2011)			257 collection sites	18		5700	age	6 (3-5, 6-11, 12-19, 20-39, 40-59, 60-79y)
							sex	2
Cycle 3 (2012-2013)			360 collection sites	16		5700	age	6 (3-5, 6-11, 12-19, 20-39, 40-59, 60-79y)
							sex	2
EHES	Europe	510.1 million (2015)	EU countries			min 4000 persons/country	age	4 (25-34, 35-44, 45-54, 55-64y)
							sex	2
GerEs (IV/V)	Germany	80.78 million (2014)	150/167 communities	150/167	Cox procedure for community sampling with sampling probability proportional to population size [Cox LH: A Constructive Procedure for Unbiased Controlled Rounding. J Am Statistical Association 1987, 82(398):520-524.] ; two-stage (1. urbanization 2. age)	1,790 /approx. 2,200	age	GerES IV: 4 (3-5y, 6-8y, 9-11y, 12-14y) GerES V: 6 (3-5y, 6-8y, 9-11y, 12-14y, 15-17y - provisional, subject to changes)
							sex	2
ELFE	France	65.86 million (2014)	Maternity	211	Maternity had been chosen to garantuee the regional coverage expected to have a representative sample of the pregnant women in continental France in 2011	4,145 pregnant women		
Esteban	France	65.86 million (2014)	Towns or groups of towns	169	PSU Stratified on two variables : Area and Urbanisation	2,503 adults and 1,104 children	Age, sex, Education level, Living alone, Children	For adults : Age (4 levels : 18-29; 30-44; 45-59; 60-74) Sexe (H/F) Education (4 levels) Living alone (Yes/No) Children in household (Yes/No) For Children : Age : 3 levels (6-10;11-14;15-17) Sexe (H/F) Education (4 levels) Living alone for parent (Yes/No)
FLEHS	Flanders (Belgium)	6.4 million (2015)	newborns: maternities	1 per province	maternity selected at random one per province number of participants/maternity: chance to be selected proportional to population size in that province			
HBM4EU	Europe	510.1 million (2015)	26 participating countries	15	selection of countries within geographical regions (N, E, W, S) according to population density		age	6 (3-5, 6-11, 12-19, 20-39, 40-59, 60-79y)
							sex	2
							SES (educational level -> ISCED)	7 -> 3