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EXTERNAL SCIENTIFIC REPORT

Review of the state of the art of human biomonitoring for chemical substances and its application to human exposure assessment for food safety[1]

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ABSTRACT

Human biomonitoring (HBM) measures the levels of substances in body fluids and tissues. Many countries have conducted HBM studies, yet little is known about its application towards chemical risk assessment, particularly in relation to food safety. Therefore a literature search was performed in several databases and conference proceedings for 2002 – 2014. Definitions of HBM and biomarkers, HBM techniques and requirements, and the possible application to the different steps of risk assessment were described. The usefulness of HBM for exposure assessment of chemical substances from food source, and for the implementation of a systematic Post Market Monitoring (PMM) approach for regulated chemical substances was evaluated. An inventory of HBM programmes provides detailed information about study design, analytical methods, reference values (RV) and biomarkers used. Environmental monitoring and associations between HBM values and food, as well as coverage of substances and remaining deficits are highlighted. The review of study results provides information on emerging chemicals, higher exposed and particularly vulnerable populations.

Conclusions: HBM can bring added value for chemical risk assessment in food safety areas (namely exposure assessment), and for the implementation of a systematic PMM approach. But further work needs to be done to improve usability. Major deficits are the lack of HBM guidance values on a considerable number of substance groups, for which health based guidance values (HBGVs) have been developed, insufficient knowledge regarding exposure sources, and incomplete dietary intake assessment. Recommendations: We recommend to foster development of HBM based guidance values and validated analytical methods/BMs, stronger inclusion of substances of interest for EFSA in European surveys, expanded monitoring of highly exposed and vulnerable subgroups, uptake of EFSA guidance concerning dietary intake assessment, as well as biobanking, surveillance synergies and targeted research, and an EU wide collaborative approach to support the future use of HBM in PMM.

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KEY WORDS

Human Biomonitoring; risk assessment; food; HBM programmes; validated biomarker of exposure; reference values; questionnaire

SUMMARY

This report is based on an extensive literature search in major relevant databases such as Medline (Pubmed) and SCOPUS, in recent conference proceedings of 19 related scientific societies, in grey literature and in publicly available information from scientific research studies as well as on supplemental searches for specific topics from January up to October 2014.

The search focussed on methodological studies and reviews discussing the use of human biomonitoring in risk assessment, on observational studies assessing the association between chemical body burden and food intake, on cohort studies and cross-sectional HBM surveys and on reviews or studies regarding reference and health-based guidance values (HBGVs), emerging chemicals and vulnerable population groups. From the 19,704 hits, the project team identified 1,201 eligible references and eventually selected 252 references (235 full text publications) for this report.

As a first part it provides an overview on human biomonitoring (HBM) and possible application to human risk assessment via a critical review of literature to address advances in HBM activities and its application to chemical risk assessment over the last decade with a particular focus on applications to the food safety area. This includes the definition of HBM, a description of HBM techniques and requirements, the possible application of HBM to the different steps of risk assessment, an in-depth evaluation on the usefulness of HBM for exposure assessment of chemical substances from food source including strengths and limitations and the implementation of a systematic Post Market Monitoring (PMM) approach for regulated chemical substances (objective 1). The second part of this report provides an inventory of the different HBM surveillance programmes/initiatives at national, EU and international levels along with a comparative analysis in order to evaluate the added value for chemical risk assessment (objective 2). Finally, the report provides a review of results from HBM studies, allowed identifications of emerging chemicals or chemical classes of possibly higher exposed sub-groups or specific vulnerable groups of a population and of other issues relevant for EFSA's risk assessment activities together with an inventory of validated biomarkers of exposure to chemicals that can be found in the diet identified through HBM (objective 3).

The overview on HBM and its possible application to human risk assessment shows that there is no official definition of HBM. HBM is commonly understood as a method for assessing human exposures to natural and synthetic compounds based on analysis of biomarkers (BM). BMs of exposure are chemical substances or their metabolites measured in human biological matrices such as blood, urine, hair, adipose tissue, teeth, saliva, breast milk or nails. HBM techniques and requirements comprise the development of a study protocol, recruitment of study persons, informed consent, sampling and thorough sample processing, chemical analysis, data management, interpretation and communication. HBM can be applied to the different steps of risk assessment, but its obvious core role lies within human exposure assessment. The evaluation on the usefulness of HBM for exposure assessment of chemical substances from food source shows that the main strength of HBM is the fact that it is the only available tool that integrates exposures from all sources and provides data to epidemiology. HBM can demonstrate trends and changes in exposure, establish distribution of exposure among the general population, identify vulnerable groups and populations with higher exposures and emerging chemical risks. It can reduce the assumptions regarding consumption rates and is often more specific and sensitive than environmental monitoring in assessing the degree of recent and past exposure to chemicals. Major limitations for use of HBM in risk assessment are the facts that HBM alone cannot

provide information about the source of exposure or how long a chemical has been in the body, and HBM raises ethical and privacy issues because it involves human samples. HBM data need to be combined with other data and tools for interpretation in risk assessment. This includes environmental monitoring data, reverse modelling or HBM-related guidance values that translate a biomarker concentration into established guidance values from risk assessment (e.g. ADI/TDI, RfD). HBM is considered useful for the implementation of a systematic Post Market Monitoring (PMM) approach for regulated chemical substances because it could verify risk assessment results. It could be used to monitor real exposure and could detect exposure in case of unexpected complaints. The strength and limitations are similar to those from exposure assessment.

The inventory of the different HBM surveillance programmes/initiatives at national, EU and international levels comprises a detailed evaluation of 37 programmes in the European Union and around the world in terms of funding, study frequency and design, study population and recruitment, analysed chemicals and matrices, Biomarkers, analytical methods and biobanking, results and interpretations, any additional measurements of exposure sources, communications of results and policy support. This inventory provided the basis for a comparative analysis among the HBM programmes. The comparative analysis of the results shows that HBM programmes in most cases are funded by the respective government and are mostly cross-sectional surveys with several longitudinal large-scale birth-cohorts established namely in Denmark, Norway, France and Japan. Long-term regular surveillance system currently exists in the USA, Germany, Czech Republic, Flanders, Slovenia, and South Korea. While retrospective analysis of time trends based on bio-banked samples is currently only conducted in Germany, there are systematic biobanks from the Danish birth cohort study and the Canadian national survey. The majority of investigated HBM programmes is performed with adults, but also elderly, adolescents, children and new-borns are increasingly included. Study populations range from less than 1000 to more than 100,000 participants. Metals (particularly cadmium, lead, and mercury), PCBs, and cotinine are the most studied chemicals among the investigated HBM programmes, whereas mycotoxins, fungus-specific IgE, a few selected fungicides, perchlorate, nitrosamine and alkaloids have only been measured in single programmes. The broadest range of chemicals has been covered in the investigated programmes of the USA, Canada, Flanders, France and Japan. Reference values (RV) tend to be stratified by region, age and gender or life-style and can be compared with HBM-related guidance values when available. Blood and urine are by far the most approved biological matrices. However, human milk is also used for persistent organic pollutants, and hair and saliva have become important specimens in more recent years. While many HBM programmes include investigation of exposure sources or additional environmental monitoring, only 7 out of 37 programmes included measurements in food and drinking water. Food-related questions have been used in roughly 60% of the investigated studies, but customised 24-hr food recall method according to EFSA recommendations were only used in France, Czech Republic, the USA and South Korea.

The review of the results from the investigated HBM studies shows that HBM contributed to the identification of pyrethroids, herbicides, parabens, acrylamide/glycidamide, and nitrosamine and nitrate as smoke flavouring as well as perfluorinated compounds (PFCs) as emerging chemicals in the sense of the EFSA definition of emerging risks. In the past HBM was able to raise awareness for unexpected risks from other substances groups such as heavy metals, dioxins and PCBs, brominated flame retardants, carbamates, and mycotoxins have been investigated as "emerging" chemicals. Pregnant women and foetuses, children, and in some cases elderly have been identified as possibly higher exposed sub-groups or specific vulnerable groups for specific groups of chemicals, including some with food as major exposure source. Higher socio-economic class can either be a protective or a risk factor to contamination from food source. Investigated programmes established reference values (RV) for roughly 70 substance groups, namely for various metals, PAH, phthalates, dioxins, pesticides, as well as for aromatic amines, perfluorinated chemicals, environmental tobacco smoke and

volatile organic compounds. Germany and the USA have developed HBM values and biological equivalent values, respectively, for direct comparisons between these values and values determined from HBM programmes.

Validated BM of exposure shall reliably and accurately reflect target tissue concentrations, and shall be measurable in a robust, consistent and reproducible way. This requires a validation of the analytical test methods, demonstrating besides other appropriate selectivity and specificity, accuracy, precision, reproducibility, and analytes stability. BM used in population studies are generally covered by standard operating procedures as well as by internal and external quality assessment schemes, and follow the agreed validation criteria. BM meeting these criteria are available for roughly 20 substance groups. For metals, dioxins, furans, PCBs, PBDEs, parabens, mycotoxins, etc. the BM is the parent substance measured in the matrices. For phthalates, polyaromatic hydrocarbons, organophosphate, organochlorine and pyrethroid pesticides, acrylamide, and nitrosamine, validated BM of exposure are metabolites or haemoglobin adducts. 8-OHdG is envisaged to be analysed as BM of oxidative DNA damage. However, there is a considerable lack of BM, HBM related guidance values and RVs for a wide range of substances, for which HBGVs have been developed by the European Food Safety Authority, the Food and Agriculture Organization of the United Nations in conjunction with the World health Organisation or by the US Environmental Protection Agency. These deficits are particularly strong for several classes of currently used pesticides, mycotoxins, veterinary pharmaceuticals, food contact materials and food additives, flavouring agents, food preservatives and also include nitrosamine, perchlorate, 3-MCPD, or mineral oil hydrocarbons.

BMs of effect and the "exposome" as attempts to establish high throughput tools and to close the causality gaps are current research priority, but further efforts are needed to allow for application in surveillance. In addition there are political obstacles in the European Union that hamper the use of HBM. These relate to a lack of legal frameworks that requests the use of HBM, and to the subsidiary principle, with major responsibilities allocated to the Member States, wheras European institutions would need comparable data on a European scale.

Therefore, it is recommended to foster the development of HBM specific health based guidance values as core tools to translate HBM data to intake limits set, and to continue work on suitable data for environmental and food contamination and reverse modelling to facilitate interpretation of results. It is recommended to promote monitoring of substances of interest for EFSA and to expand substance coverage and ensure long-term HBM programmes throughout EU Member States in order to increase the number of HBM RVs. The monitoring in different age groups and of different dietary schemes should be expanded to get better information on particularly exposed subgroups, and longitudinal and cross-sectional approaches should be combined for an improved knowledge on potential health risks. In addition it was beneficiary to promote coherent use of customised 24-hr food recall method according to EFSA recommendations and reporting on food quality and quantity in order to improve knowledge on exposure source, and to establish a coherent documentation for HBM data in order to ensure better comparability of reported RVs. Wider use of biobanking and biobanked samples should be promoted in order to be able to trace back time trends for newly identified threats, and surveillance synergies should be further explored to limit costs and increase participation rates. It is recommended to evaluate the added value of BM of effect and OMICs technologies for food risk assessment and to continue targeted research, as well as efforts towards reducing the political obstacles in the European Union, which hamper the use of HBM by supporting development of an European wide collaborative approach, such as the recently started European HBM Initiative (EHBMI). These steps would support the future use of HBM in exposure assessment and PMM in risk assessment in the food safety area as relevant for EFSA.

Detailed information on the approaches of and results from literature search are presented in Appendix A. (search strategy from Tables 22-23), Appendix B. (results of the reviewed HBM programme from Table 24-37, summary of analytical methods used at Table 38 and an inventory of validated biomarkers at Table 39), Appendix C. (summary of reference values, health-based guidance values, HBM and BE values from Tables 40-43) and Appendix D. (HBM-established reference values by substance from Table 44-Table 110).

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BACKGROUND AS PROVIDED BY EFSA

Human biomonitoring (HBM), defined as systematic standardized measurement of concentration of a substance or its metabolites in human tissues (such as blood, urine, milk) has become an important tool in evaluating exposure to chemicals in the general population and specific subgroups (Angerer et al., 2007). The measured concentrations are commonly referred to as "body burdens" of these substances, and biomarkers are indicators of the chemical burden in the human body.

HBM have been applied in exposure assessment to evaluate human exposures to chemical contaminants acquired through the environment, including food consumption. Over the years, many emerging chemicals of concern, such as brominated flame retardants (BFRs), perfluorinated compounds (PFCs), phthalates and phenols [including bisphenol A (BPA)] have been identified through HBM, measuring their increasing presence in populations (Casas et al., 2013; Llop et al., 2011). Modern analytical methods make it possible to measure a wide range of chemicals in the human body even at very low levels. HBM can thus be used to monitor combined or mixed exposure, an issue of increasing concern in risk assessment (Silins & Hogberg, 2011).

HBM can identify (i) new chemical exposures, trends and changes in exposure; (ii) establish distribution of exposure among the general population; and (iii) identify vulnerable groups and populations with higher exposures. It is generally recognised that HBM data have the advantage in providing information on: (i) the internal exposure of humans to chemicals or their metabolites; (ii) exposure from all sources including food; (iii) the whole body burden of a chemical taken up by ingestion and other routes. However, it should be noted that HBM by itself does not provide information on the source(s) or route(s) of exposure, and environmental exposure data are rarely collected at the same time as HBM. Additional research studies to identify the relative contribution of the numerous sources and routes by which humans are exposed to environmental chemicals are often needed.

HBM can be used also to estimate a biological effect if a relationship has been established between the biological measurement and the health outcome. In this case, the associated effect to chemical exposure is quantified by measuring reaction products in human tissues or specimens. For a few chemicals only, such as lead, human data from occupational and other clinical studies allow the identification of body burdens for a chemical that may result in an adverse effect. For most chemicals, however, there are no adequate human data to be certain about health effects, particularly at very low chemical concentrations. In addition, most environmental exposures involve multiple substances, and attributing cause to a single hazard can often be difficult (Paustenbach & Galbraith, 2006). Thus, HBM studies can only provide information on correlations between health effects and internal exposure, but not a causal correlation.

Measuring levels of chemicals in human body fluids and tissues has been in routine use in industry and parts of the wider public health community for more than 50 years. Currently, many countries like the United States, Canada, Germany, Denmark, Czech Republic, Belgium and France have established biomonitoring programmes that report representative values of selected biomonitoring values in non-occupationally exposed populations (CDC, 2011; Cerna et al., 2012; Fréry et al., 2012; Health Canada, 2010; Kolossa-Gehring et al., 2012; Schoeters et al., 2012a; Thomsen et al., 2008; Wojtyniak et al., 2010). These programmes complement a range of other monitoring activities to investigate the levels of chemicals in the environment, including food. In other countries biomonitoring has not been institutionalised; however there are many biomonitoring studies that have taken place.

The value of HBM was recognised by its central role in the European Environmental and Health Action Plan 2004-2010 (COM 2004). However, its potential is not yet utilised. Limitations are mainly caused by lack of standardization in methodology (i.e. sample collection), validated biomarkers availability, and data integration and interpretation. Action 3 (Development of a coherent approach to HBM - European Environmental and Health Action Plan or EHAP 2004-2010) provided a background for the establishment of an expert network of European Union (EU) Member States (MS) as a first step towards a harmonised HBM study. EU MS are contributing to the harmonization of HBM methods in Europe through different projects (Consortium to Perform Human Biomonitoring on a European Scale (COPHES) http://www.eu-hbm.info/cophes; Demonstration of a study to Coordinate and Perform Human Biomonitoring on a European Scale (DEMOCOPHES) http://www.euhbm.info/democophes) (Joas et al., 2012).

Considering the possible major implications of HBM methodology for human exposure assessment of chemicals, the recent advancements and the challenges evidenced from national, EU and international programmes and research studies, it is not clear to which extent HBM can be reliably applied to risk assessment. For this reason, this procurement aims to critically review the state of the art of HBM with a view to discussing its application to chemical risk assessment in the area of food safety.

TERMS OF REFERENCE AS PROVIDED BY EFSA

The aim of this procurement project is to conclude a direct contract for the execution of specific tasks over a clearly defined period as defined in these tender specifications.

The overall objective of this study is to provide an overview on HBM and possible application to human risk assessment via a critical review of literature (published and grey, when relevant) to address the last decade's advances (i.e. from 2002 onward) in HBM activities and its application to chemical risk assessment, with a particular focus on applications to the food safety area.

The assignment should cover the following specific objectives:

Objective 1:

To provide an overview on HBM and possible application to human risk assessment, including:

1.1 Definition of HBM and description of HBM techniques and requirements, such as possible biological matrices, recruitment and sampling procedures, feasible parameters, suitable and reliable analytical methods, data interpretation and communication;

1.2 The possible application of HBM to the different steps of risk assessment (exposure assessment, hazard identification, hazard characterisation and risk characterisation) in food safety areas (as relevant for EFSA) where HBM (and related biomarkers) can make a significant or unique contribution (e.g. assessment of chemical contaminants, or regulated chemical substances such as food contact materials, pesticides, etc.);

1.3 An in-depth evaluation on the usefulness of HBM for exposure assessment of chemical substances from food source (chemical contaminants and regulated chemical substances), including strengths and limitations, and for the implementation of a systematic Post Market Monitoring (PMM) approach for regulated chemical substances.

Objective 2:

To provide an inventory of the different HBM surveillance programmes/initiatives at national, EU and international level and the relevant HBM studies published in the literature, with a comparative analysis of the studies in order to evaluate the added value for chemical risk assessment. Associated monitoring studies to investigate levels of the chemical in the environment (in particular in food) should be reported when available.

Objective 3:

To provide a review of results from HBM studies, aimed at identifying:

3.1 Emerging chemicals or chemical classes and possibly higher exposed sub-groups or specific vulnerable groups of a population from HBM investigations, with a particular focus on the exposure to foods;

3.2 An inventory of validated biomarkers of exposure to chemicals that can be found in the diet identified through HBM (e.g. metals, polycyclic aromatic hydrocarbons (PAHs), phthalates, phenols, polychlorinated compounds, pesticides, etc.);

3.3 Any other issue that the contractor deems relevant for EFSA's risk assessment activities.

Proposed methodology

HBM information and data should be gathered through an extensive search of the literature from different sources in the public domain (e.g. scientific literature, reports from EU/national/international authorities' and various other sources). Priority should be given to information from peer-reviewed sources; however, other sources of available data (grey literature) shall also be taken into consideration when relevant. References shall be collected in an EndNote™ Library or in a format that is compatible with EndNote™. The literature search strategy (from different bibliographic database platforms such as MEDLINE, EMBASE, etc.) and selection criteria (inclusion/exclusion) for the review shall be based on the EFSA Systematic Review Guidance (EFSA, 2010).

Data on exposure biomarkers shall be extracted from studies reported into selected literature and summarised in a tabular-form inventory (e.g., Excel spreadsheet). The document shall outline for each selected study: the chemical substance and concentrations, marker (substance/metabolite), biological matrix, method, study design, study period, chemical substance source (when available, in particular for food), population studied (including age, sex, and number of participants), geographic area, and bibliographic reference (first author and year). Moreover, reference values of the background exposure in the (specific) population and health-based limit values derived from toxicological and epidemiological studies should be provided, when available.

This contract/grant was awarded by EFSA to: a Consortium established by BiPRO GmbH and University of Copenhagen

Contractor/Beneficiary: BiPRO GmbH, Grauertstraße 12, 81545 Munich, Germany and University of Copenhagen, Blegdamsvej 3B, 2100 Copenhagen, Denmark

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Contract/grant number: OC/EFSA/EMRISK/2013/01

1. Introduction and Objectives

In Europe, the rising incidence rates for a number of chronic diseases of public health relevance raised concern and resulted in increasing public interest and awareness in environmental health. This is of particular importance as the majority of major chronic human diseases are likely to result from the combination of external "environmental" exposures and human genetics with environmental (e.g. chemical) determinants, yet their effects still being often poorly understood.

Also, the importance of sources is changing. While at the end of the last century outdoor air was the main source of chemical pollution, food has been proven to be the major source of many toxicants today. Chemical substances occur as food additives, pesticides, pharmaceuticals or are contained in packaging. Other chemicals enter the food chain as pollutants. Further toxicants such as mycotoxins or acrylamide arise from natural sources or processing. Community food legislation and food risk assessment aims at a high protection level and at the reduction of contaminants. However, there is lack of primary information about the real-life exposure of European populations that could be used to verify the risk estimates.

Human biomonitoring (HBM) provides the tools for exposure assessment by direct measurements. It is the advantage of HBM that it is a measure of internal exposure and effect integrating all sources and routes of uptake. HBM can identify new chemical exposures, trends and changes in exposure, establish distribution of exposure among the general population, and identify vulnerable groups and populations with higher exposures. However, there are limitations by lack of standardization, validated biomarker availability, data integration and interpretation. In addition HBM by itself does not provide information on the source(s) or route(s) of exposure, and environmental exposure data are rarely collected at the same time as HBM.

Considering the possible major implications of HBM methodology for human exposure assessment of chemicals, the recent advancements and the challenges evidenced from national, EU and international programmes and research studies, it is not clear to which extent HBM can be reliably applied to risk assessment. For this reason, this procurement aims to critically review the state of the art of HBM with a view to discussing its application to chemical risk assessment in the area of food safety.

2. Materials and Methods

In order to achieve the overall project objective and the tasks as specified to the full satisfaction of the European Food Safety Authority (EFSA) we have developed a project concept including 6 work packages that correspond to the envisaged tasks. The work has been arranged in two preparatory work packages (WP1&2) and in three compiling and evaluating work packages (WP3-5). In the preparatory phase (WP1&2), a literature search strategy has been identified, and a review protocol has been prepared.

The review protocol determined how references have been managed, how the search process has been documented and reported, which selection criteria are suitable for inclusion/exclusion of literature and studies. Based on this strategy, the literature research has been carried out.

The work packages WP3 to 5 dealt with the actual elaboration of narrative reports on the study objectives and the provision of overview tables of collected data. WP 6 was an iterative work package dealing with the overall project management. Figure 1 provides an overview on how these tasks are reflected in work packages.

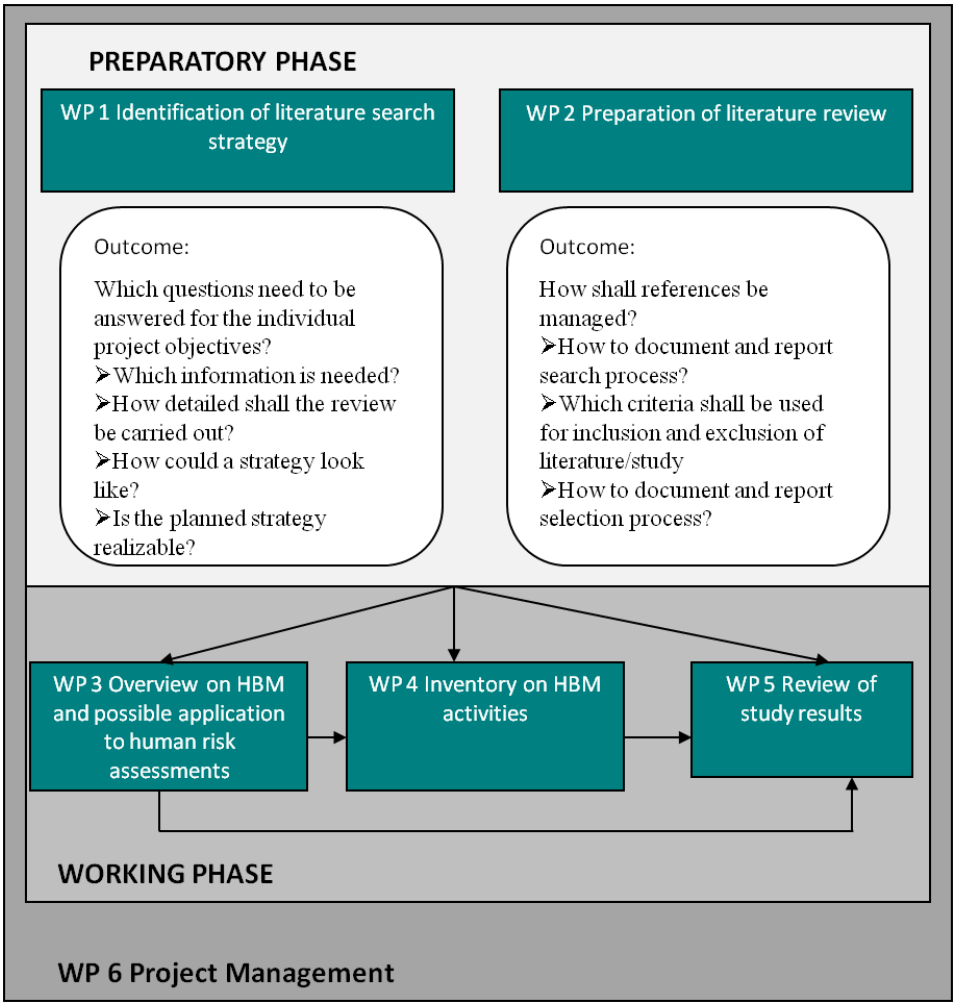

Figure 1 Overview of the work packages.

2.1. Literature search strategy

In WP 1, the project team identified all questions that needed to be answered within the project (WS 1.1 Question types and key elements of questions for search) and discussed about their characteristics in line with the EFSA Systematic Review Guide (EFSA, 2010). Subsequently, the project team concluded on the feasibility of pure systematic reviews or narrative reviews for the individual questions (WS 1.2 Identification of the areas for systematic, critical and narrative reviews). Considering the identified questions, it was deemed appropriate to perform a comprehensive literature search and a narrative review of the results identified. This approach was applied in particular for the application of HBM in human exposure assessment for food safety (Objective 1), whereas a systematic review of national HBM programmes was used for the inventory of different HBM surveillance programs (Objective 2). The literature search strategy included also the necessary specific information for Objective 3 (biomarker, reference values, and guidance values) although the clear focus of this task was on the evaluation of the HBM inventory. The strategy included an iterative process, i.e. testing and scoping of literature search results in order to fine tune the search terms.

A major aim of the search was to identify relevant HBM studies/programmes (national, EU, and international level), evidencing exposure of general population to environmental chemicals. The

priority targets were studies with associated investigation of source (and route) of exposure, particularly food, but the search was not limited to these studies but included all relevant HBM studies even if the source of exposure to the environmental chemical is not clear.

The final search strategy set the time frame as well as the search terms, the languages to be reviewed, the databases to be used, the substances to be focused on, and the distribution of work between the consortium partners in the project team.

WP2 covered the preparation of the review protocol. This included the elaboration of search terms and substances to be covered as well as data management and documentation. All approaches were summarised in a review protocol that was agreed upon with EFSA Services.

The following sections provide a descriptive overview of the literature search.

2.1.1. Data sources investigated

PubMed, MEDLINE and SCOPUS were chosen as the primary databases for the literature search with additional searches in other supplementary databases such as DIMDI, EMBASE, Toxnet, Web of Knowledge, Cochrane, OVID and Open Grey (database of grey literature in Europe).

Relevant reports from national HBM programs or conferences not identified via database searches were reviewed. While most of the reports are published in English, additional references in German, Danish, Swedish, Norwegian, French, Dutch, Spanish, Korean, and Japanese were also considered in this report. Furthermore, the project team investigated the following conference proceedings from 2013 and 2014.

- International Society of Environmental Epidemiology (ISEE)
- International Society of Exposure Sciences (ISES)
- International Conference on Environmental Mutagens (ICEM)
- International Symposium on Biological Monitoring (ISBM)
- ISEE-ISES-ISIAQ 2013
- ICDAM Conference on Dietary Assessment Methods
- FENS Federation of European Nutrition Society
- WMF meets IUPAC 2012
- ISM-MycoRed 2013
- MoniQA 2013
- International Union of Toxicology (IUTOX)
- European Environmental Mutagen Society (EEMS)
- International Congress on Environmental Health (ICEH)
- International Conference on Heavy Metals in the Environment (ICMET)
- European Public Health Association (EUPHA)
- International Network on Children's Health, Environment and Safety (INCHES)

- Society of Toxicology (SOT)
- Society for Environmental Geochemistry and Health (SEGH)
- International Society of Indoor Air Quality (ISIAQ)

Based on the experiences made in the first search run, it was possible to apply a refined search strategy for the conferences and conference proceedings. The strategy included searches with general terms such as "human biomonitoring" (level 1) with an "and" combination of "Food", "Food Safety" and "Risk assessment" (level 2). For the 6 references obtained after the selection process, full texts were retrieved.

2.1.2. Search terms

A detailed list of search terms was elaborated on the basis of the targeted review questions for objective 1 (questions 1.1.a-1.1.i, 1.2a-d, 1.3 a, and b), for objective 2 (questions 2.1., 2.1.a, 2.2.a., and 2.3a) and for objective 3 (questions 3.1a and b, 3.2 a).

Multiple search terms were combined in the database search by using AND (rather than OR) to avoid a surplus of ineligible or inconsequent references. Search focussed on the terms "human biomonitoring" OR "HBM" in combination (AND) with programme/survey/cohort or definition as well as search terms for:

- Study design (longitudinal, OR cross-sectional, OR recruitment, OR participation, OR sampling, OR reporting, OR communication);
- Matrices (human tissue, OR sample matrix, OR blood, OR serum, OR urine, OR hair, OR saliva);
- Food source (food, OR food safety, OR diet, OR nutrition, OR food contaminants, OR pollutants food, OR environmental chemicals AND food);
- Different steps of risk assessment (risk assessment OR exposure assessment AND food, OR hazard identification AND food, OR hazard characterisation AND food, OR risk characterisation AND food);
- Countries/regions of interest;
- Vulnerable population groups (vulnerable group AND food);
- Emerging chemicals (emerging OR new AND chemicals OR substances, AND food);
- Biomarkers of exposure (food OR diet OR validated).

Search terms were focussed on a search in "Title", "Keyword", and "Abstracts". Search terms and combinations of terms were expanded, reduced and refined in a testing and scoping procedure, depending on the number of initial hits. In the case where there are only a few number of retrievable references, the search was expanded from "Title", "Keyword", "Abstracts" to "Any Field."

In addition the search included a long list of substance groups and substances in combination with "human biomonitoring" OR "biomonitoring".

A full list of all search terms used in the literature search to answer the specific review questions for objectives 1 to 3 is provided in Table 22 of Appendix A. The full list of substance groups and substances that were covered in the literature search is provided as Table 23 of Appendix A.

Information needed to address Objectives 2.1-2.3 (review questions 2.1 b, 2.2b, 2.3 b) as well as review question 3.2b were mostly extracted from the identified HBM programmes (see chapter 3.7) with additional supplement searches to fill in missing data gaps (c.f. chapter 2.1.5).

Table 1 Review questions answered via a comprehensive analysis of HBM programmes identified

	Review questions
2.1.b 2.2.b 2.3.b	• Who is the Initiator/Funder of the study • What is the duration of the study? • What study design is chosen? • Which study population (age, gender, number of participants, geographical coverage, and timing of study)) is chosen? • Which chemicals are investigated? • Which matrices are used? • Which recruitment strategy is used? • What analytical methods are used? • Which markers have been used? • What are the results, chemicals concentrations found? • How are results interpreted? • Are there any accompanying activities to investigate exposure sources, if yes, which? • Are reference values available, if yes, which? • How are results communicated to study participants/public/scientific world, etc.? • How is the policy support addressed?
3.2.b	• What are the criteria for their validation?

2.1.3. Data documentation and Endnote database

In WS 2.1 and 2.2, the project team identified a strategy for managing and documenting the references. All references were documented in an EndNote™ Library. For a transparent documentation of references, groups according to the Objectives and subgroups according to the search terms were created within the EndNote library, and eligible references were appropriately sorted in the groups/subgroups. Furthermore, the following information has been documented separately for the data search in the different databases:

- Database name;
- Date and start and end time of search;
- Search terms used / combinations used/ elimination of duplicates required
- Number of records retrieved;

2.1.4. Eligibility criteria for full text search

Literature search was designed in a way that all studies with HBM and HBM plans published in peer-reviewed journals as full articles and abstracts were included even if the language is not English. The

search occurred mainly from January to March 2014 and focussed on the time period between 2002 and 2014. An additional search on PubMed was conducted in October 2014 to search for the latest relevant publications.

To address Objective 1 ("An overview on HBM and possible application to risk assessment"), mostly reviews discussing the use of human biomonitoring in risk assessment were identified and imported into the EndNote library. Concerning chemical substances of interest, a focus was put on known chemicals from HBM studies such as BFRs, PFCs, phthalates, phenols, metals, PAHs, polychlorinated compounds and pesticides. However, the search was not limited to these chemicals. Other chemical substances identified from HBM studies that can be found in the diet, such as contaminants in the food chain and undesirable substances such as food contact materials, were considered as eligible for review.

For Objective 2 ("An inventory of HBM programmes"), the following eligible studies were included: (1) observational studies assessing the association between chemical body burden and food intake, (2) cohort studies and (3) cross-sectional HBM surveys performed in humans that were published after January 2002. Reports providing information on the design of the programme as well as any observed concentrations and time trends (where possible) were included.

Lastly, for Objective 3 ("A review of the HBM study results"), relevant reviews and studies regarding biomarkers, reference and health-based guidance values, emerging chemicals and vulnerable populations were considered and imported into the library. It should also be mentioned that information on kinetics (e.g. half-lives), dose-response relationship (e.g. NOAELs) and modelling (e.g. PBPK) of a chemical was taken into consideration when available in the investigated studies. However, these topics are not considered as key aspects in this report.

According to the review protocol, the following studies were excluded:

- No measurement of human fluids or tissues (e.g. soil, air or food measurements);
- Solely *in vitro* (i.e. cells) or *in vivo* (i.e. animals) studies;
- Exclusively related to occupational exposure;
- Only reported data older than 2002;
- Analysis of chemicals related to radioactivity, nutritional biomarkers (food additives), illicit drugs, war agents, and pharmaceuticals.

For HBM studies, the following additional exclusion criteria were applied:

- Exclusively health outcome-oriented (e.g. HBM of cancer patients, determination of endocrine disruptive effects)
- Not related to food-related exposure but to other exposure pathways (e.g. inhalation)

Exclusively narrative reports about potential and options of HBM as well as narrative reviews about HBM and the use of biomarkers were not taken into account. Assessments of chemicals body burdens based on measurements in food and modelling of food intake were only included if measurements of biological samples were made in conjunction (c.f. Norway's MoBa study). In addition, we excluded citations exclusively discussing the development of specific novel biomarkers, modelling methods or assessment tools. Studies which examined associations between chemical and health effects were not considered eligible if they did not examine exposure.

However, in order to complete the overall picture, some exceptions were made, e.g. studies featuring specific interest groups but with a smaller study population. Such studies could be important to show the overall picture of a country/region, or if the study was conducted by a health authority, it could be included in line with the agreements that have been taken with EFSA at the beginning of the project. Also, occupational "control" populations were considered if combined with environmental exposure settings or if associations regarding food intake and chemical exposures were made. Accordingly, studies related to nutritional biomarkers (i.e. food additives) and pharmaceuticals were generally not considered eligible, except for veterinary drugs or pharmaceutical residues that could be considered as food contaminants.

When references pertained to the same study, only the most extensive and most recent ones were retained in order to avoid redundancies.

2.1.5. Supplemental searches

In order to close gaps in the database search for the HBM inventory (WP4), additional information on the European HBM programmes and projects were collected based on the expertise of the project team, and government-published reports from other HBM programmes (e.g. Germany's GerES, Italy's PROBE, etc.) were retrieved from the respective governmental websites. Therefore, a total of 120 additional references (i.e. books, other governmental/regulatory reports, literature older than 2002, etc.) was imported into the EndNote library and sorted under "Expert literature."

In addition, information of the following European research projects related to HBM was evaluated by the project team:

- Expert Team to Support Biomonitoring in Europe (ESBIO)
- Consortium to Perform Human Biomonitoring on an European Scale (COPHES)/Demonstration of a Study to Coordinate and Perform Human Biomonitoring on an European Scale (DEMOCOPHES)
- Environmental Cancer Risk, Nutrition and Individual Susceptibility (ECNIS)
- EnviroGenomarkers – Genomics Biomarkers of Environmental Health
- Integrated Assessment of Health Risks from Environmental Stressors in Europe (INTARESE)
- Newborns and Genotoxic Exposure Risks (NewGeneris)
- EXPOsOMICs
- The Human Early Life Exposome (HELIX)
- Health and Environment-wide Associations based on Large Population Surveys (HEALS)

After consultation with EFSA Pesticide Unit on the HBM inventory, additional targeted investigations were performed on specific pesticide classes of interest for EFSA, namely imidacloprid (a neonicotinoid), and a number of pyrethroids and triazoles. First, references on specific pesticides were searched among the abstracts in PubMed using the following terms: imidacloprid OR *pyrethroid of interest* OR *triazole of interest* AND from 2002 onwards. All identified references have been stored in a separate Endnote library for potential future use for EFSA. Next, within this library, a targeted selection procedure was conducted among the abstracts of these groups using search terms "human" AND/OR "biomonitoring," and using the aforementioned exclusion criteria, a visual selection procedure reduced the number of eligible scientific studies to 38 (4 studies for imidacloprid, 34 studies

for pyrethroids, and 0 study for triazoles). These were considered for the report, imported into the EndNote library and sorted in the group set "EFSA pesticides of interest."

Finally, a search in Open Grey (http://www.opengrey.eu/), a database of grey literature in Europe, was performed in October 2014. The combinations of terms used in this search were the following: (1) "Human biomonitoring" OR "HBM" AND "food", (2) "Human biomonitoring" OR "HBM" AND "risk assessment" and (3) "Human biomonitoring" OR "HBM" AND "exposure."

2.1.6. Quality control measures

For quality assurance purpose, the selection process was carried out by 2 experts of the project team in order to reduce the introduction of errors and personal biases. The results of the selection processes were compared. In case of differences, another key experts of the project team checked the opinions and took a decision based on the eligibility criteria.

2.1.7. Quality appraisal

Selection of the eligible studies included a quality appraisal, which was based on the following aspects in line with the recommendations of the Newcastle–Ottawa Scale (NOS) and the RTI item bank:

1. Level of detail in methods and materials (design description, result documentation)
2. Level of detail in discussion (including strength and weaknesses)
3. Efforts undertaken to identify confounders

In case there were several scientific articles providing conflicting information, the project team used the date and the author's reputation as an additional aspect. The impact factor of the journal did not need to be used as a selection criterion in this report.

2.2. Structure of this report

This report is structured into the assessment of the possible application of HBM to human risk assessment (chapter 3.2), an inventory of the different HBM surveillance programmes/initiatives at national, EU and international level with a comparative analysis in order to evaluate the added value for chemical risk assessment (chapters 3.7 and 4.1) and a review of results from HBM studies (chapter 4.2).

The first part (WP3) includes the definition of HBM, a description of core HBM techniques and requirements, a discussion of the possible application of HBM to the different steps of risk assessment in food safety areas, and an evaluation on the usefulness of HBM for exposure assessment of chemical substances from food source and for the implementation of a systematic Post Market Monitoring (PMM) approach for regulated chemical substances including strengths and limitations.

The inventory (WP4) is focussed on information on the following topics: chemical substance and concentrations, biomarker used (substance/metabolite), biological matrix, method, study design (longitudinal, cross-sectional), study period, chemical substance source (in particular for food), population studied (including age, sex, number of participants), geographic area, participation rate, bibliographic reference (first author and year), reference values of background exposure in the (specific) population, and health-based limit values derived from toxicological/epidemiological studies. Information on the key features of each programme was listed in a comprehensive excel matrix. Information on associated monitoring studies to investigate levels of the chemical in the environment (in particular in food) is provided where available. Blank fields in the Excel matrix were

subject to a second more targeted screening, and cross-checking with latest internal information was done to collect the relevant information. Quality check and cross check of data (WS 4.5) was performed for quality assurance. The quality check was done in accordance with the defined eligibility criteria in the review protocol and involved a four eye principle. For the appropriate assessment of information received and collected throughout the project and for selection of the most appropriate information, we used a systematic and justified weight-of-evidence approach.

The discussion section (chapter 4) contains the comparative analysis of activities at national, EU and international level, and an evaluation of the added value of HBM for chemicals risk assessment on the basis of the inventory made. In this context, comparative analysis means that it was particularly searched for differences in study design (e.g. biological matrices, analysed substances etc.), associations and links between external and internal exposure (via associated food/HBM data or via other means to correlate food intake and elevated body burdens), and any casual links or associations between measured body burdens and health effects. This working step had a particular focus on the requirements of chemical risk assessment, and the regulated substances under food safety legislation (e.g. mycotoxins, dioxins, heavy metals, nitrates, chloropropanols) or chemicals regulated in the context of food contact materials (e.g. phthalates).

The discussion also comprises a narrative review of the results of the investigated programmes. In the review (WP5), the project team has focussed on identifying emerging chemicals or chemical classes and possibly higher exposed sub-groups or specific vulnerable groups. In addition, the review of results has targeted on an inventory of validated biomarkers of exposure to chemicals that can be found in the diet identified through HBM (e.g. metals, polycyclic aromatic hydrocarbons (PAHs), phthalates, phenols, polychlorinated compounds, pesticides, etc.). Information on criteria for the validation has been included where available, and biomarkers of susceptibility and effect have been included in the review only when evaluated in the HBM studies selected for exposure assessment. Lastly, the inclusion of guidance values, the development of new biomarkers, and the use of food monitoring/questionnaires of intake have been elaborated.

3. Results

This chapter provides an overview to the use of human biomonitoring (HBM) (chapter 3.2), information on the definition of HBM (chapter 3.2), the related techniques and requirements (chapter 3.4) as well as it applicability in different steps of risk assessment and post-market monitoring (chapter 3.5) and an assessment of its usefulness in exposure assessment including limitations and strengths (chapter 3.6). Furthermore, it provides a description of the core parameter of the analysed HBM programmes (chapter 3.7).

3.1. Literature search

This chapter covers the results from the literature search and provides a short discussion of the limitation of the selection process including a justification of the selection priorities.

3.1.1. Selection of references

Since the search process in PubMed, Medline, SCOPUS and DIMDI revealed a lot of redundancies and the EMBASE, Toxnet, Web of Knowledge Cochrane and OVID databases extract publications from the same sources as SCOPUS, the final search was focused on SCOPUS, PubMed, and MEDLINE.

This strategy yielded 19 704 references in all searched databases (7 187 in PubMed, 39 references in DIMDI, 3 208 references in MEDLINE and 9 309 in SCOPUS), see Appendix A. A.

The following Table 2 gives an overview of the obtained hits for the searched terms in combination with the database name and the time of search after the selection process.

Table 2 Database search and references obtained

Database name	Start and end of search date	References obtained
PubMed	January-March 2014; October 2014	7 187
DIMDI	January-March 2014	39
MEDLINE	February 2014	3 208
EMBASE	Included in SCOPUS/Medline	-
Toxnet	Included in SCOPUS/Medline	-
Web of knowledge	Included in SCOPUS/Medline	-
SCOPUS	February 2014	9 309
Cochrane	Included in SCOPUS/Medline	-
OVID	Included in SCOPUS/Medline	-
In total	PubMed/Medline and SCOPUS, no repeats	2 316*

The search in conference proceedings only yielded a few results that were not covered from the database searches (Table 3).

Table 3 Conference and conference proceedings searched for identified search terms

Database name	Start and end of search date	References obtained	References in PubMed
ISEE	February 2014	-	
ISES	February 2014	3	1
ICEM	February 2014	3	1
ISBM	February 2014	3	
ISEE-ISES-ISIAQ	February 2014	6	1
ICDAM	February 2014	10	
FENS	February 2014	-	
WMF meets IUPAC	February 2014	1	
ISM-MycoRed	February 2014	-	
MoniQA	February 2014	3	1
IUTOX	February 2014	3	
EEMS	February 2014	1	1
ICEH	February 2014	3	
ICMET	February 2014	2	
EUPHA	February 2014	1	
INCHES	February 2014	-	
SOT	February 2014	-	
SEGH	February 2014	1	1
ISIAQ	February 2014	-	

For these references, the eligibility of the full texts was assessed in order to exclude those records that failed to meet the inclusion criteria. The search in Open Grey, the database for Grey Literature in Europe, yielded 12 references. However, these references were excluded from the report as they did not fit into the inclusion criteria of this report.

In several iterative steps, the selection process was accomplished according to the EFSA systematic review methodology guidelines (EFSA 2010).

Of the 19 704 references resulting from the searches in PubMed, SCOPUS and MEDLINE, 5 075 were excluded as duplicates. From the 14 629 retrieved individual references, 13 418 were excluded after screening of titles (12 313 excluded) and abstracts (1 115 excluded), resulting in 1 201 references eligible for inclusion. The full texts for these references were searched, and a rating was given for each reference (ranging from the lowest of 1 to the highest of 5) depending on its relevance for the report.

The eligible references were sorted in groups according to each objective and subsequently in subgroups according to the search terms. Figure 2 shows some of the key groups and subgroups defined within the EndNote library.

Figure 2 The key groups/subgroups defined within the EndNote library with the numbers of sorted references.

As aforementioned, supplemental searches (c.f. chapter 2.1.5) for HBM studies involving pesticides of interest (namely imidacloprid, pyrethroids, and triazoles) and by the project team (e.g. books, older references, presentations, websites, etc.) resulted in 38 and 126 eligible references, respectively, totalling to 164 additional references imported into the EndNote library. The pesticide references were sorted in the group "EFSA Pesticides of interest," and the expert references were sorted in the group "Expert literature." Altogether, with the 1 201 eligible references identified from the database searches and the 164 additional references, 1 365 references were imported into the EndNote library for this report, and 742 full texts were retrieved.

Altogether, a total of 252 references were finally selected and included in this report. Full texts for 235 out of the 252 references were retrieved and imported into the EndNote library. The remaining 17 non-retrievable references are mainly book chapters or websites. Figure 3 shows the flow chart of selecting the eligible studies from the database searches and by the project team.

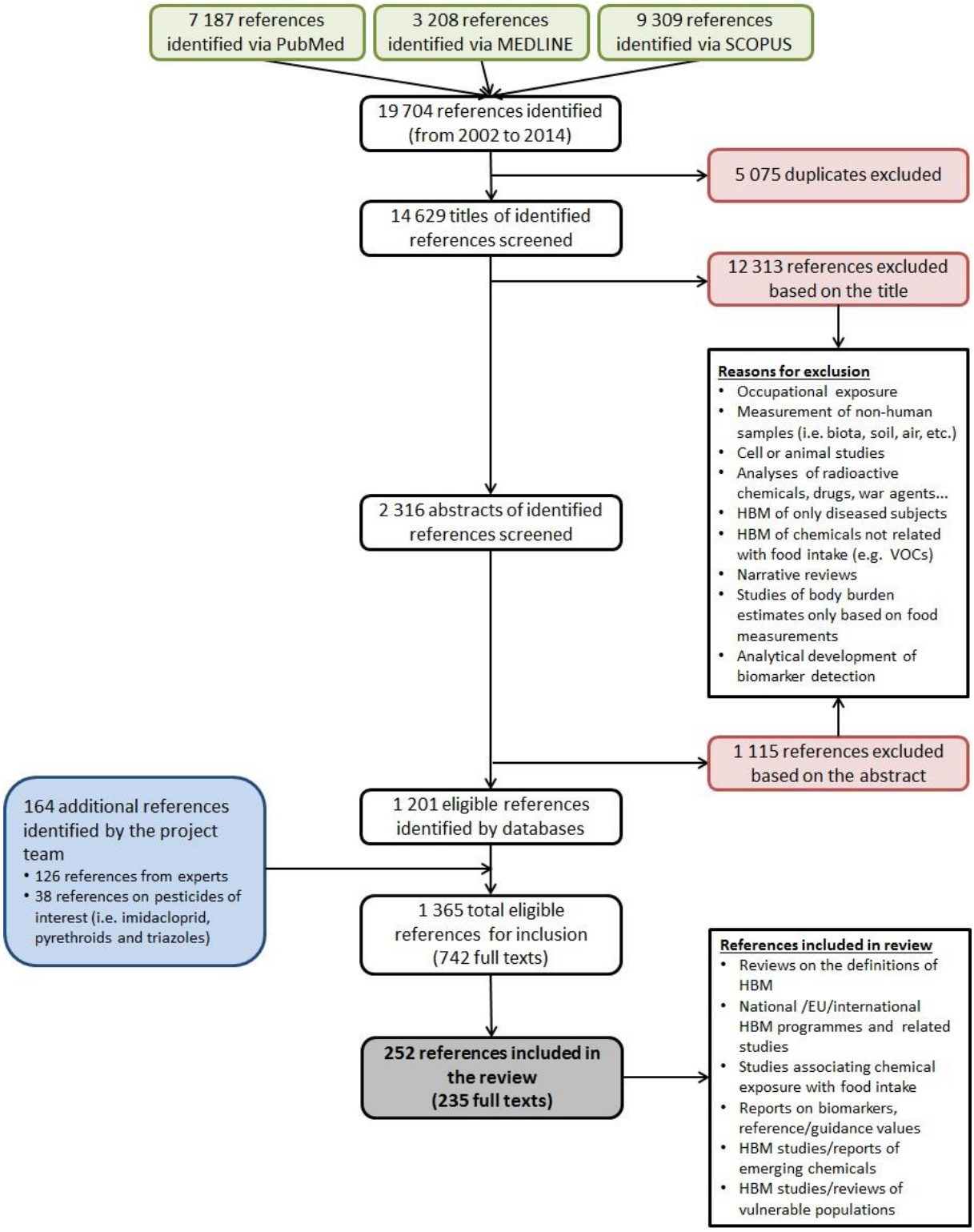

Figure 3 The flow chart depicting the study selection process for this report

3.1.2. Limitations of the review

The aims of this report are to assess the potential application of HBM to chemical risk assessment, particularly in the area of food safety and to provide a broad overview of the existing HBM activities throughout Europe and beyond. While an extensive search for HBM programmes and related studies was conducted in order to create a HBM inventory, it is by no means an exhaustive review, i.e. not all HBM programmes have been covered.

Initially, national HBM programmes with large sampling (general) populations were selected for review. However, after the database search, it was observed that a number of European countries only has national HBM programmes with small sampling populations (<1000 participants) or cohort studies (i.e. mother-child cohorts). Thus, in order to gain a better picture of current and past HBM activities throughout Europe, these smaller HBM programmes were covered in this report.

The USA's NHANES and Canada's CHMS programmes were included in the review because they are currently some of the most extensive existing HBM programmes, whereas the HBM programmes in South Korea, Japan and China (including mother-child cohorts) were covered in this report to provide additional understanding of the current or previous HBM activities in Asia. However, it should be brought to attention that there are upcoming national HBM activities throughout the world such as those in Australia, Brazil, etc.

After the search process, the following national HBM programmes (i.e. not pilot studies) were identified but not discussed in the report:

- SEBIOREC – Italy
- Infancia y Medio Ambiente (INMA) Project – Spain
- EDEN and PELAGIE cohorts – France
- National Children's Study – USA
- Maternal-Infant Research on Environmental Chemicals (MIREC) – Canada

The SEBIOREC study in Italy investigated the levels of POPs (e.g. dioxins, PCBs, PBDEs) and heavy metals (e.g. As, Cd, Hg, Pb) in pooled blood/serum samples (n=84) or milk samples (n=52) from donors living in the Campania region (De Felip et al., 2014). Due to the study design (e.g. measurements of pooled samples in one region and low sample size), this programme is not reviewed in this report but should be mentioned. Meanwhile, the other identified programmes are all cohort studies involving mothers and/or children. As our initial aim and search strategy focussed mostly on HBM programmes of the general populations, these programmes were not considered for the HBM inventory. Nevertheless, some mother-child cohorts and small scale HBM studies have been included in the HBM inventory due to lack of national HBM programmes from countries of interest (e.g. Denmark, Norway, and Sweden) or in order to get the overall impression of HBM activities in Asia.

Even though not all the existing HBM programmes were reviewed for the inventory, it was observed that the study designs, sampling collection process, types of chemicals analysed, etc. were similar among the programmes. Therefore, even without inclusion of the aforementioned excluded programmes in the inventory, the outcome of this report should not affect the overall impression of the application of HBM on risk assessment and on food safety.

3.2. Overview on HBM and possible application to human risk assessment

3.2.1. Introduction to the use of Human biomonitoring in the European Union

Human biomonitoring (HBM) and biomarkers (BM) have a long tradition in health care. They are used in curative and preventive medicine in several domains, and may be applied in different context also in environmental health.

In occupational medicine, HBM plays an important role within the measurement of the body burden of toxic substances and their metabolites for more than a century. HBM is also used in particular for detection of exposure and adverse health risk and for assessing the efficiency of preventive measures and for controlling working place limit values set. For certain industries and professions testing is mandatory. HBM as a surveillance tool in occupational medicine is regulated by legislation on health and safety in the workplace. Health surveillance in occupational medicine besides other is performed in the context of Occupational Exposure Limit Values (OELVs) for chemicals in the workplace established on European scale based on scientific recommendations of the Scientific Committee on Occupational Exposure Limit Values (SCOEL).

In public health, HBM is used in population screening to identify people at risk for developing a specific disease in an early stage. Tests are administered not only to individuals who have no apparent symptoms but also to population groups with potentially elevated risk. Examples of routine population screening currently used in the health care field include the measurement of blood fats or glycosylated haemoglobin in the prevention of cardiovascular diseases, the prostate-specific antigen (PSA) to predict prostate cancer risk or a variety of other markers for malfunction or upcoming disease.

In environmental health, HBM is used together with other methods such as environmental monitoring and modelling for research, surveillance and awareness raising. In research studies, biomarkers are used to improve the knowledge on causal links between environmental factors and health, often addressing or including (early) effect biomarkers and genetic factors (biomarkers of susceptibility).

In environmental health, surveillance the focus is generally put on exposure biomarkers and measurements are intended to produce information on the prevalence of exposure to environmental agents and the related public health impact (Casteleyn et al., 2009). Environmental health surveys in general are designed to support, lead and assess policy and preventive actions in the field of environmental health and to raise awareness of the general population and of policy makers. However there are no EU initiatives of a comparable scope for the moment in population survey and environmental health whereas legal and administrative framework and decision procedures are well established since several decades in occupational health.

3.2.2. Examples of the use of HBM in risk assessment

The best known examples of HBM as a tool for exposure estimation are measurements of heavy metals such as lead and mercury in blood, urine or hair. Measurements of blood lead concentrations, a biomarker of exposure, were used for risk management in industries with high lead exposures. Workers with high blood lead concentrations, above the recommended safety levels, were transferred to less polluted work tasks, and could only return to their original tasks when the blood lead levels had declined.

NHANES data documented an initially sharp decline of blood lead concentrations in children from 1976–1980 and a further continuous decrease to 2001–2002. This decrease (from 160 µg/L in 1976 to <20 µg/L in 2001–2002) corresponds with the removal of lead in gasoline in the USA, starting in the

mid-1970s; the banning of lead solder in domestic food cans was also enacted during this time period, and later the lead abatement programmes in housing were initiated (Needham et al., 2005).

Blood lead levels have been monitored in children and clear associations were reported with environmental exposure with increased levels in schoolchildren living in the vicinity of roads during the leaded fuel period and a decline after the removal of lead from petrol (Strömberg et al., 2008). Biomonitoring data also can be used to calculate the social and economic benefit (e.g. increase in IQ) of phasing out the use of leaded petrol. The relevance of biomonitoring in children exposed to lead is supported by the well-known association with adverse neurological effects. According to the HBM results, allowed exposure values for lead have steadily declined, and nowadays the recommended maximum exposure level for children of 100 mg/L should be lowered further, based on recent findings of adverse neurobehavioral effects (Grandjean, 2010; Jakubowski, 2011).

Another well-developed case of use of HBM is mercury, occurring as metallic mercury (elemental mercury), inorganic and organic mercury, which are interchangeable from natural and microbiological processes. HBM of methylmercury in hair reflects the recent exposure, e.g. exposure during the past months if sampling is done with hair cut 3 cm from the root. Levels above 1 µg/g hair are considered high and were found in the DEMOCOPHES study (Esteban et al., 2014). Possible applications of HBM related to Hg are shown in Table 4.

The World Health Organization (WHO) intends to use HBM to assess baseline mean concentrations of mercury in children's hair and to follow the levels over time, to determine whether reductions in mercury occur after implementation of the Minamata treaty to reduce mercury exposure to humans (WHO, 2012).

Table 4 Example of possible applications of HBM in risk assessment of human exposure to Hg.

Sources of exposure	Methods of quantification	Human exposure pathways	HBM provides integrated measure	Health outcomes
Thermometers, lamps, etc.	Questionnaires, sales.	Intake, inhalation, skin contact	Blood, urine, hair, nails for measurements of Hg and of methylmercury	• Neurological effects • Developmental effects • Reproductive effects • Immunological effects • More to be discovered
Dental amalgam	Questionnaires, follow up on regulation	Intake		
Lifestyle	Questionnaires on use (e.g. skin care, shampoo) and sales on quantity and quality	Intake, inhalation, skin contact		
Food	Questionnaires on food intake (e.g. fish) and sales on quantity and quality	Intake also of products from biotransformation in the environment		
Local industrial emission and waste	Environmental measurements	Including biotransformation of Hg to Methylmercury		

HBM surveys in Flanders (2007-2011) identified regional differences in urinary cadmium and toxic arsenic in industrial hot-spot areas, which could be related to socio-economic factors and were used to trigger preventive policies (Vrijens et al., 2014).

In Germany, cadmium levels in blood and urine declined as a consequence of a revision of the German Drinking Water Ordinance (Kolossa-Gehring et al., 2008). Furthermore, the reduction of exposure via a ban of pentachlorophenol (PCP) and other persistent biocides in wood preservatives resulted in a clear decrease of the median level of PCP in urine from 4.5 µg/l to < 0.6 µg/l in 1989 (Kolossa-Gehring et al., 2008).

In the late nineties, HBM surveys detecting highly elevated dioxins & PCB and other POP levels in human milk triggered the setup of strict limit values for dioxins and dioxin-like PCBs in food and feed and of dietary intake recommendations for populations at particular risks (e.g. pregnant women in the Baltic Sea area. Other examples are the ban of c-penta and c-octaBDE following the detection of increasing levels of polybrominated flame retardants in blood detected in Swedish samples (Darnerud et al., 2001; Noren & Meironyte, 1998).

The most prominent example for a global approach is the WHO survey on POPs in human milk. It started after reaching international agreement to phase these substances out. The results indicated that mean concentrations of persistent organic pollutants in breast milk began to decline. After DDT was banned in Germany in 1972, the average concentration of DDT in breast milk decreased by 81%.

According to (Salter Green, 2010), a World Wildlife Fund (WWF) HBM campaign (1999 to 2006) that showed a widespread human contamination with persistent bio accumulative and toxic chemicals (PBTs) and hormone disruptors in relation to its use in consumer products and food had a clear impact on development of the chemicals legislation REACH, the strategy for endocrine disruptors and other restrictive legislation in the field of pesticides, cosmetics and biocides.

HBM was used in Germany for verification of policy effectiveness and identification of new risks related to phthalates by means of retrospective analysis of biobanked data. It showed that the reduction in DnBP/DiBP consumption due to stepwise restriction in cosmetics and toys at the end of the 1990s and early 2000 was coupled with a parallel decline in body burdens of corresponding phthalate metabolites, whereas the levels of the unrestricted compounds remained stable (Kolossa-Gehring et al., 2011). In addition, the German HBM survey (GerES IV) in 2003-2006 showed unexpected possible elevated exposure to organophosphate pesticides from fruit juice (Kolossa-Gehring et al., 2008).

As reported by (Kass, 2009), a study on mercury and pesticides exposure in New York City could illustrate how well-designed HBM surveys can provide the evidence base for policy recommendations and that they have a strong educational and awareness raising potential. The New York City study and several German HBM studies among which GerES IV were also able to demonstrate impacts of socio-economic factors on environmental health in terms of elevated or reduced risks (Kolossa-Gehring et al., 2008). Therewith these studies influenced preventive measures, public health promotion and recommendations for policy.

Due to the success of national, regional or local HBM programmes in tracing policy effects or in identifying policy needs HBM is increasingly obtaining a legal standing on national level, permitting repeated cycles of measurement.

3.2.3. Development of a harmonised approach to use of HBM as a policy tool in the European Union

Within the European Union, significant resources are being spent on HBM in the environment and health field for scientific research, surveillance and awareness raising activities. However, the fragmentation and lack of a coherent approach and integration between countries and studies highly limit the use of the study results for European health impact assessments and cross-border comparison. To allow a better use of the data obtained and to allow evaluations at European scale, harmonisation of activities was considered required (Joas et al., 2012).

Therefore in 2003, the European Commission and the European Member States started efforts to construct an efficient HBM framework across the European Union within the European Environment & Health Strategy (Science, Children, Awareness, Legal instrument, Evaluation or SCALE) and in particular the EU Environment and Health Action Plan (EHAP 2004-2010). As a result a preparatory feasibility study (ESBIO) was conducted from 2005 – 2007 (Joas et al., 2012; Viso et al., 2009) that discussed the pros and cons of a harmonised approach in the EU in close collaboration with the EU Parliament and a consultative forum (CF), that was set up in 2002 as the stakeholder consultation body for the development of SCALE. Based on the work of ESBIO (Reis et al., 2007), discussions within the CF and a number of supportive reports such as the midterm evaluation report of the EHAP (Commission of the European Communities, 2007), the pilot phase for harmonised HBM in Europe was started with the Consortium to Perform Human Biomonitoring on a European Scale (COPHES) in 2009, that laid the basis for a first feasibility study DEMOCOPHES (DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale) starting in 2010. The main objective of COPHES/DEMOCOPHES was the development of a functional framework for a coherent approach to HBM in Europe in order to achieve comparable HBM data that support environmental, health and chemicals policy (Joas et al., 2012).

Broad national HBM programmes established in that period, particularly in France but also in Austria and Italy, were developed in close collaboration with the work in ESBIO and COPHES. HBM programmes following the COPHES approach shall also be established in other European Member States.

3.3. Definition of HBM

HBM is a scientific technique for assessing human exposures to natural and synthetic compounds in the environment. It is based on analysis of human tissues and fluids and provides the only direct method of determining if people have been exposed to particular substances, what the magnitudes of their exposures are, and how these may be changing over time.

The National Research Council of the United States of America in 2002 defined HBM "as a method for assessing human exposure to chemicals by measuring the chemicals or their metabolites in human tissues or specimens such as blood or urine" (CDC, 2005).

According to (Kamrin, 2004), HBM is a growing discipline used for exposure and risk assessment in environmental and occupational health, and has become a more useful tool in recent years as the result of advancements in the capability to measure more and more minute amounts of chemicals in the human body.

HBM relies on the use of biomarkers, measurable indicators of changes, or events in biological systems. Biomarkers are measurement of the concentrations of chemical substances, their metabolites,

or reaction products in human tissues or specimens, such as blood, urine, hair, adipose tissue, teeth, saliva, breast milk, and sperm.

WHO defined biomarkers in 1993 in relation to risk assessment, where the term "biomarker" is used in a broad sense to include almost any measurement reflecting an interaction between a biological system and an environmental agent, which may be chemical, physical or biological. Three classes of biomarkers are identified:

- **Biomarker of exposure:** an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism;
- **Biomarker of effect:** a measurable biochemical, physiological, behavioural or other alteration within an organism that, depending upon the magnitude, can be recognized as associated with an established or possible health impairment or disease;
- **Biomarker of susceptibility** - an indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific xenobiotic substance.

In this context internal exposure can be determined by means of the direct measurement of the chemical substances or their metabolites, whereas biochemical effects are measures by means of protein adducts and DNA adducts and biological effects are measured by means of ALA, cytogenetic parameters or changes in enzyme activities (Angerer et al., 2006).

Since 1993, when this definition reflected discussions in environmental and occupational health, the biomarker concept has been introduced into a number of other fields such as forensic medicine, clinical surveillance and drug development.

The main advantage of using biomarkers is intrinsic in their nature, representing an integrative measurement of exposure to a given agent (i.e., the internal dose), that results from complex pathways of human exposure and also incorporates toxicokinetic information and individual characteristics such as a genetically based susceptibility.

Through the use of biomarkers, it is not only possible to monitor exposure, but it also becomes feasible to detect early health effects. Ideally, both the biomarker of effect and the biomarker of exposure should be associated closely with the overall individual exposure so that it provides an exact measure of the internal dose or the individual health risk. It should be sensitive, specific, biologically relevant, feasible, practical, and inexpensive.

Seldom does a biomarker meet all of these criteria - most biomarkers represent a compromise of these criteria. Many biomarkers are currently used in population studies to estimate exposure or adverse health effects. The nature of these markers is very heterogeneous. Some markers are stable over time while others have very short half-life; some markers are easy to measure with standard laboratory techniques while others require specialised techniques, equipment, etc. (NRCWE, 2007).

Examples of biomarkers of exposure and intermediate effects are given in 0.

Table 5 Examples of types of biomarkers in different biological matrices

	Examples
Specific biomarkers	
Concentration of specific substance in urine	Cadmium concentration in urine, normally adjusted to creatinine excretion
Concentration of specific metabolite of a substance in urine	Cotinine concentration in urine which is a metabolite of nicotine reflecting exposure to nicotine from typically tobacco smoking
Concentration of specific substance in blood	Lead in blood reflecting the body burden as the half-life is long and lead is accumulated
Concentration of specific metabolite of a substance in blood	Cotinine concentration in blood which is a metabolite of nicotine reflecting exposure to nicotine from typically tobacco smoking
Concentration of specific substances in exhaled air	Concentration of benzene in exhaled air reflects the recent exposures by inhalation
Protein adducts	Haemoglobin adducts of ethylenoxide, propylene oxide, benzene, PAHs, acrylonitrile and acrylamide developed with the target of occupationally exposed persons and also showing background exposures in general population from smoking and from diet
	Haemoglobin adducts of nitrotoluene developed in rat studies and applied to occupationally exposed population enabling risk assessment
	Aflatoxin-albumin adducts provides a measure of intake of the carcinogenic mould contamination product Aflatoxin B1
	'Proteomics is in a unique position to contribute to new protein discovery for the betterment of public health and in linking toxicology and pathology to a systems view of protein dysfunction in toxicity and environmental disease.'
DNA adducts	DNA adducts of e.g. PAHs have been associated with cigarette smoking and exposure to combustion products
Unspecific biomarkers	
Urinary mutagenic activity	Handling of cytostatic drugs may confer risk to nurses and exposure may be demonstrated by excretion of mutagens in the urine
Acetylcholinesterase activity in blood	Organophosphorus pesticide exposure lowers activity of enzymes and interventions may be initiated from levels decreased by 25%
DNA damage	Comet assay provides a measure of single strand break that correlate well with genotoxic exposures in animal studies while several confounding factors need to be controlled in human studies including diet (antioxidants), exercise (oxidative stress), sunlight exposure.

	Examples
DNA repair	DNA repair may be induced by exposures and also confers protection against DNA damage of special relevance if active in the transcribed DNA
SCE	SCE is sensitive to exposures, however the mechanism is not known and no predictivity of increased cancer risk has been demonstrated
CA	CA is a robust biomarker with predictivity related to cancer risk. Susceptibility factors may be more important in the causal relationship exposure-cancer. The testing of CA has high demands on laboratory skills and very time consuming and few cytogeneticists are trained.
MN	MN is a very promising biomarker with predictivity of cancer, automatisation of scoring and smaller demands on skills.
'Omics'	Omics technologies develop a new breed of biomarkers of environmental health which, in contrast to traditional ones, allow the use of the same generic methodology (e.g., microarrays) for the detection of cellular responses to different categories of chemicals and types of toxicity and provide mechanistic information at an unprecedented scale. By simultaneously obtaining, in human biosamples, a global picture of the functional state of the cell at the levels of DNA, RNA, proteins and metabolites, and integration into a holistic view of the perturbation of cellular pathways by the environment, provides a paradigm shift for environmental biomarker research and molecular epidemiology (EnviroGenomarkers).

Ideally, HBM should provide information about health risk by linking the exposure to adverse health outcome. Another way of closing the gap between exposures and health outcomes lies in the use of effect biomarkers. Biomarkers of biologically effective dose are more closely related to adverse health effects however, require validation in large studies.

Few effect biomarkers have been introduced in environmental health studies, and only very few (e.g. micronucleus test (Fenech & Bonassi, 2011) and markers for kidney function have been validated and linked to exposures and health effects. High-throughput technologies have recently revolutionised the field and make it possible to generate simultaneous information on thousands of gene transcript, proteins, metabolites, epigenetic marks and -omics (Wild, 2005).

The challenge is to link these signatures to both exposures and health. The metabolome, is dynamic through life and can reflect the accumulated effects of multiple exposures or give signs of susceptibility to disease and underlying pathology. The human metabolomic profile can be influenced by genetic and epigenetic alteration leading to altered gene expression (Nicholson et al., 2011). Metabolites of endogenous molecules have recently been associated with environmental exposure (cadmium), diet and blood pressure (Ellis et al., 2012).

Epigenetic changes can be driven by environmental factors and may, for example with Arsenic exposure, be a historical biomarker of that exposure. These epigenetic changes may be conserved through subsequent cell division, and additionally fertilisation and thus through generations (Jirtle &

Skinner, 2007). Changed methylation patterns in promoter regions of specific genes have been discovered that are associated with chemical exposures and diseases (Perera et al., 2009).

MicroRNAs (miRNAs) are short non-protein-coding RNA species that have regulatory function in modulating protein translation from specific mRNAs. Certain miRNAs exhibit marked tissue specificity, and appear to be dysregulated in response to specific pathological conditions and exposure to toxic agents. miRNAs are detectable in various biological fluids, paving the way for their use as accessible biomarkers of exposure and effect (Weiland et al., 2012) . Many miRNA species are regulated by epigenetic change in and miRNAs are considered to be the possible means by which epigenetic marks are transferred to the zygote after fertilisation. miRNAs, seen altered in response to either exposure or the effects of exposure, will be analysed for potential epigenetic control regions and these analysed for epigenetic change associated with exposure.

A combination of independent measures of exposure and a range of biomarkers is the best tool available in human health risk assessment.

3.4. HBM techniques and requirements

HBM is performed on human tissue (feasible parameter in biological matrices) and implies recruitment of study persons, informed consent, sampling, sample processing, and sample analysis with suitable and reliable analytical methods, data reporting, interpretation and communication. These steps are normally described in a study protocol approved by ethics committees and sponsors including the following elements:

1. **Study Population** where the representatively is considered, age groups, gender, habitation, occupation
2. **Study Design** where the number of study persons are defined, the cross-sectional or cohort design, power of the study
3. **Selection of Participants/Samples** where the actual number of study persons is specified and distribution into age classes, gender, exposures and the number of samples to request from each study person
4. **Recruitment** of participants is described (via census registries, via local newspapers or organisations, workplaces)
5. **Field Work** is often developed from a pilot study setting the optimal program for sampling and processing of samples. For example, urine samples are normally provided as the first morning void or collection of urine from a 24-hour period. The samples must be handled in a uniform manner (e.g. cooling procedure) securing reproducible results.
6. **Questionnaires** will provide information about a number of critical issues related to the study person such as demographic data, socioeconomic data, lifestyle and specific exposures in the environment (e.g. from traffic and/or from occupation).
7. **Chemical Analysis** of the samples should follow well-defined standard operation procedures for analyses to ensure validity of the result.
8. **Interpretation** of HBM results involves the use of external monitoring data and pharmacokinetic modelling. It should be based on health based guidance values, which translate the measured dose to health risks.
9. **Communication** involves study participants as well as translation of aggregate results to policy makers and the general public at various levels. It is based on a communication plan

with targeted information tools from the start of the fieldwork to the dissemination of individual and aggregate levels results.

10. **Harmonisation of Data Treatment and Evaluation** is necessary when comparing measurements and for publication purposes.

11. **Quality Control** is to be included in all steps of the process.

12. **Feedback of results** to participants - at an individual level if agreed and on group level to sponsoring institutions while respecting the data protection.

The steps involve the following stakeholders: researchers, statisticians, participants, communities, participant representatives, research ethics committees (regional or national) regulators, politicians, industry and the media (Pedersen et al., 2007).

According to (Angerer et al., 2007), HBM of dose and biochemical effect nowadays has tremendous utility providing an efficient and cost-effective means of measuring human exposure to chemical substances. HBM can identify new chemical exposures, trends and changes in exposure, establish distribution of exposure among the general population, identify vulnerable groups and populations with higher exposures and identify environmental risks at specific contaminated sites with relatively low expenditure. The sensitivity of HBM methods moreover enables the elucidation of human metabolism and toxic mechanisms of the pollutants.

HBM can be done for most chemical substances which are in the focus of the worldwide discussion of environmental health. This especially applies for metals, PAH, phthalates, dioxins, pesticides, as well as for aromatic amines, perfluorinated chemicals, environmental tobacco smoke and volatile organic compounds. A number of sensitive analytical methods have been developed to measure low concentrations including trace amounts of various chemicals in biological samples such as urine and blood (WHO, 2012).

Blood and urine are by far the most approved biological matrices (Angerer et al., 2007). In addition human milk has frequently been used particularly for persistent organic pollutants (Berlin et al., 2005; LaKind et al., 2005). In more recent years hair has become an important biological specimen, alternative to the usual blood and urine samples. Saliva has been used to evaluate a broad range of biomarkers, drugs, and environmental contaminants, including toxic metals and pesticides. Sometimes the ratio between the concentration of a metabolite product and that of the parent chemical in blood or urine is the biomarker not the chemical or the metabolite per se. (Manno et al., 2010a).

Protein adducts, especially haemoglobin (Hb)-adducts, are used as surrogates of deoxyribonucleic acid (DNA)-adducts as they can specifically and sensitively measure exposure as well as biochemical effect. They are better means to estimate cancer risk than measuring genotoxic substances and their metabolites in human body fluids. Although the analytical procedures are intricate, Hb-adducts of alkylating agents, aromatic amines and nitro aromatic compounds are nevertheless determined routinely today.

DNA-adducts indicate the mutagenicity of a chemical substance as well as an elevated cancer risk. DNA-adducts, therefore, would be ideal parameters for HBM. However, although there are very sensitive techniques for DNA adduct monitoring like P^{32}-postlabelling and immunological methods, they lack specificity. For elucidating the mechanism of carcinogenesis and for a broad applicability and comparability in epidemiological studies, analytical methods must be elaborated, which are strictly specific for the chemical structure of the DNA-adduct.

In HBM studies with exposure to genotoxic chemicals, the measurement of DNA strand breaks in lymphocytes and 8-hydroxy-2'-deoxyguanosine (8-OHdG) in white blood cells has become very popular. However, there is still a lack of well-established dose-response relations between occupational or environmental exposures and the induction of 8-OHdG or formation of strand breaks, which limits the applicability of these markers.

Most of the biomarkers used in population studies are covered by standard operating procedures (SOPs) as well as by internal and external quality assessment schemes. Therefore, HBM results from the leading laboratories worldwide are analytically reliable and comparable. There are specialised laboratories that are able to elaborate the analytical prerequisites for chemicals that gain political or scientific interest in limited time. On the other hand, it is getting more difficult for the laboratories to keep up with a progress in instrumental analyses.

As biomarker concentrations vary both within and between individuals, the variation in biomarker concentrations observed in a population biomonitoring study is not easy to interprete. In addition the biological media selected for sampling affects biomarker concentrations independent of other factors. Finally also disease states in particular renal or hepatic diseases impacts on biomarker variation (Aylward et al., 2014).

In general, urinary concentrations are not necessarily directly informative about concentrations at target tissues of interest in the body. However, as urine collection is a non-invasive procedure that is easily applicable for almost all population (sub-) groups, it remains an essential matrix in all population HBM surveys or for studies that require repeated sampling (Smolders et al., 2009).

Blood biomarker concentrations provide a measure of exposure that is more closely relevant to target tissue concentrations. However, relationship between the biomarker being measured and the toxicologically active compound has to be taken into account. If the biomarker is a deactivated metabolite, the relationship between the blood concentration of that metabolite and the active compound at the target site of interest may not be straightforward (Aylward et al., 2014).

Aylward et al. (2014) states that any discussion of the application of HBM to chemical exposure characterisation and assessment of variability in biomarkers needs to take into consideration different exposure definitions, such as exposure characterised in terms of external media concentrations, exposure characterised in terms of intake dose or absorbed dose, or exposure defined as peak concentration from a sensitive time point to lifetime. Factors affecting variation in biomarker concentrations may influence the relationship between biomarker concentration and the various exposure definitions in different ways.

Given the wide range of biomarkers, biological matrices, analytical methods and influencing factors the study design is a critical aspect in efficient use of HBM in risk assessment. This comprises the planning of which biomarker(s) should be measured, in which biological fluid or tissue, when and how many samples should be collected and from which study populations. The choice of matrix and biomarker depends on factors such as the toxicokinetics, the validity (specificity and sensitivity) and toxicological significance of the biomarkers available, their stability and reproducibility, the purpose of the HBM program, the size and characteristics of the study population, and many others. Further important aspects are the choice of the statistical methods to be used, and an estimate of the cost-benefit and/or risk-benefit analysis, and an evaluation of the ethical procedures and constrains (Manno et al., 2010b).

As Biomarker studies allow processing and storage of biological samples an efficient study design should ideally include provisions for processing the original samples, such as cryopreservation, DNA isolation, preparation of specimens for future exposure assessment and other potential uses (Holland et al., 2005).

3.4.1. Strength and limitation of HBM in risk (exposure) assessment

HBM is the only available tool that integrates exposures from all sources and provides data to epidemiology enabling studies of strengths of associations, dose response relationships. Biomonitoring data reflect the internal dose at a point in time.

However, HBM data does not differentiate the exposure by source, and HBM alone cannot provide information about the source of exposure or how long a chemical has been in the body. For translation of HBM data into daily exposure estimates there is need of a detailed understanding of the potential analytical/methodological pitfalls and of the toxicokinetics of the individual chemical.

As the human body burden and the development of potential health effects depend on many factors, such as fluid/tissue type, time of collection, containers used, preservatives and other additives, storage temperature, transport means and length of transit time, may affect the quality and stability of the samples and the measurement of biomarkers (Manno et al., 2010b), and the linking to specific sources can be very difficult, results from HBM studies needs proper and careful interpretation and clarification by experts in order to serve as a policy tool. Finding a chemical does not imply that it will cause a disease to develop.

In particular, for non-persistent chemical with short elimination half-lives, within-day, between-day and between-person variabilities can be high. Toxicokinetic studies in humans are needed to show major metabolisation pathways, excretion routes and timing of the elimination process. First-pass effects, conjugation and elimination characteristics highly influence the results.

With low tissue levels in the ng/kg body weight range, the detection of biomarkers can be an analytical challenge that is additionally complicated by contamination and the potential instability of conjugates. With urine sampling, the type of sampling (spot urine, 24h urine or morning void) is an important factor as is the use of volume-based or creatinine-based urinary concentrations. Changes in protein/fat composition and enzyme activity impact on reliability of human milk samples.

Analytical sensitivity in terms of detection and quantification rates (LOD and LOQ) is a crucial aspect for a reliable determination of internal dose.

Given the variability of the internal dose, documentation shall include a measure for the central tendency by means of geometric mean (GM) and the median (P50) as well as information on high exposures by means of the 95th percentile (P95). The P95 of the urinary concentration has different interpretations depending on whether spot urine samples, first morning urine samples, or 24-h samples are used.

Furthermore, anti-contamination measures during sample work-up and the analytical procedure are important to limit the issue of potential contamination during the collection and storage of human samples.

The core criteria for use of HBM data in the (risk) exposure assessment comprise the following:

- The recovery of the method (the percentage of the true concentration of a substance recovered during the analytical procedure depending on the internal dose)
- The repeatability of the method (relative standard deviation RSD)
- The limit of detection and/or limit of quantification [expressed as multiples of the signal-to-noise ratio (S/N) of the (chromatographic) background signal]
- The selectivity of the method (consideration of interferences)
- Measures to reduce or avoid background contamination
- Method-performance data

In addition, HBM raises important ethical and privacy issues due to the fact that it involves taking samples in humans and partly even needs to be invasive (blood samples).

To extend the spectrum of biochemical effect monitoring, further methods should be elaborated, e.g. cleavage and separation of the adducted protein molecules as a measure of sample preparation. This way, all sites of adduction as well as further proteins, like serum albumin, could be used for HBM.

For elucidating the mechanism of carcinogenesis and for a broad applicability and comparability in epidemiological studies, analytical methods must be elaborated, which are strictly specific for the chemical structure of the DNA-adduct. For induction of 8-OHdG or formation of DNA strand breaks, there is still a lack of well-established dose-response relations between occupational or environmental exposures, which limits the applicability of these markers.

In spite of all limitations, it is worthwhile to aim for the ultimate summit of HBM because it is the only way to identify and quantify human exposure and risk, to elucidate the mechanism of toxic effects and to ultimately decide if measures have to be taken to reduce exposure. Risk assessment and risk management without HBM could lead to wrong risk estimates and cause inadequate measures. In some countries like in the USA and in Germany, thousands of inhabitants are regularly investigated with respect to their internal exposure to a broad range of environmentally occurring substances. For the evaluation of HBM results, the German HBM Commission elaborates the use of reference- and HBM-values (Angerer et al., 2007).

3.5. Possible application of HBM to the different steps of risk assessment in food safety areas

A specific challenge related to risk assessments of chemicals is the assessment of the risk stemming from contaminants in food and feed. The presence of such chemical contaminants or other unwanted substances in food and feed is often unavoidable as these substances may occur ubiquitously. EFSA has established for this purpose the Panel on contaminants in the Food Chain (CONTAM Panel). In addition regulated chemical substances such as food contact materials, pesticides or veterinary pharmaceuticals may be present in food as unwanted substances that need to be assessed.

The risk assessment of chemical contaminants in food is based on the integration of two aspects: knowledge about the human exposure to these substances via food and other routes, and their potential to cause adverse health effects.

The safety of chemicals is assessed following the four steps of risk assessment, namely hazard identification (genotoxic, carcinogen, endocrine disruptive, etc.), hazard characterisation (dose-response relationship, mechanisms/mode of action, kinetics, etc.), exposure assessment (external,

internal), and risk characterisation. Important considerations in risk assessment include windows of susceptibility. Human exposure is a key element in risk assessment (Alexander et al., 2012). In conventional exposure assessment to contaminants from food, occurrence levels in food are linked with consumption patterns across European populations (available in a database due to national surveys etc.). Whenever possible, the CONTAM Panel sets an exposure level where there is no appreciable health risk. This is known as a health-based guidance value (HBGV) such as an ADI or TDI or Tolerable Weekly Intake (TWI) (see chapter 4.2.3.2). If human exposure to the substance from food and other sources is below the HBGV, the CONTAM Panel usually concludes that such exposure does not pose an appreciable risk to human health. However, the HBGV approach is not suitable for genotoxic substances. For unintentionally-occurring substances, no additional toxicological information is provided by the manufacturer, and databases are often incomplete and limited (e.g. for certain marine biotoxins and many mycotoxins). For substances that cause genotoxicity by a mechanism involving reaction with DNA, the EFSA Scientific Committee proposed the margin of exposure (MOE) approach as a harmonised approach for the risk assessment of substances that are both genotoxic and carcinogenic.

However, the CONTAM Panel seeks to find ways to improve and refine its human and animal risk assessments. They rely on further integration of prospective data, and there is increasing evidence that HBM could play an important role in future exposure assessment. There are still considerable uncertainties to translate findings in selected experimental model systems to an understanding of human toxicology (e.g. various routes of exposure).

According to the risk management paradigm as formulated by the EU, both the dose-response relationship and the exposure data is required to characterise the health risk of a specific chemical hazard to subsequently decide whether the risk is such that management is required. In the standard European Union risk assessment process, the risks for industrial operators, for consumers and for 'man through the environment' are assessed. The last category relates to health risks of the general public potentially caused by exposure from chemical substances in the environment. For a comprehensive risk management, more qualitative and quantitative data related to toxicokinetics, toxicological endpoints, and the strength of evidence are requested.

HBM data is strengthened with the knowledge of the kinetics and toxicological effect levels of a substance of interest. Often information of the toxicokinetics is gained from animal studies, and interspecies extrapolation is necessary. The toxicokinetics together with sufficient toxicological knowledge (e.g. reproductive or carcinogenic effects) complement the HBM data and increases the weight of evidence for risk assessments and risk-based decision making.

Based on but not limited to occupational risk assessment, Manno et al. (2010) identified potential of HBM in the different steps of the classic, general definition of risk assessment by the USA's National Research Council.

3.5.1. Hazard identification

For hazard identification, all classical toxicological test results must be assessed and this is conventionally performed in toxicology studies in vivo or in vitro. HBM has a role in exposure assessment and for some toxicological studies where the actual in vivo exposure can only be found from biological monitoring. In addition HBM can provide the observation of an increased individual or group level of a potentially toxic chemical, or its metabolite(s), in blood, urine or other biological samples from exposed populations as compared to those of control individuals (Manno et al., 2010a). According to the ECHA Guidance on Derivation of DNEL/DMEL from Human Data, human data can be used in hazard assessment under the obligation to derive limit or guidance values (DNEL/DMEL) (ECHA, 2010) and as part of the Chemical Safety Assessment. Forward or reversed dosimetry

comparing human and experimental animal concentrations bridge toxicology and human effects (Clewell et al., 2008).

3.5.2. Hazard characterisation

HBM can contribute to estimate either side of the dose-response equation, i.e. it may help to measure the dose (as the biological level of a chemical or its metabolite(s) corresponding to a given level of exposure) or to detect the response (the proportion of individuals showing some early adverse effect at a given level of exposure) or both (Manno et al., 2010b).

According to (Angerer et al., 2012), it is possible to study with HBM human metabolism and toxicokinetics under conditions of background exposure. This enables the collection of information on mode of actions in order to select valid parameters for HBM and to calculate dose and health risks.

In food risk assessment, the CONTAM Panel has been able to model human data and to incorporate information from biomarkers of exposure or of effect in the characterisation of the hazard, e.g. cadmium and lead (EFSA, 2009; EFSA CONTAM Panel, 2009, 2010). This allows the use of a body burden approach, where an estimate of systemic exposure (body burden), rather than external dose, is used in the risk characterisation, but the use of HBM is still limited.

Besides this aspect, hazard characterisation relies on toxicological test. Data from different test types, ideally retrieved from the OECD pick list form the basis of hazard characterisation. The test types are:

- acute oral toxicity (OECD phrase ID 1703)
- acute toxic class method (OECD phrase ID 51)
- avoidance (repellency) (OECD phrase ID 1745)
- chronic (OECD phrase ID 1797)
- combined repeated dose and carcinogenicity (OECD phrase ID 1807)
- combined repeated dose and reproduction / developmental screening (OECD phrase ID 4842)
- epidemiological
- fixed dose procedure (OECD phrase ID 770)
- other (OECD phrase ID 1243)
- reproduction toxicity (OECD phrase ID 2316)
- short-term dietary toxicity (OECD phrase ID 2357)
- standard acute method (OECD phrase ID 1578)
- subacute (OECD phrase ID 2398)
- subchronic (OECD phrase ID 2399)
- up and down procedure (OECD phrase ID 1653)

Toxicological data are commonly derived from animal experiments and biomarkers of exposure are becoming more common in these studies to verify and quantify the actual exposures and to bridge with human exposure situations. Analytical methods and standards developed during the toxicological study however, are transferrable to human biomarkers.

3.5.3. Risk characterisation

Risk characterisation combines the information from hazard identification and exposure assessment. Based on but not limited to occupational risk assessment (Manno et al., 2010b), HBM can be used to perform or validate risk assessment when environmental monitoring and health surveillance are unavailable or inadequate due to an intrinsically low sensitivity and/or specificity. HBM also allows assessing specific, otherwise inaccessible, components of risk, such as metabolic polymorphism, enzymatic inhibition or induction of the metabolizing enzymes and other susceptibility factors which may be responsible for a different response to chemicals.

In addition, the results of HBM surveys can be used for risk management. As internal dose (biomarkers of exposure) are determined by lifestyle factors, environment and personal factors, elevated levels in certain subgroups allow to trigger policy interpretation and remediation measures, public information and sensibilisation and the definition of vulnerable subgroups (see also chapter 4.2.2).

3.5.4. Exposure Assessment

Whereas the potential of HBM in hazard identification and hazard characterisation is limited, HBM has a critical role in exposure assessment as HBM will provide the ultimate data on actual exposure. HBM has the advantage that it integrates exposures from all sources: environmental exposure, lifestyle exposures and individual susceptibility (see Figure 4). HBM provides the summary impact of environmental pollution, lifestyle factors such as dietary habit, smoking or consumer products use and personal susceptibility determined by gender, age, genetic background, and body composition.

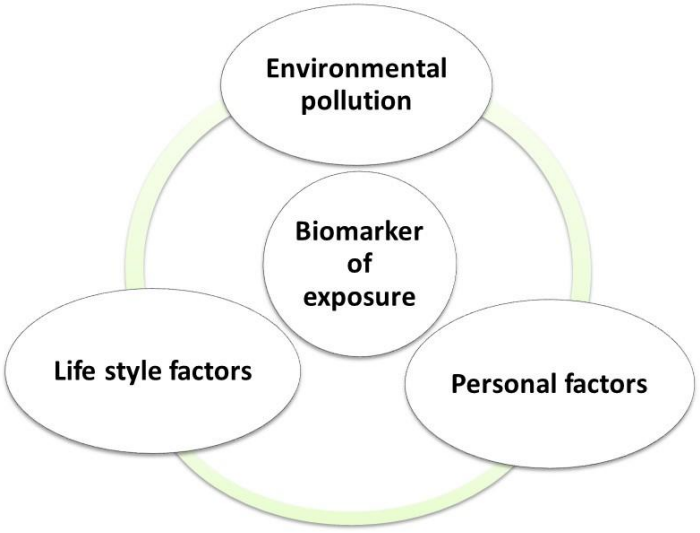

Figure 4 Biomarkers of exposure as the sum of environmental pollution, lifestyle factors and personal susceptibility, adapted from (Schoeters et al., 2012b)

Biomonitoring is a direct approach to estimate the human exposure from all sources and via all uptake routes (Angerer et al., 2007). It reflects the absorption following inhalation, ingestion, dermal absorption of all exposure sources such as water, air, soil, dust, personal care products and food. The approach is called direct because it can be directly related to the internal dose, which has actually

entered the systemic circulation (see Figure 5). If a substance is not absorbed, it will not enter the body circulation and the health effects may be none.

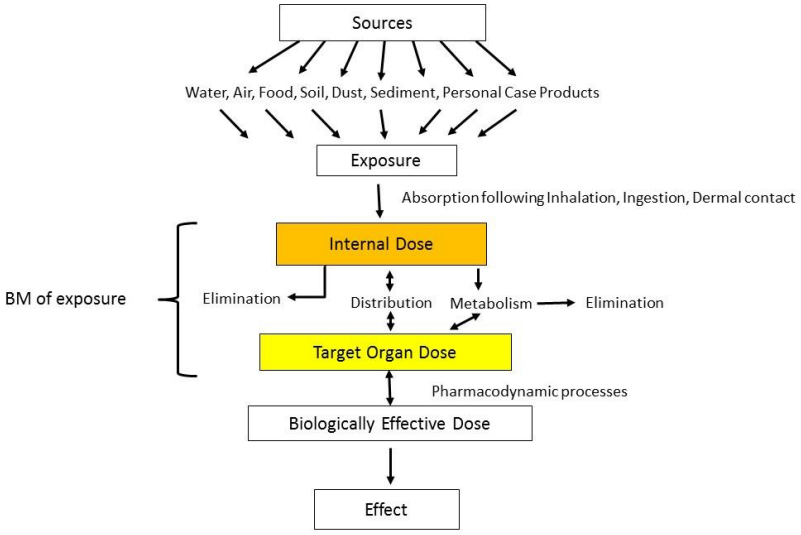

Figure 5 The role of HBM in the causal exposure-effect relationship, adapted from (Needham, 2005)

According to (Aylward et al., 2014), "HBM has become a primary tool for exposure assessment in a wide variety of contexts, including population monitoring at national level, and individual exposure assessments in the context of epidemiological research into potential adverse health effects of chemical exposures" besides other "due to improvements in analytical chemistry, including growing lab capacity and reductions in cost, coupled with the increasing focus on more subtle exposure levels that involve more complex exposure sources and routes of exposure".

The major advantage of HBM is the possibility to reduce the number of assumptions that have to be made regarding consumption rates. Another major advantage is the integration over all routes and sources that may elucidate exposures that have not been anticipated or have been neglected in external aggregate exposure assessments and/or models. For the complex health risk assessment for the general public, HBM surveys are the ideal tool to collect exposure data from European populations. Biomonitoring data may be especially valuable for combined exposure estimations (e.g. for consumers).

Environmental monitoring and HBM are complementary tools. However, biological measures of exposure should be preferred, if available, to environmental exposure data as they are closer to the target organ dose and provide greater precision in risk estimates and in dose–response relationships. HBM is often more specific and sensitive than environmental monitoring (e.g. food monitoring) in assessing the degree of recent and, by all means, also past exposure to chemicals from all routes (Manno et al., 2010b). HBM is particularly valid to assess chemical persistence, can provide a measure of the past exposure, the early adverse effect, and the individual susceptibility to these persistent environmental chemicals and may be particularly useful to assess and control the risk of long-term outcomes associated with their exposure. An example for the role of HBM in exposure assessment and its relation to other HBM techniques and requirements (e.g. questionnaire data, environmental monitoring data) is provided in Figure 6.

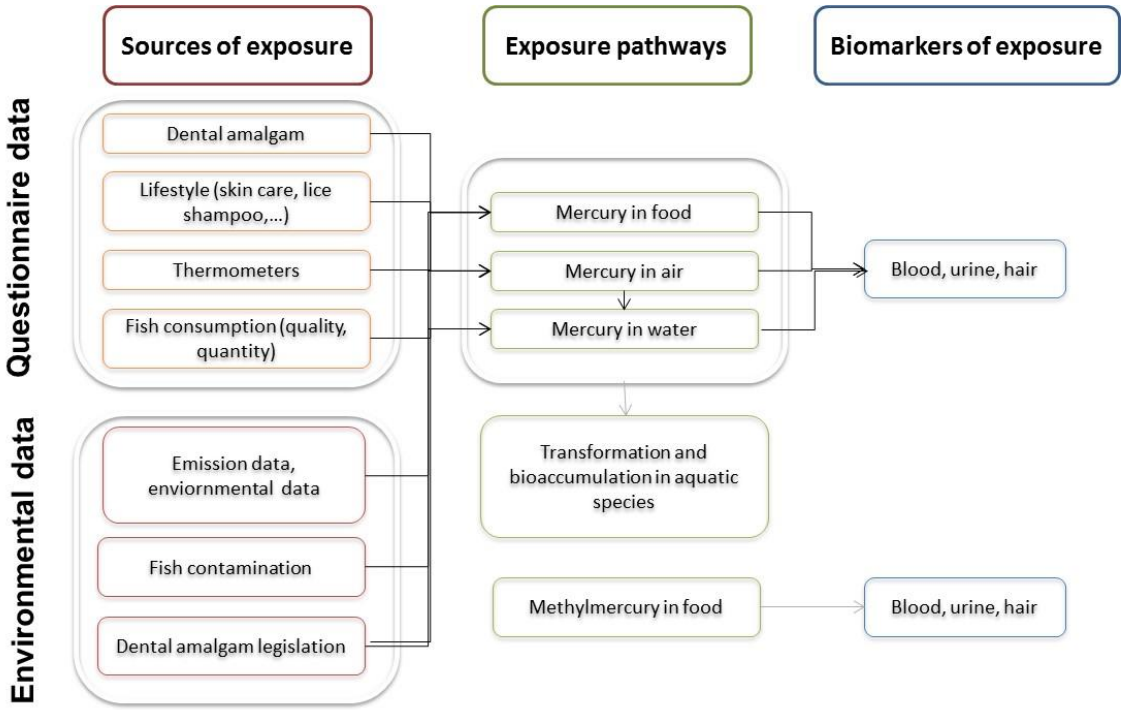

Figure 6 The role of HBM and other data sources in mercury exposure, adapted from (Schoeters et al., 2012b)

In combination with questionnaire information, HBM data may provide information about sources such as patterns of dietary habits. Higher levels of acrylamide adducts in haemoglobin, for example, have been observed in populations with high intake of fried food (Vikstrom et al., 2012).

It has been emphasised that HBM data is particularly valuable for establishing baseline measures of human exposure, but that the evaluation of potential health risk remains a difficult and uncertain task (Clewell et al., 2008).

Due to the fact that HBM data reflect internal exposure whilst the traditional risk assessment and the resulting estimates of safe exposure are generally based on external exposure, health HBM data need to be interpreted by means of forward or reverse dosimetry. PBPK models provide a useful way of accounting for the various factors controlling overall compound elimination and how variations in the various factors are translated into concentrations of compound/metabolite in blood and tissues (Aylward et al., 2014).

HBM survey data can be interpreted for risk management purposes by means of HBM-related guidance values, which are currently developed only in the USA and in Germany. In Germany, these type of HBM-related guidance values are called HBM values (HBM-I and HBM-II). In the United States, they are called Biomonitoring Equivalents (BE; see also chapter 4.2.3.3). These values translate established HBGVs (e.g. TDIs, RfDs) into a biomarker concentration value (Angerer et al., 2011). The use of HBM surveys in combination with HBM values or BEs will allow initial screening of population exposure to chemicals, assisting in priority setting and ultimately leading to improved product stewardship and risk management, and the use of actual HBM data coupled with the corresponding BEs has the advantage of allowing a risk assessment under real-world conditions.

Population-based sampling can provide valuable information as to whether exposures are likely to reach or exceed the health-based reference value even for substances even with short half-life (e.g. BPA, toluene). HBM data can reduce uncertainties of exposures estimates, and properly designed targeted studies could inform the exposures of people with unusual exposure conditions (Boogaard et al., 2011).

3.5.5. Possible application of HBM for the implementation of a systematic Post-Market Monitoring (PMM)

PMM, also known as post-launch monitoring (PLM) or post-market surveillance (PMS), is a concept that has not been specifically defined but has been used in the context of testing the conclusions drawn from the pre-market risk assessment, e.g. confirmation of the extent to which the product is being consumed by its target group and estimation of exposure in other population groups (Hepburn et al., 2008). The concept has received attention recently as a potential tool in the approaches available for evaluating the safety of novel foods and ingredients (EFSA GMO Panel, 2011; Hepburn et al., 2008). In principle, however, the PMM methodology is applicable to all food groups.

As mentioned in the EFSA guidance document of the Panel on Genetically Modified Organisms (EFSA GMO Panel, 2006), risk assessment studies cannot fully reproduce the diversity of the populations who will consume the marketed product, and risk assessment relies on an estimate of the intake of the food which is variable and subject to uncertainty.

According to (Hepburn et al., 2008), PMM (e.g. for novel food) may provide the means to evaluate the actual intake of a food by consumers and may increase the probability of detecting adverse effects in small, well characterised segments of the population deemed most at risk in the pre-market assessment, when they are exposed to the food during long periods of time under conditions of everyday life. It may thus provide helpful reassurance that the potential for an adverse effect, judged a priori during the pre-market assessment to be of low probability, is indeed unlikely for the significant majority of consumers PMM is a hypothesis-driven, scientific methodology for obtaining information through consumer investigations. Elements of PMM focus on the description and quantification of at-risk groups and target groups, and on the description and quantification of any health effects consequent on dietary behaviour. PMM has been used as a complement to safety assessment in a few specific cases, but has not been routinely undertaken to date, nor has it been routinely required.

The following specific purposes of PMM as complement to risk assessment are considered to be in particular:

- Reassurance that any occurrence of known risks in the general population is of low frequency and intensity and not exceeding the estimated daily intake and any significant adverse effects occur
- The monitoring of real consumption patterns if estimated daily intake (EDI) is close to the acceptable daily intake (ADI)
- Monitor the extent of use by the target population and/or by other groups in the population if a product was intended for use in foods for certain target populations
- Monitor potential misuse of a product (over-consumption, or use in applications not originally intended)
- Collection of any ‘signals,’ which may be suggestive of a health-related event

- Exploration of any health related hypotheses generated by new issues after the established risk assessment
- Investigation of unexpected complaints

Consequently, the determination of real-life exposure for verification of risk estimates if a major objective of PMM.

Given the fact that HBM is a valid tool for individual and group level exposure assessment to environmental contaminants and chemicals (see chapter 3.5.4), HBM is generally useful for the implementation of a systematic PMM approach for regulated chemical substances, if appropriate analytical methods and validated biomarkers are available and if the up-take of the regulated substance is predominantly via dietary intake.

One recent example that HBM can be a very powerful tool for PMM providing data on actual intake related concentrations in the human body is the high level of methylmercury in hair detected in sushi-eating females that lowers when the amount of tuna fish intake is minimised [*The Unborn.* (2014) TV documentary. DR1 (Denmark), 3 Nov.].

3.6. Usefulness of HBM for exposure assessment of chemical substances from food source

HBM is useful for exposure assessment of chemical substances from food source. HBM can demonstrate trends and changes in exposure, establish distribution of exposure among the general population, identify vulnerable groups and populations with higher exposures and emerging chemical risks. The sensitivity of modern analysis methods allows insight into human metabolism and toxicokinetics of chemicals. Depending on biomarkers used HBM does not only allow to monitor exposure but also to detect early health effects.

HBM has not a major role in hazard identification, but could be used for verification of an increased individual or group level in an exposed/diseased subgroup compared to controls. In hazard assessment HBM can contribute to estimate either side of the dose-response equation as it may help to measure the dose or to detect the response or both. The core role of HBM in risk assessment is human exposure assessment. The major advantages of HBM are the possibility to reduce the assumptions regarding consumption rates. HBM is often more specific and sensitive than environmental monitoring in assessing the degree of recent and past exposure to chemicals. HBM data is particularly valuable for establishing baseline measures of human exposure. In risk characterisation HBM can be used to perform or validate risk assessment. HBM allows in addition to assess specific, otherwise inaccessible, components of risk, such as metabolic polymorphism, enzymatic inhibition or induction of the metabolizing enzymes and other susceptibility factors which may be responsible for a different response to chemicals.

In PMM, HBM could be a valuable tool to verify risk assessment results. It could be used to monitor real exposure if estimated daily intake (EDI) is close to the acceptable daily intake (ADI), to collect any ‘signals’, which may be suggestive of a health-related event, to explore any health related hypotheses that are generated after the risk assessment has been established and to investigate unexpected complaints.

But further efforts have to be taken to increase the usability. This relates to the interpretation of HBM results, where HBM data need to be interpreted by means of forward or reverse dosimetry, such as PBPK modelling or HBM Values and BE that translate established reference values into a biomarker concentration as well as to the availability of validated biomarkers of exposure for priority substances

related to food. Data storage and accessibility as well as comparable data collection and communication are further challenges that have to be tackled together with the issue of high costs.

Major challenges are the integration of HBM in surveillance infrastructure (synergies), the prioritisation of substances of concerns (biomarkers) to be monitored, the development of appropriate reference values for exposures and of health based guidance values, the development of European wide comparable study protocols, and analytical methods, the establishment of quality assurance/control (QA/QC) systems and the sample and data storage for retrospective trend analyses and international cooperation/exchange in the light of ethical and data protection issues. In this context there is need for a consistent interpretation of data across Member States.

If biomarkers and HBM are to contribute to EU environment and health policy and interventions, they have to be relevant and accurate, provide information that cannot be obtained otherwise and bring about acceptable consequences for the study subjects. This includes a strong need for external quality assessment schemes to ensure comparability of biomonitoring results.

The questions that need to be answered and information that needs to be available in order to be able to use HBM as policy tool are as follows:

1. Existence of valid accurate and relevant biomarkers,
2. Reliable and scientifically robust analysis data
3. Appropriate infrastructural framework and data accessibility
4. Effective translation of study results into policy decisions
    a. Combination with environmental and health data and modelling work
    b. Comparison with reference ranges and guidance value,
    c. Thorough data interpretation and communication
5. Feasible cost-benefit relations and funding systems
6. Well accepted chemical parameters and study design

For most exposure biomarkers, the relationship with health effects remains currently unclear. This limits the interpretation of biomonitoring data in terms of health risk (Casteleyn et al., 2009). In addition, there is urgent need to develop suitable HBM methods for emerging chemicals in food safety.

3.6.1. Strength and limitation of HBM in risk (exposure) assessment and for the implementation of a systematic PMM approach

HBM is one of the existing tools to determine the causal chain between environmental or occupational hazards and potential health effects. HBM in this context can be used principally both for uptake monitoring and for effect monitoring as indicated in the figure above. Exposure monitoring identifies the pollutant or chemical concentration in human tissue (biomarkers of exposure). Effect monitoring determines the reaction to pollutants or chemical burden in human bodies including potential health effects (biomarkers of effect or biomarkers of susceptibility).

Major advantages of HBM in risk assessment are the analysis of contamination levels and trends, the personalisation of exposure and potential risks (awareness raising effect), and the verification of exposure and risk estimates.

One strength and advantage of HBM in exposure assessment is the fact that it reveals the actual body burden of an individual person independent from the source and route of exposure by summing up and integrating the combined effect and taking into account processes like metabolism, bioaccumulation and excretion. Another advantage is that it is closer to health effects than environmental monitoring, that it getting pollution personal, and having a strong awareness raising and educational effect. Finally it can show geographical and socio-economic differences in exposure and body burdens.

HBM can support monitoring/surveillance of control the efficiency of political risk reduction measures or substitution of regulated substances, it can provide data for identification of needs & priority setting in policy, and contribute to a decision basis for management measures such as the establishment of limit values. Findings from HBM surveys may also encourage initiation of further investigations and identifications of potential substances of very high concern (SVHC) or chemicals of equivalent concern. The major limitations of HBM in risk assessment include the inability to differentiate by source, the variability of results and the difficulty to trace back past exposure for short-lived substances.

HBM offers the confirmation of human exposures enabling parallel assumptions by dosimetry of adverse human effects from effects seen in toxicological studies. In such comparisons, however, the toxicokinetics must be included. By comparisons of exposures in different population studies, more solid data on associations can be provided. HBM is limited by availability of reliable and sensitive analytical methods, and the biomarkers must reflect the risk. Table 6 provides specific strength and limitations of HBM in the four different steps of risk assessment.

Table 6 Strength and limitations of HBM in the risk assessment process

Step in process	Benefits of HBM	Limitations of HBM
Hazard identification	May contribute from epidemiological studies bridging exposures and adverse effects	BM is not performed in all experimental toxicological studies, thus not enabling comparison to human levels
Hazard characterisation	May contribute from epidemiological studies bridging exposures and adverse effects	If BM is a part of the experimental toxicological studies, the species-specific toxicokinetics have to be taken into account
Exposure assessment Post-Market-Monitoring	HBM provides the ultimate proof of human exposure	Analytical limitation (insufficient sensitivity) may develop false negatives
Risk characterisation	The size and power of the HBM study may specify the human risk if epidemiological data can confirm	The biomarkers may not reflect the risk

HBM data derived in a reliable and comparable way integrates the exposures from food as well and lifestyle taking individual characteristics of age, gender, body composition, disease in the study persons into account.

Such information collected for groups can be used by regulators and politicians for standard setting and for communication of eventual risks to the populations, eventually identifying susceptible groups. Regional and national comparisons may reflect specific food habits, e.g. fish eating in the Mediterranean countries resulting in highest mercury levels found in Europe.

However, as with any method of characterising exposure, there are numerous factors that influence variation in biomarker concentrations in addition to exposure magnitude and have to be taken into account. Measured biomarker concentrations may hence not be interpreted as direct surrogates for exposure level, and biomarker concentrations may not be assumed to be linearly related to external exposure levels but factors related e.g. to timing of sample collection, biological matrixes and chemical toxicokinetics need to be taken into account (Aylward et al., 2014).

Regarding hazard identification, BM of concentrations in experimental studies reflecting the uptake, distribution, metabolism and excretion in the animal studies have only recently been introduced and are currently not requested in all toxicological studies. Furthermore, the toxicokinetics may differ between human and experimental species, limiting the extrapolation between the results of adverse effects at given concentrations in experimental studies and eventual human effects during hazard characterisation.

In addition, the lack of appropriate BM of exposure and effect, the complexity of method development, the comparability of results in the light of varying study design and the costs are further aspects that limit the use of HBM.

In PMM as a specific form of exposure assessment, all strength and limitations of HBM for exposure assessment apply equally.

In Table 7, strength and limitations of HBM are specified for the individual steps that are of relevance in PMM from the study person via the selection of the biological sample, sampling and analysis to the potential for identification of the relevant exposure source.

Table 7 Strength and limitation of HBM in implementation of a PMM

	Strength	Limitation
Element of HBM in PMM		
Study persons	Provide human evidence of actual exposure	May be selected from non-exposed and provide non informative results
Biological matrix	May mimic target tissue e.g. blood that comes into contact with vital organs	The half-life of the substance may invalidate the results in a given matrix
Sampling	Provides real exposure data from humans at fixed time points	If half-life is short false negative result may arise is samples are taken long time after exposure
Analysis	Signifies exposures if validated analytical techniques are used	The detection limits may not be sufficiently sensitive to reflect the actual exposures
Source identification	Proper questionnaire and/or interview may identify known and unknown sources	Instruction in proper response to questionnaires is often difficult
Risk/safety evaluation	If toxicology is well described with NOAEL risk assessment may be complete	Proper information for risk assessment is often lacking with new compounds
Communication	Satisfies the participants and consumers	May violate ethics if not respecting data protection

One of the common criticisms is that HBM represents only a snapshot in time, but this deficit also apply to the conventional exposure assessments. Following (Hays & Aylward, 2012), sources of

variability that impact interpretation of biomonitoring data are often less than the uncertainties associated with conventional external dose-based exposure assessments.

The EFSA's Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) reported in its scientific opinion on BPA (EFSA CEF Panel, 2015) that "Internal exposures to total BPA, as estimated by forward modelling, are in good agreement with the backward-modelling estimates obtained from urinary biomonitoring, suggesting that it is likely that no major exposure sources have been missed for the forward-modelled exposure assessment. It is, however, important to highlight the fact that the internal exposure estimation of total BPA includes conservative assumptions resulting in likely overestimation of exposure that could in theory have hidden other possible sources of exposure. The CEF Panel noted also that there are considerable uncertainties in the forward and backward estimates of internal exposure."

3.7. Inventory of the different HBM surveillance programmes/initiatives at national, EU and international level

This chapter provides a systematic review of major existing HBM programmes or studies in Europe (Germany, Flanders, France, Spain, Italy, Czech Republic, Slovenia, Sweden, Finland, and Norway), in North America (Canada and USA), and in Asia (primarily South Korea, Japan, and China). After an extensive literature search, only HBM studies measuring the exposure levels in the general population (i.e. not occupational workers or measurements in non-human samples) existing from 2002 on are covered in this report. For each HBM study, the funding source(s), study duration and design, the participants and its recruitment strategies, the analysed chemicals and the analytical methods used, the summary and interpretation of the study findings, the communication of results to the participants/scientific world/public, and its implications towards policy-making are addressed.

Table 8 Overview of the included HBM studies at national, European and international level

Country	Title of study	Year(s)
Germany	German Environmental Specimen Bank for Human Tissues (ESBHum)	1974- present
	German Environment Surveys (GerES I – IV)	1985- present
Flanders	Flanders human biomonitoring network (FLEHS)	2002-present
France	The French Nutrition and Health Survey (ENNS)	2006-2007, 2013-2014
	Étude longitudinal française depuis l'enfance (ELFE)	2011-present
	Étude de santé sur l'environment, la biosurveillance, l'activité physique (ESTEBAN)	2014-present
Spain	BIOAMBIENT.ES	2009-2010
Italy	Programme for biomonitoring the Italian population exposure (PROBE)	2008-2010
Czech Republic	Human Biomonitoring (Cz-HBM) as part of the Environmental Health Monitoring System (EHMS)	Since 1994
Slovenia	Slovenia's national HBM programme	2010-2012
Austria	Schadstoffe im Menschen ("Pollutants in Humans")	2008-2011
Sweden	First-time healthy mothers in Uppsala	1996-2006

Country	Title of study	Year(s)
Denmark	Danish HBM studies	2006-2012
Norway	The Tromsø cohort study	1997-2007
	The Norwegian Mother and Children Cohort Study (MoBa)	1999-present
Finland	Effects of nationwide addition of selenium to fertilizers	1985-present
AMAP	Arctic Monitoring and Assessment programme	Since 1997
Canada	Canadian Health Measures Survey (CHMS)	2007-2009 2009-2011
United States of America	U.S. National Health and Nutrition Examination Survey (NHANES)	1999-present
South Korea	The Korea National Health and Nutrition Examination Survey (KNHANES)	1998-present
	Korea National Survey for Environmental Pollutants in the Human Body (KorSEP)	2005-2008
	Korean Environmental Health Survey in Children and Adolescents (KorEHS-C)	2011-2012
	The Mothers and Children's Environmental Health (MOCEH) Study	2006-present
Japan	The Tohoku Study of Child Development	2001-2003
	The Hokkaido Study on Environment and Children's Health	2002-present
	Japan Environmental and Children's Study (JECS)	2010-present
China	National Monitoring on POPs in human milk of China	2007
EU-wide	Consortium to Perform Human Biomonitoring on an European Scale (COPHES)/Demonstration of a Study to Coordinate and Perform Human Biomonitoring on an European Scale (DEMOCOPHES)	2009-2013
	Environmental Cancer Risk, Nutrition and Individual Susceptibility (ECNIS)	2005-2013
	EnviroGenomarkers – Genomics Biomarkers of Environmental Health	2009-2013
	Integrated Assessment of Health Risks from Environmental Stressors in Europe (INTARESE)	2005-2010
	Expert Team to Support Biomonitoring in Europe (ESBIO)	2005-2008
	Public Health Impact of Long-Term, Low-Level Mixed Element Exposure in Susceptible Population Strata (PHIME)	2006-2011
	Newborns and Genotoxic Exposure Risks (NewGeneris)	2005-2010
	EXPOsOMICs	2013-2018
	The Human Early Life Exposome (HELIX)	2013-2018
	Health and Environment-wide Associations based on Large Population Surveys (HEALS)	2013-2019

3.7.1. Germany

3.7.1.1. German Environmental Specimen Bank for Human Tissues (ESBHum)

Initiator/Funding source: The German Environmental Specimen Bank for Human Tissues (ESBHum), a part of the German Environmental Specimen Bank (ESB), is a permanent monitoring system and an archive for human specimens. The storage of human specimens over the last 30 years allows retrospective monitoring, especially of phthalates and bisphenol A. Retrospective monitoring also allows the identification of temporal trends as well as spatial differences of various pollutants. The ESB-Hum is funded by the German Federal Ministry of the Environment, Nature Conservation and Nuclear Safety (BMUB), and the German Federal Environment Agency (UBA) Wiesmüller et al. (2007).

Duration: The ESBHum was initiated in 1974 by Professor Fritz H. Kemper. From 1974 to 1983, a pilot study started in Münster, Germany to examine the optimal storage conditions of human tissues, the recruitment process, and the sampling procedure. In 1984, the permanent collection, storage, and archiving of human tissue specimens had begun and is currently still ongoing.

Study design: ESBHum is a retrospective cohort study with an annual routine sampling period, which the collected specimens are stored at -150°C. First, standardised self-reported questionnaires are given to the participants in order to collect personal meta-data (e.g. sex, age, place of birth), medical data (e.g. medical history, health status, use of medicine, body height, and body weight), personal behaviour (e.g. nutrition, use of chemicals) and other sources of exposure (e.g. home and living situation). Various tissues are then collected, stored, and analysed after collection period.

Study population/Recruitment: Routine sampling occurs in 4 areas in Germany representing varying contamination levels (the potentially polluted area of Halle, moderately polluted areas of Münster and Ulm, and the relatively unpolluted area of Greifswald), and 500 students from the Universities in the sample areas (males and females; ages 20-29) are recruited each year (about 125 people per location per year).

Investigated chemicals/Matrices/Analytical methods: ESBHum analyses the following substances: **bisphenol A**, **fluorocarbons** (PFOA, PFOS), **metals** (As, Cd, Cu, Pb, Hg, Se, Sr, Tl, Zn), **organochlorine pesticides** (HCB, PCP), **PCBs** (PCB 138, 153, 180), and **phthalate metabolites**. The following metabolites were used as biomarkers of exposure to phthalates: MBzP (for BBzP), MiBP (for DiBP), MnBP (for MnBP), MEP (for DEP), and MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, MECPP/5cx-MEPP (for DEHP).

Pb, POPs (HCB, PCB 138, 153, and 180), PCP, PFASs (PFOA and PFOS) are measured in blood, whilst metals (As, Cd, Hg, Sr, Tl, Zn), PCP, BPA, and phthalate metabolites are measured in 24h urine. Blood, 24-hour urine, scalp, pubic hair, and saliva samples were collected until 2004. Since 2005, saliva, scalp, and pubic hair were no longer routinely taken. Collection and storage of perinatal specimens such as placenta, umbilical cord blood, and amniotic fluid began around 2005. To ensure high quality of the samples over time, the samples (blood and urine) are stored at the minimum of -150°C. The analytical methods for the tested substances are reported on the German Environmental Specimens Bank's website (http://www.umweltprobenbank.de/en/documents/10027).

Results/Interpretations: All the results are available on the German Environmental Specimen Bank's website (http://www.umweltprobenbank.de/en/documents/investigations/analytes). The chemical levels found in student volunteers from Münster in 2008 are presented in Table 24.

Real-time monitoring is performed after completing sampling processes of one year. Results are interpreted as time trends. While concentrations of several substances (e.g. As, Cd, and Hg) are remained unchanged over time, other substances (e.g. Pb and PCP) show a clearly perceptible decrease. While over time the body burden of dioxins as well as PFOS and PFOA decreased, the PBDE concentrations in human blood increase. The observed decrease of blood lead and PCP levels over time is a consequence of legal prohibition and restriction. The time-dependent concentrations of the aforementioned substances agree with results of other national studies (Wiesmüller et al., 2007).

Investigation of exposure sources: The Environmental Specimen Bank (ESB) not only includes the collection and analysis of human tissues but also marine specimens such as fish. Accompanying activities to investigate exposure sources comprise collection and measurements at regular intervals of limnetic, marine, and terrestrial specimens from typical ecosystems all over Germany, including coastal regions, urban settlements, and mountainous terrain to assess the levels of contaminants in the environment. In particular, specimens representing various levels of the food chain (e.g. algae, mussels, fish, and herring gulls) are collected at the 4 aforementioned participating locations for comparison. The following groups of substances have been measured in limnetic, marine, and terrestrial specimens: metals (Co, Ni, Cu, Cd, Hg/MeHg, Pb, As, Se), PCBs, pesticides (HCB, DDE/DDD, α-, β-, γ-HCH), HBCD, etc.

Reference values: The results from the previous years would serve as basis for the comparison of the latest ESBHum findings. This comparison would determine temporal changes (if any) of substance levels in people living in the 4 participating locations.

Communication to participants/scientific community/public: The results and list of publications are available online (http://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/german-environmental-surveys) and to study participants. In case of exceedance of health based guidance values or strong exceedance of the reference value, participants are recommended to do a follow-up.

Policy support: The results from ESBHum are used to provide scientific evidence for the BMUB on exposure trends. Because ESBHum is a retrospective study, it is possible to evaluate whether past legislation on chemical restrictions had a sufficiently positive effect towards human health and/or the environment. In addition ESBHum is used to identify new risks that would require action to protect human health and the environment.

3.7.1.2 The German Environmental Survey (GerES)

Initiator/Funding source: The German Environmental Survey is a nationwide human biomonitoring study that has been periodically conducted in Germany since the mid-1980s. Each study focuses on specific population of people living in Germany such as residents of East or West Germany and children. The study was conducted by the UBA, and the Robert Koch-Institute (RKI) carried out the field work on behalf of the UBA. It was financed by the BMUB and the Federal Ministry of Education and Research (BMBF).

Duration: The GerES I for adults (aged 25-69) was carried out in 1985/1986 (West Germany), followed by GerES IIa (adults aged 25-69) in 1990/91 (West Germany) and GerES IIb (adults aged 18-74) in 1991/92 (East Germany). In GerES II, the children (aged 6-14) and adolescents (aged 15-17) of participating parents were also included. In 1998, GerES III for adults (aged 18-69) was conducted in the reunified Germany. GerES IV, focused exclusively on children (aged 3-14), was carried out from 19 May 2003 to 6 May 2006. GerES V, focused on children and adolescents aged 3-17, started in

2013 and goes until 2016. (http://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/german-environmental-surveys)

Study design: All cycles of the GerES were nationwide cross-sectional studies, each focusing a representative sample of the general population. There are 3 key features to the GerES: (1) human biomonitoring, (2) ambient biomonitoring, and (3) standardised interview-based questionnaires. For completed GerES IV study, the participants (children) were randomly selected from the cross-sectional sample of the "German Health Interview and Examination Survey for Children and Adolescents" (KiGGS consisting of 17,641 participants) (Schulz et al., 2012a). Multiple questionnaires (including FFQs) were administered to the subjects or their parents to retrieve information on exposure conditions (i.e., food selection, housing conditions, quality of the residential environment and exposure relevant behaviour) and food intake. Blood and urine samples were taken from the participants; furthermore, extended monitoring of the subjects' environment (e.g., analyses of tap water, house dust, and indoor air) was conducted. Similar to GerES IV, the currently ongoing GerES V study aims to recruit participants (children and adolescents) who have previously participated in the KiGGS. Questionnaire will be administered to gain information regarding the child's health. However, in this cycle, only morning urine samples (no blood samples) are collected from the participants. Extensive ambient monitoring (e.g. analyses of drinking water, contents of a vacuum cleaner bag, noise level at the child's window, indoor air) will also be conducted (http://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/german-environmental-surveys/5th-german-environmental-survey-from-2013-to-2016).

Study population/Recruitment: A total of 1,790 children (907 girls and 883 boys), aged 3 to 14, were randomly selected from the KiGGS and voluntarily participated in the GerES IV from 2003 to 2006. Overall, 150 study locations were chosen from the total number of German communities, which are stratified according to the Federal States and the type of community (Schulz et al., 2012a). For GerES V, children and adolescents aged 3-17 have been recruited from more than 160 German towns and municipalities since 2013. The participants of the representative age and gender groups will be chosen randomly from the registers of residents in the areas of interest. The UBA intends to recruit as many participants as possible as higher number of participants will provide more meaningful results.

The potential participants of GerES IV (children aged 3-14 who previously participated in the KiGGS) were first identified via local inhabitant registries of the selected sampling locations. The sample population was then drawn from a multistage random sampling procedure, and the selected participants voluntarily partook in the study. For GerES V, the parents of the participant can receive the results of the chemical analysis of their child's urine and the analysis from the ambient biomonitoring by request. The participants will also receive 20 € as a token of gratitude.

Investigated chemicals/Matrices: For GerES IV, **metals** (Pb, Cd, Hg), **organochlorine pesticides** [HCB, α-HCH, β-HCH, γ-HCH, DDE (metabolite of DDT)], and **PCBs** (PCB 138, 153, 180) had been measured in whole blood samples, whereas **chlorophenols** (2-MCP, 4-MCP, 2,4-DCP, 2,5-DCP, 2,6-DCP, 2,3,4-TCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,6-TeCP, PCP), **cotinine** (as a biomarker of tobacco smoke exposure), **metals** (As, Cd, Ni, Hg), **nicotine**, **organophosphate metabolites** [DMP, DMTP, DMDTP, DEP, DETP, DEDTP (for DAP)], **PAH metabolites** [1-Hydroxypyrene (for pyrene), 1-Hydroxypheanthrene, 2/9-Hydroxyphenanthrene, 3-Hydroxyphenanthrene and 4-Hydroxyphenanthrene (for phenanthrene)], and **pyrethroid metabolites** [Br_2CA (for deltametrin), F-PBA (for cyfluthrin), cis-Cl_2CA, trans-Cl_2CA, 3-PBA (for cypermethrin, deltamethrin, and permethrin)] had been measured in urine samples.

For the ongoing GerES V, the following substances are to be measured only in morning urine samples: **cotinine**, **metals** (As, Cd, Au, Hg, Pt, Pd, etc.), **organophosphate metabolites** [DMP, DMTP,

DMDTP, DEP, DETP, DEDTP (for DAP)], **PAH metabolites** [1-Hydroxypyrene (for pyrene), 1-Hydroxypheanthrene, 2/9-Hydroxyphenanthrene, 3-Hydroxyphenanthrene and 4-Hydroxyphenanthrene (for phenanthrene)], **parabens**, **phthalate metabolites** (metabolites of DEHP, DnBP, DiBP, BBzP, DEP, DiNP, DiDP, DMP, DnPeP, DnOP, DChP, and the more recent phthalates DPHP, and DINCH).

In addition, the following classes of chemicals that had been analysed in the previous cycles of GerES (i.e. GerES I-III): **bisphenol A**, **chlorophenols** (2-MCP, 4-MCP, 2,4-DCP, 2,5-DCP, 2,6-DCP, 2,3,4-TCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,6-TeCP, PCP), **cotinine**, **fungus-specific IgE** (*Penicillium (notatum) chrysogenum, Aspergillus versicolor, Alternaria alternata, Wallemia sebi, Eurotium spp*), **metals** (Sb, As, Ba, Cd, Cr, Cs, Cu, Ir, Pb, Hg, Ni, Pd, Pt, Sr, Tl, U, V, Zn), **nicotine**, **organochlorine pesticides** [4,4'-DDE (metabolite of DDT), 4,4'-DDT, HCB, α-HCH, β-HCH, γ-HCH], **organophosphate metabolites** [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for DAP)], **PAH metabolites** [1-Hydroxypyrene (for pyrene), 1-Hydroxypheanthrene, 2/9-Hydroxyphenanthrene, 3-Hydroxyphenanthrene and 4-Hydroxyphenanthrene (for phenanthrene)], **PCBs** (PCB 28, 52, 101, 138, 153, 180), and **pyrethroids and their metabolites** (F-PBA, Br_2CA, cis-Cl_2CA, trans-Cl_2CA, 3-PBA, cypermethrin, permethrin).

Whole blood and morning urine samples were collected and analysed except for GerES V, which only will collect morning urine. Hair samples had been collected in GerES I.

Analytical methods: Phthalate metabolites were measured via LC/LC-MS/MS after enzymatic hydrolysis. BPA was measured via GC-MS/MS (Becker et al., 2009). As was measured via HG-AAS, Hg via CV-AAS, and Pb and Cd via ET-AAS. Cotinine and nicotine were measured by HPLC (Schulz et al., 2007). Organophosphorus metabolites were measured by GC-MS after extraction with diethylether/acetonitrile and derivatisation with pentafluorobenzylbromide (Becker et al., 2006).

Results/Interpretations: The extracted results from the published GerES IV report (Becker et al., 2008) are presented in Table 25.

Results were interpreted by region, age and gender, as well as socio-economic background. They have been related to potential exposures and were compared to guidance values such as HBM values and reference values from previous monitoring rounds whenever possible. The following interpretations are extracted from the GerES IV report (Becker et al., 2008):

Heavy metals (Pb, Cd, Ni, Hg, As) in blood and urine: Arsenic level was significantly higher in boys than in girls and decreased with age. The levels detected in migrants, children from the West Germany and children from large communities were higher than those in children from the respective control group. An association with fish consumption within 48 hours prior to sampling was observed. For Cd in blood, the majority of levels measured was below the limit of quantification (LOQ). Being a migrant, increasing age, and smoking are factors that can increase Cd levels in both blood and urine. The mean Ni level was found to decrease with increasing age. Comparatively lower Ni levels in urine were found in children with a high socioeconomic status (SES) and in non-migrants. Age, SES, migrant status, size of the community and fish consumption were significant predictors of mercury levels in blood. The percentage of quantifiable mercury levels in urine increased with increasing number of teeth with amalgam fillings. Quantifiable levels of mercury in urine were more often detected in boys and migrants than in girls and non-migrants, respectively.

Organochlorine compounds in blood: The levels of lower chlorinated PCB (PCB 28, 52, 101) were mostly below the LOQ. PCB levels (except PCB 138) found in boys were higher than those found in girls. The levels decreased with increasing age and increased for children with a high SES or living in West Germany and for non-migrants. The DDE levels also decreased with increasing age. Similar to PCBs, the levels found in children with a high SES was higher than that in children with a lower SES.

However, unlike PCB levels, DDE levels detected in migrants were higher than those in non-migrants. In East Germany and in large communities, the level was higher than in West Germany. The predictors for HCB were the same as for PCB, with the exception of gender, which was of no relevance for HCB levels. The predictors relevant for β-HCH were identical with those for DDE. For all substances described, significantly higher levels were found in children who had been breastfed as compared to children who had not been breastfed.

Nicotine and cotinine in urine: Nicotine and cotinine could be detected by analysis in 44% and in 51 % of the children, respectively. The levels of both substances increased significantly with increasing age. Significantly higher levels were found in migrants and children with a low SES. Smoking has shown a significant and very clear association with nicotine and cotinine levels.

Organophosphate metabolites in urine: The highest detectable organophosphate metabolite levels were from the 2 dimethyl phosphates, DMP (15.8 µg/L) and DMTP (16.8 µg/L). The DEDTP levels detected were within a comparatively narrow range of values. DETP was not detectable in about 40 % of the samples, and no dependency on the descriptive variables was found.

Chlorophenols in urine: Because PCP was only detectable in 49% of the samples, the LOQ (0.6 µg/L) was considered as the mean level. None of the variables was seen to have had a significant influence on the percentage of values representing quantifiable PCP levels.

PAH metabolites in urine: The results have shown excretion of 1-hydroxypyrene and hydroxyphenanthrenes being related to children's smoking habits. For all PAH metabolites except 4-hydroxyphenanthrene, the level in the urine of children living in East Germany was higher than that in children living in West Germany.

Pyrethroid metabolites in urine: F-PBA and Br_2CA could be detected by analysis in 19% and 45 % of the examined children, respectively. In girls, the mean levels of cis- and trans-Cl_2CA as well as of 3-PBA were significantly higher than in boys. Age was seen to be a significant variable for three of the metabolites examined.

The findings in relations to exposure sources have been further summarised in (Kolossa-Gehring et al., 2008). The most important and health relevant source is tobacco smoke as children's exposure increased slightly since 1992. DDT, PCBs, PCP, and DnBP in house dust show a small but significant contribution to children's body burden. Levels of metals in drinking water (except uranium) not significantly correlated with the children's exposure levels. Food is a major exposure source for organochlorines, biocides, and phthalates. Exposure to organophosphate pesticides is mainly influenced by age, consumption of fresh fruit and fruit juice. The organochlorine levels (such as HCB, HCH, DDE and PCB) in blood are higher in children with a higher SES and in breast-fed children. The exposure levels in children decreases with increasing age. Children with immigrant status or living from East Germany show higher DDE but lower PCB levels than non-immigrants or children from West Germany, respectively. Immigrants also show higher β-HCH levels.

Investigation of exposure sources: The contribution of the domestic environment to chemical exposure was assessed by analysing domestic drinking tap water (mainly for metals such as Cd, Cu, Pb, Ni and U) and samples from indoor air and house dust. Information on exposure conditions was collected in addition via standardised interview-guided questionnaires from parents and children of 8 years and older. The collected information included topics such as smoking habits, consumption of special food products, health status, housing situation, and the quality of the residential environment. A special FFQ gathered the consumption of fifty food groups for statements about the food selection of the children. In the programme "noise, hearing capability and stress hormones" for children aged 8 years or older, the programme was extended by physical measurements (noise level measurement and screening audiometry) and by an additional interview. For participants of the additional programmes

on chemical and biogenic indoor contamination, further measurements and interviews were added (Kolossa-Gehring et al., 2008).

Reference values: Reference values (RV_{95}) were determined based on the 95% confidence interval of the 95th population percentile of the concentration level of the respective parameter in the matrix obtained from the reference population. RVs determined from previous GerES surveys are up-dated with new incoming results.

Communication to participants/scientific community/public: The findings from GerES IV are published by UBA as a report (Becker et al., 2008), which is free for the public to access (http://www.umweltbundesamt.de/publikationen/german-environmental-survey-for-children-200306). In addition, scientists and researchers, who intend to pursue further evaluations of the study, can retrieve data from the UBA of the pollutant concentrations and questionnaire data from all of the participants. Every participant was or will be informed about the concentrations of the analysed substances in her/his biological (e.g. blood and urine), drinking water, and indoor air samples. Additionally, an environmental-medical assessment of these data was or will be supplied.

Policy support: GerES IV provides representative data on exposure of adults and children aged 3–14 years to environmental factors in Germany, which is up-dated in regular intervals. The representative data serve to: (1) provide a basis for establishing reference values for the exposure of children to environmental contaminants in blood and urine as a basis for a consistent evaluation throughout Germany, (2) detect temporal trends and regional differences in exposure, (3) identify and quantify exposure sources and pathways that are important for risk assessment, management and communication, (4) determine connections between certain environmental factors and the health situation of children, (5) establish concepts for prevention, intervention and reduction strategies in the context of measures of health and environmental policies (e.g. the guideline values of the Drinking Water Ordinance for domestic drinking water, the new chemicals acts on REACH, etc.), and (6) evaluate the success of policy and exposure reduction measures.

3.7.2. Flanders [The Flemish Environment and Health Study (FLEHS)]

Initiator/Funding source: In 2003, the Flemish government voted the Decree on Preventive Health Care, which mandated a human biomonitoring programme in Flanders to study the relationships between environmental pollutants and human health. The FLEHS is implemented by the Flemish Centre of Expertise for Environment and Health, and within this Centre, researchers from all Flemish universities and two research institutes provide expertise in various fields: medical sciences, toxicology, epidemiology, food sciences, biostatistics, environmental chemistry and social sciences. It is funded and steered by the Flemish government (Department of Economics, Science and Innovation; Flemish Agency for Care and Health; and Department of Environment, Nature and Energy) (Schoeters et al., 2012a).

Study design/Duration: This cross-sectional study measured selected pollutants and certain health effects in humans (mainly detection of biomarkers). The programme started in 2002, and since then, two cycles of human biomonitoring have been conducted. The first cycle (FLEHS I) ran from 2002 to 2006. The second cycle (FLEHS II) expanded the list of analysed substances and ran from 2007 to 2011. The third cycle (FLEHS III) started in 2012 and is expected to finish in 2016. (http://www2.vlaanderen.be/weten/steunpunten/steunpuntenG3/beheersovereenkomsten/steunpuntmilieuengezondheid_meerjarenplan.pdf)

Study population/Recruitment: In Flanders HBM programmes started in 2001 with FLEHS I (2001-2006), which determined contamination levels for a number of chemicals in three selected regions. For

FLEHS I, more than 4400 participants (males and females) were recruited by a stratified clustered multi-stage design and were categorized into 3 age groups: [1] newborns and their mothers (n=1200), [2] 14-15 years old adolescents (n=1600), and [3] 50-65 year old adults (n=1600). FLEHS II (2007-2011) was designed to establish reference values for a broad range of chemicals in the general population and including three hot-spot areas. 9 study areas were selected based on the differences in pollution levels (Schroijen et al., 2008). The Flemish Centre of Expertise for Environment and Health was interested in 3 specific groups of interest (both males and females): [1] newborns (n=250), [2] 14-15 years old adolescents (n=200), and [3] 20-40-year-old adults (n=200). Eligible participants from all five Flemish provinces were randomly selected and recruited also by a stratified clustered multi-stage design (i.e., maternity care for newborns, schools for adolescents, and provincial institutes for adults) from May 2008-July 2009. The participants must have the following inclusion criteria: (1) residing at least 10 years in Flanders; (2) giving written informed consent, and (3) being able to fill in an extensive Dutch questionnaire. Participants (and parents if the participants were children or adolescents) were asked to fill out extensive questionnaires regarding personal background, lifestyle factors, and food intake, and blood and urine samples were collected from the participants.

For the recruitment of newborns, mothers were contacted at the time of delivery. At the selected maternity wards, all mothers were given a short explanation about the study and asked to give cord blood by the maternity nurse. The adolescents were contacted via the schools. Prior to the invitation, the study nurses explained the FLEHS to the students that were selected for participation. The schools forwarded the invitation letters, information brochures and the letter of informed consent to the pupils. In the adult study, invitation letters, information brochures and letter of informed consent were sent to the potential participants via the administration of the provincial institutes. After completion of the study, participants received incentives (baby cape with logo of the study for the newborns; cinema tickets or book voucher for the adolescents; book voucher for adults).

Investigated chemicals/Matrices: Cord blood, maternal blood, and hair samples were collected from the newborns and their mothers while urine and blood samples were collected from the adolescents and adults. Adolescent hair samples were also collected.

FLEHS covered Cd, Pb, dioxins, PCBs, HCB, DDT, PAHs, benzene. FLEHS II expanded to 50 BM. In detail the following substances have been analysed in FLEHS: **bisphenol A**, **BFRs** (PBDE 28, 47, 99, 100, 153, 154, 183, 209, HBCDDs, TBBPA), **chlorophenols** (2,5-DCP), **cotinine** (as a biomarker of tobacco smoke exposure), **dioxins** (1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD), **fluorocarbons** (PFOA, PFOS), **furans** (1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF), **herbicide** (2,4-D), **metals** [As (including toxic relevant As such as As(III), As(V), MMA and DMA), Cd, Cu, Pb, Mn, Hg/MeHg, Ni, Tl], **organochlorine pesticides** (DDE as metabolite for DDT, HCB), **organophosphate metabolites** [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for dialkyl phosphates/DAP)], **PAH metabolites** [1-Hydroxypyrene (for pyrene), 1-Hydroxynaphthalene (1-Naphthol) and 2-Hydroxynaphthalene (2-Naphthol) (for naphthalene)], **PCBs** (PCB 138, 153, 180), **phenols** (butyl paraben, ethyl paraben, methyl paraben, propyl paraben, triclosan), **phthalate metabolites** [MBzP (for BBzP), MnBP (for DnBP), MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, MECPP/5cx-MEPP (for DEHP)], and **pyrethroid metabolites** [F-PBA (for cyfluthrin), 3-PBA (for cypermethrin, deltamethrin, and permethrin)].

Table 26 shows the list of biomarkers of exposure tested in various samples (Schoeters et al., 2012a). Also, measurements of 8-hydroxydeoxyguanosine (8-OHdG; a biomarker of oxidative DNA damage)

and the Comet assay have been performed in FLEHS to determine the amount of DNA damage (http://www.milieu-en-gezondheid.be/English/results/Greet Schoeters - deel1.ppt).

Analytical methods: Metals were measured in whole blood by high resolution ICP-MS. In spot urine samples, total As and Cd were measured by ICP-Dynamic Reaction Cell-MS. Total Hg and MeHg were measured in hair samples by combustion-AAS and by headspace injection-GC-atomic fluorescence spectrometry, respectively. POPs, BFRs, HBCD, and TBBPA were measured in plasma (cord blood) and serum (adolescents) using SPE and GC-ECNI-MS. CALUX assay was used to measure the dioxin-like compounds. Perfluorinated compounds in plasma/serum samples were measured with HPLC-MS/MS. BPA and triclosan were measured in urine samples after enzymatic hydrolysis with GC-MS in negative ionization mode. Urinary phthalate metabolites were measured with UPLC-MS after enzymatic release of the conjugated compounds. Metabolites of organophosphate pesticides and 2,5-DCP were measured in urine samples using derivatisation and GC–MS detection. Cotinine was measured in urine by quantitative solid-phase chemoluminescent immunoassay using the Immulite Nicotine Metabolite kit on Immulite 2000 Analyser. 1-Hydroxypyrene was enzymatically released overnight followed by on line extraction and detection by HPLC and a fluorescence detector (Schoeters et al., 2012a).

Results/Interpretations: An overview of the results from FLEHS I can be found in Table 27 (Schoeters et al., 2012a). For FLEHS II, the comprehensive results of all substances analysed can be found in the Flanders Human Biomonitoring 2007-2011 Results Report (published in Dutch as "Vlaams Humaan Biomonitoringsprogramma 2007-2011 – Resultatenrapport: deel referentiebiomonitoring").

The main achievement of the study is the large set of reference values for a wide range of pollutants that was obtained in a representative and well-selected study group. Some general observations of the FLEHS were made (http://www.milieu-en-gezondheid.be/English/results/Elly Den Hond.ppt). (1) No alarming trends in exposure of pollutants were detected. (2) All FLEHS participants have blood lead levels lower than the WHO guideline (100 µg/L). (3) Area of residence determines exposure. (4) People living in rural areas have high exposure to persistent chlorinated compounds. (5) Cd and As are problematic in some regions. (6) Although DDT is forbidden, metabolites are still detected in the human body in considerable amounts. (7) Factors such as age, sex, smoking and nutritional intake are important determinants of exposure.

Investigation of exposure sources: The Flemish Centre of Expertise for Environment and Health has intentions of comparing human biomonitoring results from suspected "hot spots" in Flanders with results obtained from the Flemish reference population. These "hot spots" not only include regions surrounding industrial plants, areas with high levels of particulate matter and traffic, dumping sites, etc. but also areas with elevated fish consumers or with high pollutant levels detected in home-grown vegetables or drinking water (Schoeters et al., 2012a). For example, significant correlations between fish consumption and arsenic concentrations in the urine samples of both adolescents and adults have been made from the FLEHS results (Baeyens et al., 2014).

Reference values: Reference values are available from the first cycle of the FLEHS. These results were used as control values for two biomonitoring campaigns in hot spot areas: one in an industrial area around a stainless steel plant (Genk-Zuid) and one in an industrial area around a shredder (Menen).

Communication to participants/scientific community/public: The results have been published (Vrijens et al., 2014). In addition, personal results were communicated to the participants after analysis

of all the samples. The personal value was reported, together with the median and the 90th percentile of the study group. For blood Pb, blood and urinary Cd, reference values were also given. A short overview of the biomarkers was given with main sources, main exposure routes and possible health effects of each pollutant. Participants also received a brochure with a summary of the group results. The end report of the study was delivered to the Flemish Government. In a next phase of the study, scientists of the research consortium and scientists of the administration of the government will work on the interpretation of the results and deduction of policy implications in the so-called "phased action plan". From January 2013 on, there will be a public use file for external scientist.

Policy support: FLEHS serves as a foundation for environment and health actions and puts forward some important concepts such as health in all policies, sustainable development, and the precautionary principles. Furthermore, it has led to concrete policy action plans tackling the most urgent and health relevant results.

3.7.3. France

3.7.3.1. The French Nutrition and Health Survey (ENNS)

Initiator/Funding source: The French National Institute for Public Health Surveillance (InVS), along with the French National Programme on Health and Nutrition (PNNS), is responsible for carrying out the ENNS study. The main objective of ENNS is to describe food consumption, nutritional status, and physical activity in the general population in France (adults and children) and to study nutritional and environmental biomarkers in humans. The collected data will serve PNNS in their objective to "improve health of the population by intervening on one of its major component, nutrition." (INVS, 2007b) ENNS is funded by the InVS, the French National Health Insurance Fund for Salaried Workers (Caisse nationale d'assurance maladie des travailleurs salaries; CNAMTS), and the University of Paris 13 (Falq et al., 2011).

Study design/Duration: ENNS occurred between February 2006 and July 2007 in order to account for the seasonal changes in diet in the general French population. This cross-sectional study comprises 3 parts: (1) a food consumption survey, (2) an interview using both face-to-face questionnaires and self-administered questionnaires, and (3) a clinical and biological examination. Examinations were conducted either in a health centre or by a nurse at the participant's home. The data collected per participant would include a description of dietary intake, biological samples, socioeconomic and demographic information along with the participant's occupation, personal activities, and exposure to pesticides (Saoudi et al., 2013).

Study population/Recruitment: A total of 4,790 French residents (3,115 adults aged 18-74 and 1,675 children aged 3-17; both males and females) participated in the ENNS study.[6] A sub-sample of 400 ENNS participants was then randomly selected to measure the exposure to organochlorine pesticides. The inclusion of subjects was performed with a probabilistic, stratified three-stage sample design. The first stratification was done by degrees of urbanization and by geographical areas (8 regions), resulting in 190 selected primary units representative of the general French population. For the second stratification, households were randomly drawn from phone listings, the phone numbers being randomly generated using the increment method. The number of households drawn from each of the 32 strata was determined proportionally according to the number of residences in each stratum. An information letter about the ENNS study would be sent to the selected households. Finally, a physician working on the study would contact the selected household, and one member per household would be recruited using the birthday method (Saoudi et al., 2013). The participation to the ENNS study was voluntary. Each participant was asked to complete informed consent documents and had the possibility to withdraw at any time the participation in the study.

Investigated chemicals/Matrices/Analytical methods: Urine, blood, and hair samples were collected, and 42 substances (11 metals, 6 PCBs, and 3 families of pesticides: organochlorines, organophosphates, and pyrethroids) were measured via various methods (Table 9). Substances includes **chlorophenols** (4-MCP, 2,4-DCP, 2,5-DCP, 2,6-DCP, 2,3,4-TCP, 2,4,5-TCP, 2,4,6-TCP, PCP), **metals** [Sb, As (including inorganic As, MMA and DMA) , Cd, Cr, Co, Pb, Hg, Ni, Sn, U, V], **organochlorine pesticides** (HCB, α-HCH, β-HCH, γ-HCH, DDT, 4,4'-DDE as a metabolite for DDT), **organophosphate metabolites** [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for dialkyl phosphates/DAP)], **PCBs** (PCB 28, 52, 101, 138, 153, 180), **pyrethroid metabolites** [F-PBA (for cyfluthrin), Br_2CA (for deltamethrin), cis-Cl_2CA, trans-Cl_2CA, 3-PBA (for cypermethrin, deltamethrin, and permethrin)].

Table 9 Analytical methods used in ENNS study (Fréry et al., 2013; Fréry et al., 2011)

Substance	Method
Sb, As, Cd, Cr, Co, Ni, Sn, U, V	ICP-MS
Pb	ET-AAS
Hg	ID-ICP-MS
PCBs and organochlorines	GC-ECD
Pyrethroid metabolites	GC-MSD
Organophosphate metabolites	GC-MS/MS with multiple reaction monitoring
Chlorophenols	GC-MS

Results/Interpretations: The results of ENNS study are presented in the InVS-published reports (Fréry et al., 2013; Fréry et al., 2011) and summarised in Table 28. The findings from the ENNS have generated reference values of exposure to various metals and chemicals in the French adult population, and the following interpretations of the ENNS are extracted from InVS report of "Exposure of the French population to environmental pollutants" (Fréry et al., 2010):

Metals: The blood Pb concentration has dropped sharply (by 60%) since 1995 due to the efforts to reduce exposure to lead in France. However, high levels of lead are still being found, particularly among people who have worked in old housing that may contain old lead-based paint. The urine Cd concentration is quite similar to those observed in previous French studies (in 1997, 2000, and 2005) and in other international studies. Urine Cd levels are higher with increasing age, in women, and in smokers. Hg levels in hair are relatively low (0.59 µg of Hg/g of hair among adults and 0.37 µg/g of hair among children) and are all lower than 10 µg/g (the WHO threshold). These levels are higher than those observed in Germany and the United States but lower than the levels in Spain. These results are most likely the effect of the differences in the consumption of fish in these countries. The urinary arsenic levels are low, which is similar to most international studies. Arsenic levels in urine are influenced by the consumption of seafood products and wine. The urinary concentrations of other metals (Sb, Cr, Co, Sn, Ni, U, and V) in adults are quite similar to those observed in other countries. Concentrations of metals found in the body are very often linked to age and gender. Some other specific factors may influence biomarker levels, such as the degree of urbanisation for vanadium, since this metal is emitted by catalytic converters on motor vehicles.

Organochlorine pesticides: It was possible to quantify organochlorine pesticides and their metabolites in nearly all individuals, with the exception of lindane (γ-HCH). On average, levels of HCBs in France are between those observed in American and German populations and are generally

lower than those observed in other European countries. Concentrations of DDT and DDE in France are low, confirming that there has been no DDT exposure in France for a long time due to the ban of these products. Overall, the French data relating to chlorophenols is similar to that reported in the United States and in Germany, except for 2,5-DCP; its mean level in France is approximately 10 times higher than in Germany. This biomarker is a metabolite of para-dichlorobenzene, which is used as a moth-killer, air-freshener and disinfectant. This observation needs further research to identify specific features in the exposure to this substance in France.

Organophosphate pesticides: DAP metabolites, common in many organophosphorus insecticides, have been found in more than 90% of urine samples. The highest levels among the six DAP metabolites were observed for DMP and DMTP. Overall, the levels of urinary DAPs in French adults are similar to those observed in Germany and higher than those observed in the United States.

Pyrethroid pesticides: Pyrethroid metabolites were found in more than 80% of samples except for F-BPA (30%) and cis-Cl_2CA (55%). The highest levels of pyrethroid metabolites were found for 3-BPAs, which is a metabolite of many pyrethroid insecticides, including cypermethrin, deltamethrin and permethrin. These levels seem to be approximately 3 times higher than those observed in the United States and even higher than levels observed in Germany.

PCBs: The substances present in the highest quantities are the NDL-PCBs (138, 153 and 180). These levels are similar to those observed in the study carried out by InVS in 2005 in areas surrounding incinerators. They are a little higher than those reported in the German population in 2002; these levels observed in Germany have probably decreased since then. The levels observed in France are also 4 to 5 times higher than those observed in the American population or in the New Zealand population. However, they are lower than those observed in the Czech Republic. This observation needs an analysis of the specific features of each country to better understand the origin of the observed differences in exposure. As for other organochlorine chemicals measured in serum, concentrations of PCBs are influenced by age, sex and body mass index.

Investigation of exposure sources: Dietary data was collected from the participants to further investigate exposure sources. The data comprised three 24-hour recalls randomly distributed over a period of 15 days. Participants were asked to describe, as precisely as possible, all foods and beverages which were consumed the day before the interview. Participants gave details on food recipients and amounts through a photography manual with typical portion sizes (INVS, 2007a).

Communication to participants/scientific community/public: The study findings have been published as InVS reports (Fréry et al., 2013; Fréry et al., 2011), which are available and publicly accessible online. The biological results were communicated to participants within two months after the examination with a letter to his own usual physician if results were abnormal. A comparison of the food consumption with the French nutritional recommendations was conducted and sent to the participant, who also received a little book with advices on how to eat well. For environmental biomonitoring results, a letter from InVS was sent, and contact with a toxicologist was provided if levels were high or if the results could imply an adverse health outcome.

Policy support: The ENNS study can be considered as a bridge head of the national strategy of HBM, elaborated by InVS in collaboration with ministries of Health, of Environment and the French Agency for Food, Environmental and Occupational Health & Safety (ANSES). The main component of this strategy will be a cross sectional survey (ESTEBAN, which is later discussed in this report) on a sample of 5000 children and adults designed to be representative for the French population aged from 6 to 74 years. The aim of ESTEBAN is to assess the exposure to environmental chemicals (around 100

biomarkers) and to establish reference values. Furthermore, ENNS could also be integrated towards the harmonisation of HBM in Europe through projects such as COPHES and DEMOCOPHES.

3.7.3.2. Étude longitudinal française depuis l'enfance (ELFE)

Initiator/Funding source: The ELFE (translated as the French Longitudinal Study of Children) study is a multidisciplinary project born out of the questions raised by researchers and the concerns expressed by various public bodies over the last ten years. It was the national health and environment plan (Plan national Santé-environnement) of 2004 that provided the decisive impetus for the project to go ahead. The study took practical shape in 2006 and has been run by a joint National Institute of Demographic Studies (INED, Institute national d'études démographiques)/National Institute for Health and Medical Research (INSERM) research unit since March 2010. It is supported by its two host institutions along with the InVS, the National Institute for Statistics and Economic Studies (INSEE), the National Family Allowance Office (CNAF, Caisse nationale des allocations familiales), and government bodies such as the Ministry of Health, the Ministry of Education, the Ministry of Research, the Ministry of Environment, and the Ministry of Culture (Vandentorren et al., 2009).

Duration: Two pilot studies were first carried out in 2007 to validate the questionnaires, sampling protocols, data collection, and analytical methods, to estimate the study's participation acceptance rate, and to assess its field feasibility. Then the ELFE study began at the end of March 2011 and will continue until the children reach adulthood.

Study design/population: The design of the longitudinal cohort study is based on an initial enrolment interview of mothers at the child's birth in order to obtain retrospective data about exposures during pregnancy followed by a prospective follow-up of the child. Biological collection will be conducted at maternity for 10,000 mother–child pairs. In addition, subsamples of 600–3000 mother–child pairs (depending on the compound) randomly selected from the cohort will be used for biomonitoring purposes. Other data to be collected include medical files (obstetric data), questionnaires (living conditions, social and demographic, housing characteristics, child's growth, development, diet and health), as well as household environment measurements (dust trap). The follow-up of the children is based on data retrieval and record linkage from existing databases (INSEE demographic data, school follow-up, health insurance records, national environment database, etc.) as well as on several waves of cross-sectional surveys to be carried out at different ages. These surveys may include biological sampling and will be based on face-to-face interview surveys or telephone interviews, clinical examinations and psychomotor development tests, self-administered questionnaires, measures of the environment, etc. (Vandentorren et al., 2009).

Recruitment: An information campaign will be conducted in all maternity units before the beginning of the study. A postal invitation to participate will be sent to all mothers during the 7th month of pregnancy via the newsletter sent by the CNAF. Fathers will also be invited to participate. A total of 20,000 infants (males and females) born during four predefined 6-day periods in 2011 will be recruited in 344 public and private maternity units randomly selected in continental France. The selected children would be monitored from birth to adulthood. Births before 33 weeks and multiple births of more than two children will be excluded. Signed informed consent has been obtained from the parents.

Investigated chemicals/Matrices: Biological samples include cord-blood, breast milk, mother's urine, hair, and venous blood. The ELFE study analyses levels of **bisphenol A**, **BFRs** (PBDE 17, 28, 47, 66, 85, 99, 100, 153, 154, 183, 209, HBCDDs, PBB 153), **carbamate pesticide** (2-isopropoxyphenol), **chlorophenols** (4-MCP, 2,4-DCP, 2,5-DCP, 2,4,5-TCP, 2,4,6-TCP, PCP), **cotinine** (as a biomarker of tobacco smoke exposure), **dioxins** (1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-

TCDD), **fluorocarbons** (PFBuS, PFDeA/PFDA, PFDoA, PFHpA, PFHxS, PFNA, PFOA, PFOS, PFOSA, Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFUA/PFUdA), **furans** (1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF), **metals** (Sb, As, Cd, Co, Pb, Hg, Ni), **organophosphate metabolites** [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for dialkyl phosphates/DAP)], **PAH metabolites** [1-Hydroxypyrene (for pyrene), 1-Hydroxynaphthalene (1-Naphthol), 2-Hydroxynaphthalene (2-Naphthol) (for naphthalene)], **PCBs** (PCB 28, 52, 77, 81, 101, 105, 114, 118, 123, 126, 138, 153, 156, 157, 167, 169, 180, 189), **phthalate metabolites** [MBzP (for BBzP), MiBP (for DiBP), MnBP (for DnBP), MEP (for DEP), MiNP, oxo-MiNP, OH-MiNP, cx-MiNP (for DiNP), MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, 5cx-MEPP, 2cx-MMHP (for DEHP), MOP/MnOP, MCPP (for DOP/DnOP), MCHP (for DCHP) (Zeman et al., 2013)], and **pyrethroid metabolites** [F-PBA (for cyfluthrin), Br_2CA (for deltamethrin), cis-Cl_2CA, trans-Cl_2CA, 3-PBA (for cypermethrin, deltamethrin, and permethrin)].

Analytical methods: A total of 14 perfluoroalkylated substances were measured using LC-HRMS (Antignac et al., 2013). Dioxins, furans, and PCBs were analysed via GC-HRMS. The phthalates metabolites were analysed via LC-MS/MS after enzymatic hydrolysis with beta-glucuronidase. BPA was measured using GC-MS using Single Ion Monitoring mode.

Results & interpretations: The levels of various perfluoroalkylated compounds, dioxins, furans and PCBs in breast milk have been published as peer-reviewed scientific articles (Antignac et al., 2013; Focant et al., 2013). The urinary levels of various phthalate metabolites (Zeman et al., 2013) and the levels of bisphenol A between pregnant women who gave birth naturally and who had Caesarean section (Vandentorren et al., 2011) have been published. As the study is ongoing, no reference values have been reported yet.

PFOS, PFOA, and PFHxS were detected and quantified in most of the analysed samples (90%, 98% and 100%, respectively) and appeared as major contributors to the total PFAS exposure (38%, 37%, 25%, respectively), whereas the other targeted PFAS were mostly below the limit of detection (LOD). Due to a limited data set, no statistically significant relation was observed between these exposure levels and developmental outcomes. Similarly, no relation was observed between the measured PFAS levels and various socio-demographical parameters such as the consumption of seafood, alcohol, smoking, or SES level. These results suggest a need for further research (Antignac et al., 2013).

Based on the data from the WHO exposure study, the French PCDD/F and DL-PCB levels are located in the high end of the European range. However, a significant decrease is observed in terms of exposure of French pregnant women to PCDD/Fs compared with an earlier study in France in 2000. The decrease likely reflects the gradual reduction of dioxin levels in the environment and subsequent decline in food, resulting in reduction of human exposure (Focant et al., 2013).

A significant exposure of French pregnant women to phthalates was observed, especially high concentrations of DEHP metabolites characterised by a very high variability. This finding suggested exposure to DEHP probably in the hospital. The study also indicated that the exposure is significant not only to DEHP, but also to DiNP, DnOP and BBzP (Zeman et al., 2013).

The median concentrations of total and free BPA in urine were similar to those in other studies, and differences between types of delivery (caesarean vs. natural) might explain the high exposure of BPA (Vandentorren et al., 2011).

Investigation of exposure sources: The children's immediate environment (water, air) will be monitored along with their exposure to certain pollutants measured by means of dust traps installed inside their homes. With the availability of the geographical coding of the children's addresses, the results obtained can then be compared with local and national pollution indicators and matched against the structural characteristics of the neighbourhood (e.g. proximity of certain industrial sites).

Communication to participants/scientific community/public: The ELFE study results will be published, producing invaluable information, not only to the proposing scientists, but also to countless researchers who will be able to interrogate the resulting data with a wide variety of research questions reflecting a range of hypotheses. From an international perspective, the comparative analyses that would ensue would be of immense public health interest.

3.7.3.3. Étude de santé sur l'environment, la biosurveillance, l'activité physique (ESTEBAN)

Initiator/Funding source: ESTEBAN is a health study on the environment, biomonitoring, physical activity, and nutrition. It will follow up on the ENNS results on diabetes, hypertension, and dyslipidaemias. A steering committee consisting of the InVS, the Ministry of Health, the Ministry of Environment, and other public health agencies decided to implement a general population, cross-sectional biomonitoring survey coupled with health examinations and involving a nutritional component. (Fillol et al., 2013)

Study design/Duration: ESTEBAN is a cross-sectional biomonitoring survey that began in March 2014 and will continue until the 3rd trimester of 2015. The study consists of visits to the participants' home, where the interviewer would administer questionnaires as well as the participant would complete self-administered questionnaires to collect data regarding occupational and environmental exposures, physical activity, medical history, socio demographics, etc. Furthermore, 24-hour food recall data and dietary records would be collected from participants aged 11-74 and children under 11, respectively. Afterwards, health examination and collection of biological samples would be performed for subsequent chemical exposure analyses.

Study population/Recruitment: Three degrees of stratified sampling (e.g., 1st degree: area of residence) were used, and after stratification, phone calls were made to randomly selected residents. A brief presentation of the study was given to the residents, and the participants would voluntarily decide whether to partake or not partake in the study. About 5,000 participants (over 4,000 adults aged 18-74 and 1,000 children aged 6-17; both males and females) are expected to be recruited over a year. Participants would be residents living in the continental France.

Investigated chemicals/Matrices: Blood (whole blood and serum), urine, and hair samples were collected and analysed. The various groups of measured substances include the following: **bisphenol A**, **BFRs** (PBDE 17, 28, 47, 66, 85, 99, 100, 153, 154, 183, 209, HBCDDs, PBB 153), **chlorophenols** (4-MCP, 2,4-DCP, 2,5-DCP, 2,6-DCP, 2,3,4-TCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,6-TeCP, PCP), **cotinine** (as a biomarker of tobacco smoke exposure), **dioxins** (1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD), **fluorocarbons** (PFOA, PFOS), **furans** (1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF), **metals (**Sb, As including As species, Cd, Co, Pb, Hg, Ni), **mycotoxins** (ochratoxin A and aflatoxins), **PAH metabolites** [1-Hydroxypyrene (for pyrene), 3-hydroxybenzo[a]pyrene (for benzo[a]pyrene), 1-Hydroxynaphthalene (1-Naphthol), 2-Hydroxynaphthalene (2-Naphthol) (for naphthalene), etc.)], **organochlorine pesticides** (aldrin, dieldrin, endrin, heptachlor, heptachlor epoxide, 4,4'-DDT, 2,4′-DDT, 2,4'-DDE and 4,4'-DDE as metabolites for DDT, oxychlordane, trans-Nonachlor, HCB, α-HCH, β-HCH, γ-HCH, mirex),

organophosphate metabolites [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for DAP)], **PCBs** (PCB 28, 52, 77, 81, 101, 105, 114, 118, 123, 126, 138, 153, 156, 157, 167, 169, 180, 189), **pesticides** (e.g. linuron, fipronil, etc.), **phthalate metabolites** [MBzP (for BBzP), MEP (for DEP), MiNP (for DiNP), MMP (for DMP), MOP, MCPP (for DOP), MCHP (for DCHP), metabolites of DEHP and DBP], and **pyrethroid metabolites** [F-PBA (for cyfluthrin), Br_2CA (for deltamethrin), cis-Cl_2CA, trans-Cl_2CA, 3-PBA (for cypermethrin, deltamethrin, and permethrin)].

Analytical methods/reference values/results/policy support: The analysis of the chemicals has not been conducted yet, so the methods or reference values have not been reported. Results are to be published after the completion of analysis in late 2015. ESTEBAN will offer an opportunity to assess the exposure levels of many chemicals within the French population. This study is meant to be complementary to other national biomonitoring studies such as the ELFE cohort, and the results will be compared with other biomonitoring surveys conducted throughout Europe.

3.7.4 Spain (BIOAMBIENT.ES)

Initiator/Funding source: In 2007, the Spanish Ministry of Agriculture, Food and Environment provided finance for a surveillance system to increase the current knowledge regarding the distribution of environmental pollutants in Spain. The Environmental Toxicology Area (TA) of the National Centre on Environmental Health of the Carlos III Institute of Health (ISCIII) was responsible for running the BIOAMBIENT.ES study, and the study was supported by TA, the Environmental and Cancer Epidemiology Unit of the National Centre of Epidemiology (also from ISCIII) and the coordinators of the Prevention Societies of the Mutual Insurance Companies that make up Corporation Mutua, the biggest Spanish Consort of Mutual Insurance Companies (Pérez-Gómez et al., 2013).

Study design/Duration: BIOAMBIENT.ES is a nationwide cross-sectional study with a stratified cluster sampling designed to cover all geographical areas, gender, and occupational sectors and aimed to obtain a representative sample of the Spanish workforce. Recruitment and sampling periods were between March 2009 and July 2010. The latest finding to the study was published in early 2014 (Cañas et al., 2014). A short self-administered epidemiological questionnaire was given to selected participants to collect basic individual information on socio-demographic data and environmental- and lifestyle-related exposure. A health exam was provided for each participant, who agreed to provide the results for the BIOAMBIENT.ES study, and biological samples were collected for analyses of pollutants.

Study population/Recruitment: In order to guarantee the nationwide coverage of this study, the country was stratified into 12 geographical regions: Galicia, Asturias and Cantabria, Basque Country, Navarre, La Rioja, and Aragon, Catalonia, Castile and León, Madrid, Castile-La Mancha and Extremadura, Valencian Community and Balearic Islands, Andalusia and Ceuta, Murcia, and Canary Islands. A total of 38 prevention centres from these regions were randomly selected as sampling units. A total of 1,892 volunteers aged 16 or older (969 males and 923 females) were recruited for and successfully participated in the study between March 2009 and July 2010. The volunteers must have lived in Spain for 5 years or more in order to be eligible for the study. The selected regions covered in 2009 a 63% of the Spanish adult population (Pérez-Gómez et al., 2013). The recruitment of the participants took place through the annual occupational medical check-ups in various health facilities within the aforementioned geographical regions. In order to improve the participation response of the questionnaires, communication materials was designed by the study group. Participation was voluntary and altruistic; only a small token USB drive was given to the participants.

Investigated chemicals/Matrices/Analytical methods: BIOAMBIENT.ES analysed the levels of the following substances: **BFRs** (PBDE 28, 47, 85, 99, 100, 119, 126, 153, 154, 183, 196, 197, 209),

cotinine (as a biomarker of tobacco smoke exposure), **metals** (Cd, Pb, Hg/MeHg), **organochlorine pesticides** (aldrin, dieldrin, endrin, heptachlor, heptachlor epoxide, p,p'-DDT, o,p'-DDT, DDE as a metabolite of DDT, HCB, α-HCH, β-HCH, γ-HCH), **PAH metabolites** [(3-Hydroxybenzo(a)pyrene (for benzo[a]pyrene), 1-Hydroxyphenanthrene, 2-Hydroxyphenanthrene, 3-Hydroxyphenanthrene, 4-Hydroxyphenanthrene, 9-Hydroxyphenanthrene (for phenanthrene), 1-Hydroxypyrene (for pyrene)], and **PCBs** (PCB 28, 52, 101, 138, 153, 180).

Cd, Hg, Pb, cotinine, and PAH metabolites were measured in first-morning urine. Cd, Hg, and Pb were also measured in whole blood. PCBs, PBDEs, and organochlorine pesticides were measured in serum. Hg was further measured in hair (Pérez-Gómez et al., 2013). Metal levels in blood and urine were carried out with ICP-MS. Hg determination in hair was determined with a direct mercury analyser DMA-80. PCB and PBDE levels in serum were performed with a SPE followed by quantification via GC-MS-NCI. PAH metabolites in urine were quantified by enzymatic hydrolysis followed by a SPE and analysed by HPLC-fluorescence detection.

Results & interpretations: Blood Pb (Cañas et al., 2014), hair Hg (Hg) (Esteban, 2010), and serum PCB levels (Huetos Hidalgo et al., 2013) have been reported and presented in Table 29. The geometric mean of blood Pb levels in the study population was 24.0 μg/L, with women having significantly lower levels than men. Mean blood Pb levels were higher in elder groups in both genders. Women of a childbearing age had a geometric mean (GM) blood level of 18.0 μg/L. Workers from the service sector had lower blood lead levels than those from the construction, agricultural and industry sectors. Small, although significant, geographical differences had been found. The Spanish population studied herein had Pb levels similar to populations in France and in Belgium but slightly lower levels than the Italian, Czech, German, or UK populations (Cañas et al., 2014).

The main PCBs detected in this study were PCB 138, 153, and 180. Women had significantly lower levels than males, while the levels increased approximately 56% for every 10-year increase in age. Service workers had higher levels than those of other sectors although the differences were not significant in the multivariate analysis. PCB levels were lower during October-December and higher during April-June when compared to the average for the year. Certain geographical areas had higher concentrations (e.g. 88% higher than the average) as well as lower concentrations (e.g. 2.5 times below the average). The BMI was inversely proportional to the serum PCB concentrations but without significant association from the multivariate analysis. Finally, there was a significant association between fish consumption and serum PCB concentrations. The values reported here are similar to those reported in other Spanish concentration studies (Huetos Hidalgo et al., 2013).

Communication to participants/scientific community/public: Findings from the BIOAMBIENT.ES study have been or will be published as scientific articles, and preliminary results of the chemical analyses have been presented at multiple conferences. This study was conducted to generate reference values, and some of the values (PCBs, Pb, and Hg) have been reported in various publications as well. An information leaflet including individual levels of the results for each participant as well as general information on each toxicant has been designed to provide the volunteers feedback about the research (Pérez-Gómez et al., 2013).

Policy support: The BIOAMBIENT.ES study provides the first overview of the body burden of certain pollutants in the general Spanish population and can be useful for evaluating temporal trends and the effectiveness of environmental and health policies.

3.7.5 Italy [Programme for biomonitoring the Italian population exposure (PROBE)]

Initiator/Funding source: The PROgramme for Biomonitoring of the Exposure (Programma per il Biomonitoraggio dell'Esposizione della popolazione generale; PROBE) was commissioned and funded by the Italian National Institute for Health (Istituto Superiore di Sanità; ISS). The study was in cooperation with the Italian Blood Volunteer Association (Associazione Volontari Italiani Sungue; AVIS) and the National Italian Association against Microcythemia (Associazione Nazionale Per La Lotta Contro Le Microcitemie; ANMI). The PROBE was managed by the National Center for Diseases Control and Prevention of the Italian Ministry of Health (Alimonti et al., 2011; Bocca et al., 2010).

Study design/Duration: PROBE is a cross-sectional population study to determine the exposure to metals of the healthy general population in Italy. The study started in 2008 and lasted until 2010. After the participants gave informed consent for the study, a questionnaire was given to the participants to collect information regarding participant's general characteristics (i.e., gender, age, height, weight, etc.), medical history, lifestyle, food intake, and environmental exposure, and morning blood samples were collected from the participants who had fasted overnight.

Study population/Recruitment: The PROBE population consisted of 1423 adults (953 men and 470 women), aged between 18 and 65 years (41% between 36 and 50 years). The selected subjects were informed about the study and voluntarily participated. The participants were residents of one of the five urban regions (Calabria, Latium, Umbria, Emilia Romagna, Piedmont), which were selected to establish representative data for South, Central, and North Italy. The exclusion criteria adopted in PROBE were the following: cardiological, respiratory, kidney or liver disorders; intestinal absorption abnormalities; active infections; assumption of thyroid hormones or lithium; psychoactive drug intake; assumption of vitamins or mineral integrators; iatrogenic exposure from metallic implants such prostheses, surgical screws or intrauterine inserts. Subjects resulting out of the physiological ranges about chemical-clinical parameters were also excluded (Alimonti et al., 2011; Bocca et al., 2010).

Investigated chemicals/Matrices/Analytical methods/Reference values: A total of 20 metals (Sb, As, Be, Cd, Cr, Co, Ir, Pb, Mn, Hg, Mo, Ni, Pd, Pt, Rh, Tl, Sn, W, U, V) were analysed directly in the blood and serum samples via SF-ICP-MS. The results are reported in Table 30 (Alimonti et al., 2011). The P95 from this study is considered as the reference value that can be used for comparisons with higher exposure scenarios in Italy. Metal concentrations higher than P95 do not necessarily mean that the metals trigger adverse health effect.

Results/Interpretations: International agencies have developed other limit values to compare and interpret other human biomonitoring data. For example, US Environmental Protection Agency (EPA) has identified biological equivalents (BEs), which help identify cases that might require further investigations rather than to imply an effect on human health. The American Conference of Governmental Industrial Hygienists has also identified the biological exposure indices (BEIs) for exposed workers that indicate the extent of exposure but are not directly related to effects on health. Different from those cited limits, German Commission for Human Biomonitoring provide the human biomonitoring values known as HBM-II, which an adverse effect on human health is associated for levels above these values. Table 10 shows the aforementioned limit values set by the US and Germany and the number of PROBE cases (n) that exceed these values.

Table 10 Limit values and the number of PROBE cases that exceed these values

	USA				Germany	
Metals	BE [µg/L]	n >BE	BEI [µg/L]	n >BEI	HBM-II [µg/L]	n > HBM-II
Cd	1.7	37	5	0		
Co			1	9		
Hg			15	1	15	1
Pb			300	0	150	3

About 2.6% of the Italian population had Cd levels higher than the BE, and 0.6% showed values above the BEI for Co, but these values are not conclusive for a risk characterisation. One subject and three subjects out of 1420 show levels of Hg and Pb, respectively, higher than the HBM-II values, and for such subjects, it can be assumed an exposure is associated with a health effect. Table 11 shows the risk factors that can influence metal concentrations in the Italian population (Bocca et al., 2013).

Table 11 Factors that affect the metal concentrations in the Italian population

Metals	Factor
Cd, Pb	Higher in smokers
Co, Rh, V	Higher in women
Hg, Pb, Pd, W	Higher in men
Pb, Pd	Increases with age
Ir, U, W	Decreases with age
Mn, Pb	Increases with alcohol

Communication to participants/scientific community/public: The findings from PROBE study have been published as a report (Alimonti et al., 2011), which is publicly accessible on the ISS's website (http://www.iss.it/binary/publ/cont/11_9_web.pdf). The PROBE study intends to further analyse the data with the stratification of sub-groups of multiple variables (such as gender, age, place of residence, etc.) to find and launch new environment and health measures to reduce the exposure to environmental metals of the Italian population (Bocca et al., 2010).

Policy support: The results from the PROBE study can be used to support REACH regulations such as encouraging further investigations (Commission Regulation No. 1907/2006, art. 45, paragraph 5), identifying substances of very high concern, persistent, bioaccumulating and toxic or chemicals of equivalent concern (Commission Regulation No. 1907/2006, Annex XIV), and assessing the efficiency of risk reduction measures or of substitutional choice in authorised substances underlying the minimization requirements (Commission Regulation No. 1907/2006, art. 60, paragraph 10) (Alimonti et al., 2011).

3.7.6. Czech Republic [Human Biomonitoring (Cz-HBM) as part of the Environmental Health Monitoring System (EHMS)]

Initiator/Funding source: HBM is part of the nationwide environmental health monitoring system EHMS funded by the Ministry of Health based on Act No. 258/2000 on Health Protection. It has the purpose (1) to document the extent, distribution, and determinants of population exposure to environmental pollutants, (2) to follow up long-term time trends and their possible changes as a result of preventive measures, (3) to establish a database from which to derive the reference values important for the characterisation of the exposure of the general population, and (4) to use the available data for health risk assessment and management. (Cerna et al., 2012).

Study design/Duration: First human biomonitoring of trace elements in the blood, serum, and urine of the Czech and Slovak populations in the 1980s and early 1990s (Kucera et al., 1995). Full integration of HBM into the nationwide environmental health monitoring system EHMS started in 1994 (Cerna et al., 2007; 1997). The CZ-HBM has been carried out as a limited representative cross-sectional study of the urban/suburban population and has covered two time periods: (1) between 1994 and 2003 and (2) between 2005 and 2009. The selection of sampling areas was based on the categorisation of the (former) districts into four categories (A–B–C–D) according to the level of environmental pollution. For the implementation of the HBM, two urban/suburban areas from the least polluted category A and two others from the most polluted category D were selected. In the first period, Benesov and Zdar and Sazavou as limited representatives of category A and Plzeed and Usti nad Labem as limited representatives of category D were chosen (Cerna et al., 1997). For the second period, the areas Prague (the capital), Ostrava (an industrial city), Liberec and Kromeriz as 2 relatively clean urban areas were selected, and the urban area of Uherské Hradiště was also included for measurements of PCB exposure. Information of each participant as well as biological samples were collected. For food intake, data was collected via two 24-hour recall processes (Puklova et al., 2010).

Study population/Recruitment: Three population groups were included in the HBM: adults (blood donors) aged 18–58, children aged 8–10, and breastfeeding primiparas. The main inclusion criteria were the following: (1) living in the selected area for at least 2 years, (2) good health status, and (3) absence of occupational exposure to chemicals for adults. Recruitment of blood donors was carried out through the transfusion department in the respective urban area. Children were recruited through schools in the first period and by paediatricians in the second period. Breastfeeding primiparas were contacted in the maternity clinics, and following the WHO protocol, breast milk was sampled in the period of 2–8 weeks after delivery.

Investigated chemicals/Matrices: Blood, urine, breast milk, hair, and teeth samples were collected, and 3 groups of biomarkers were analysed: (1) selected heavy **metals** (Pb, Cd, Hg) and essential elements (Cu, Se, Zn) in blood and urine of adults and children, (2) indicator **PCBs** (PCB 28, 52, 101, 118, 138, 153, 180) and **organochlorine pesticides** (o,p'-DDT, p,p'-DDT, o,p'-DDE and p,p'-DDE as a metabolite of DDT, HCB, and α-, β-, and γ-HCH) in human milk and blood serum of adults, and (3) cytogenetic changes in peripheral lymphocytes in blood of adults and children (Cerna et al., 2012).

Analytical methods: Individual metal elements were determined by ET-AAS or F-AAS. Hg was determined directly without mineralization using a single purpose instrument, an advanced mercury analyser AMA 254. Certified reference materials were used throughout the study. A GC-MS/MS method was used for the determination of the following compounds: PCBs (PCB 28, 52, 101, 118, 138, 153, and 180), HCB, α- to δ-HCHs, and o,p'- and p,p'-isomers of DDT, DDE, and DDD. Isotope dilution or internal standard methods were used for the quantification of the target compounds. Cytogenetic analysis was performed using the conventional Hungerford method on short-term (50 h)

cultures with all cells being in the first division. Peripheral blood was collected by venepuncture into heparinized tubes. For each subject, 100 well-spread metaphases containing 46 ± 1 centromeres were examined. Metaphases were analysed in coded slides. The four categories of chromosome aberrations were evaluated: chromatid and chromosome breaks and chromatid and chromosome exchanges. Cells bearing breaks or exchanges were classified as aberrant cells (AB.C.). Gaps were recorded but not scored as aberrations (Merlo et al., 2007; Rossner et al., 2002; 2005).

Results/Interpretations: The summary of results has been published as a peer-reviewed article (Cerna et al., 2012) in the *International Journal of Hygiene and Environmental Health*, which is accessible for scientific researchers in universities and research institutes. The statistical data concerning the general characteristics of women who took part in the CZ-HBM and their overall concentrations in breast milk has been summarised (Mikeš et al., 2012), and the RVs for Cd, Hg, and Pb levels (Cerna et al., 2012) and for POPs (mainly PCBs and organochlorine pesticides) in breast milk samples have been published (Mikeš et al., 2012). If an obtained result substantially exceeded the existing RV for the population, the analysis would be repeated; if confirmed, the subject would be asked to undergo body fluid re-sampling and re-analysis, and the possible exposure sources were investigated. The study manager team communicated the results to the respective participants. Furthermore, environmental monitoring is part of the EHMS, and yearly reports (http://www.szu.cz/topics/environmental-health/environmental-health-monitoring?lang=2) are published showing trends in exposures, biomarkers and health.

The blood Cd (B-Cd) levels in adults were about 3 times higher in smokers than in non-smokers. A slight but significant descending trend was observed with the median value decreasing from 0.6 µg/L in 1996 to 0.3 µg/L in 2003 (Puklova et al., 2005). Similarly, the median B-Cd levels in non-smokers measured in different areas of the country showed a similar decrease from 0.59 µg/L to 0.3 µg/L in 2009. Increased urinary cadmium levels were observed in Czech children compared to German children. A significant downward time trend was observed for the blood Pb levels in adults and children. The blood and urinary Hg levels were higher in women than in men. The HBM results did not indicate any substantial sub-saturation of the Czech population with Cu and Zn. The continuous monitoring of the blood Se levels conducted since 1996 revealed an upward trend starting in 2000 (Batariova et al., 2005; Cerna et al., 2007). However, no further increase in blood Se levels has been observed in the last few years.

Indicator PCBs (PCB 28, 52, 101, 118, 138, 153, and 180) and selected chlorinated pesticides have been monitored in human milk since 1994. Since 2005, these compounds have also been analysed in blood serum of adults. The PCB congeners 138, 153, and 180 accounted for more than 95% of the sum of the indicator PCBs. To simplify the presentation of results, PCB 153 was selected as a representative of the NDL-PCBs. A significant long-term downward trend in human milk was observed in the period of 1994–1997. A slight downward trend was also recorded in the second period of 2005–2009 even with an addition of measuring a PCB hot-spot area of Uherské Hradiště (Cerna et al., 2012). However, the levels of indicator PCB congeners in the Czech human milk samples were still higher than in most other European countries because such existing PCB hot spots. The levels of organochlorine pesticides showed a substantial continuous downward trend.

The cytogenetic analysis of human peripheral lymphocytes is a method used in the Czech Republic since the late 1970s as a group-based biological exposure test to assess occupational exposure to clastogenic carcinogens (Rossner et al., 1995; Sram et al., 2004). Therefore, this biomarker of both exposure and effect was included from the beginning among the spectrum of analytes followed up in the CZ-HBM (Cerna et al., 1997). The main purposes were to establish the spontaneous (baseline, reference) data for different population groups, to find potential association with the environmental

toxicants monitored and potential time trends (Rossner et al., 2002; 1998). The percentages of aberrant cells in non-exposed adults and children followers showed a U-shaped curve during the monitored period 1994-2008, with an initial downward trend followed by an upward trend since the early 2000s, with no clear causal explanation. Because the conventional method of chromosomal aberration analysis seemed inadequate to differentiate the impact of environmental stressors (Sram et al., 2007), it was excluded as a biomarker in 2008 (Cerna et al., 2012).

Investigation of exposure sources: In the case of mercury, different food groups (e.g. meats, fish, vegetables, rice, etc.) as well as drinking water samples were analysed to determine the potential sources of mercury body burden. There, it was confirmed that fish consumption and mercury burden were correlated, but otherwise, there was not a substantial mercury burden in the Czech population. In addition, the EHMS supports CZ-HBM with regular data collection on environmental pollution (Puklova et al., 2010).

Policy support: The EHMS was set up by the Government of the Czech Republic (Govt. Resolution No. 369/1991). Later on, it was incorporated in Act No. 258/2000 on Health Protection with the purpose to document the extent, distribution and determinants of population exposure to environmental pollutants, to follow up long-term time trends and their possible changes as a result of preventive measures, to establish a database from which to derive the reference values important for the characterisation of the exposure of the general population, and to use the available data for health risk assessment and management (Cerna et al., 2012).

3.7.7. Slovenia (National HBM programme)

Initiator/Funding source: The Ministry of Health funded Slovenia's national HBM programme, which is a part of the EU-project PHIME (Public Health Impact of long-term, low-level Mixed Element exposure in susceptible population strata). The Minister authorises the performers and appoints the collaborating experts/group. The programme is coordinated by the Jožef Stefan Institute with the cooperation with external experts from regional institutes.(Horvat et al., 2011)

Study design/Duration/Population/Recruitment: This national HBM programme is a cross-sectional study that began as a pilot study from 2007 and 2009. The follow-up HBM study started in 2011 and is currently ongoing. Women of childbearing age (aged 20-35) and their partners were recruited from three geographically different areas in Slovenia: urban (the capital, Ljubljana), rural (Kočevje), and contaminated (Bela krajina for its past industrial activities). Children (aged 6-11) were recruited from urban, rural, and industrial area (Idrija known for former mercury mines). Older women (aged 50-60) were also recruited but only in Ljubljana. Approximately, 50 women (aged 20-35), 50 men, and 50 children were recruited from each of the selected area and 50 women (aged 50-60) from Ljubljana. In total, 127 women (aged 20-35), 147 men, 174 children, and 66 women (aged 50-60) were sampled for hair, blood, and urine, and 117 lactating mothers collected breast milk samples as well (Tratnik et al., 2013). The study participants must have permanent residence of at least 5 years in the selected geographic study areas, which are determined by postcode (Perharic and Vracko, 2012). Participation was voluntary. All participants were administered a short questionnaire on lifestyle, work, medical status and food consumption, and biological samples were collected from the participants (Perharic & Vracko, 2012).

Investigated chemicals/Matrices: Hair, blood, urine, and breast milk samples were collected, and the following substances were measured directly in the samples: **BFRs** (No PBDE congeners were specified), **dioxins** (No PCDD congeners were specified), **furans** (No PCDF congeners were specified), **metals** (As, Cd, Cu, Pb, Hg, Se, Zn), and **PCBs** (PCB 28, 52, 101, 138, 153, 180, etc.).

Analytical methods: Hg in hair and blood was determined by the Direct Mercury Analyser (DMA-80), integrating sample thermal combustion, amalgamation and detection by AAS. Hg in urine and milk was determined by semi-automated CV-AAS. Other elements were determined by ICP-MS. Results in urine were corrected for creatinine levels, and creatinine was determined by Jaffé reaction on biochemical analyser Dimension (Siemens).

Results/Interpretation/Reference values: No results have been published in peer-reviewed journals as of July 2014, but preliminary results of biomonitoring of selected trace elements in women, men and children from Slovenia are available and will supplement further analyses for reference values (Tratnik et al., 2013). Also, multiple presentations of the study have been given at conferences.

Most of the subjects had the levels for non-essential toxic metals below the reference levels and the levels for essential elements Zn, Cu and Se within the reference intervals. Concentrations of metals and As did not differ between genders, while significantly higher levels of Se were observed in men and significantly higher levels of Cu in women. Comparing women of different ages, higher Hg levels and lower Cd and Pb levels were found in blood of younger women (aged 20–35) than in older women (aged 50–60). Se levels were higher in older women while Cu and Zn levels were higher in younger women. In comparison to children, women (both age groups) and men showed higher Cd, Pb, Se, and Zn concentration in blood. Hg concentration was higher in women (aged 20–35) and men than in children. Looking at the difference between different geographical areas where subjects were recruited, they found higher Cd and Pb levels in blood of rural children than in children from urban area. Hg in blood and urine was in contrary, higher in children from urban area than in children from rural area. In adults, As was observed to be the highest in urban area. Levels of essential elements differed between different areas in Slovenia as well. The study provides the basis to establish preliminary reference values for the selected population, depending on different parameters assessed by questionnaires. (Tratnik et al., 2013).

Investigation of exposure sources: The Slovenian government has also been performing environmental biomonitoring in scientific weighted grid-sampling/observations in aquatic and terrestrial ecosystems harmonized with examined areas in the HBM programme.(Kononenko & Horvat, 2008)

Policy support: The HBM study was coordinated by the competent authority for chemicals and carried out by health and other public institutes authorised by the Minister. Conditions regarding the professional and technical competence of public institutes for performing the biomonitoring shall be set out by the Minister. The Slovenian HBM study is developed on the legislative basis of Slovenian Chemicals Act (O.J. RS No. 16/2008), in particular "Chapter IX: Protection of Human Health and the Environment; Article 51.a: Biomonitoring of Chemicals" with the following provisions: (1) for the purpose of preparing and monitoring of measures to limit the risk of chemicals to people and the environment, monitoring of presence of chemicals and their breakdown products in people and organisms (hereinafter: biomonitoring) shall be conducted in professionally justified intervals of time, (2) biomonitoring is coordinated by the competent authority for chemicals and carried out by health and other public institutes authorised by the Minister, for people and organisms together or separately, (3) biomonitoring performers shall cooperate with the competent authority for chemicals and among themselves on: preparing a short- and long-term biomonitoring programme, its intersectoral coordination, monitoring of its implementation, performing expert evaluation and proposals for measures, (4) conditions regarding the professional and technical competence of public institutes for performing the biomonitoring from the preceding paragraph shall be set out by the Minister, and (5) provisions for biomonitoring from this article do not infringe upon provisions for biological monitoring at the workplace which are governed by regulations on occupational safety and health.

3.7.8. Austria [Schadstoffe im Menschen ("Pollutants in Humans")]

Initiator/Funding source/Duration: This is the first Austrian population-based human biomonitoring study, which aimed to determine the exposure of the Austrian general population and to prove the feasibility of a representative HBM study. It was managed by the Environmental Agency Austria and funded by the Austrian Ministry for Agriculture, Forestry, Environment and Water Management (Hohenblum et al., 2012). It started in 2008 and finished at the end of May 2011.

Study design: This cross sectional study aims at documenting the extent, the distribution and the determinants of human exposure to industrial chemicals. The study consisted of two parts: (1) a questionnaire which information pertaining to socio-demographic characteristics, medical history of the family, food frequency, and the living conditions were collected and (2) morning urine (mother, children), blood (parents), and hair (everyone) samples were taken for chemical analysis.

Study population/Recruitment: A stratified random sampling method was used to select the study participants taking into account the factors such as gender age, size of community, and location. A total of 150 participants from 50 families (males and females; aged 6-49) were involved in this study, and 50 of them were children aged 6-11. Five different communities (Vienna, Linz, St. Pölten, Tamsweg, Ried im Traunkreis) were selected for the study. Except for Vienna, the other 4 communities were randomly selected. The study team called randomly-selected households, and after describing the study, the household members voluntarily participated.

Investigated chemicals/Matrices: Urine, blood and hair samples were collected, and the following substances were measured: **bisphenol A**, **BFRs** (PBDE 28, 47, 66, 85, 99, 100, 126, 153, 154, 183, 196, 197), **metals** (MeHg), **phenols** (nonyl-phenol and octyl-phenol), and **phthalate metabolites** [MEP (for DEP), MBzP (for BBzP), MCHP (for DCHP), MiBP (for DiBP), MnBP (for DnBP), MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, 5cx-MEPP (for DEHP), MOP/MnOP (for DOP/DnOP), MiNP (for DiNP)]. The analysed substances were chosen in this study based on the known exposure sources of these substances in Austria. PBDEs can be absorbed by particles in household dust and other environmental media even in remote alpine areas, can accumulate in spruce needles and in humus in the soil, and can be detected in sewage sludge and sediments. Triphosphates have been replacing PBDEs as flame retardants or plasticisers, and subsequently, large amounts of triphosphates have been found in house dust samples. BPA is found in many plastic bottles, and humans are primarily exposed to methyl mercury via fish consumption.

Analytical methods: Phthalate metabolites and phenols in urine were measured via HPLC-MS/MS in the negative mode, and triphosphates in urine were measured via HPLC-MS/MS in the positive mode. PBDEs in blood were measured via GC-MS with isotope dilution. MeHg in hair was measured via HPLC coupled to ICP-MS.

Results/Interpretations/Communication to public: The findings have been published as a report (Hohenblum & Hutter, 2011), publicly accessible on the Austrian Environmental Agency's website, and as a short communication (Hohenblum et al., 2012).

BPA in urine was only detected in 4 out of 25 subjects, who were already pre-selected for analysis as these subjects might have high phenol exposure. The LOQ was 0.6 µg/L, and the range of detected concentrations was from <LOQ to 11 µg/L. Nonylphenol and octylphenol in urine were detected in 1 and 2 out of 25 samples, respectively. MeHg in hair was detected in 51 out of 104 samples (arithmetic mean = 46 µg/kg Hg; P95 = 196 µg/kg Hg). Only 3 out of 100 samples had levels above the LOQ for any of the 8 triphosphate compounds (Hohenblum & Hutter, 2011). Sixteen of the 18 PBDE congeners in blood could be detected in at least one sample. PBDEs 153 (81% of all samples; mean=8 ng/L; P95

= 9.1) and 197 (52% of all samples; mean = 6 ng/L; P95 = 8.3) were the most abundant species in the Austrian population. (Hohenblum et al., 2012). The findings of phthalate metabolites from this study can be found in Table 31 (Hohenblum & Hutter, 2011).

The LOQ for BPA was set at 0.6 µg/L, which is higher than the German LOQ (0.15 µg/L). This difference might explain why there was a low number of detectable BPA urine samples. The total mean MeHg level (46 µg Hg/kg) is much lower than the results from Denmark (800 µg/kg) or Germany (250 µg/kg). Only 11% of the sample population consume fish regularly (at least two times a week), which might explain for the lower Hg level compared with other regions. Triphosphates are metabolised very quickly and excreted via urine. Although only 3 out of 100 samples had detectable triphosphate levels, the authors hypothesised that the inappropriate triphosphate markers were analysed. After the completion of the study, an improved method of detecting triphosphate metabolites had been developed at the University of Erlangen-Nuremberg. The authors emphasised the importance of analysing this substance group given its neurotoxic properties and its effects on cognitive ability, especially in children. The levels of PBDEs were lower than expected given the high concentrations of PBDE in house dust samples and people primarily exposed to PBDEs via air and ingestion of house dust. However, these findings indicate that the background body burden detected is not negligible (Hohenblum et al., 2012). The measured levels of phthalates in Austria are below the levels detected in the USA and in Germany. Children have higher levels of phthalate metabolites than adults, inferring the role of food as an exposure source of phthalates (Hohenblum & Hutter, 2011). Overall, the first analytical results suggest that the body burden of the Austrian volunteers is comparable or even lower than in other European populations although the methods of sampling were different.

Policy support: The design of this study guaranteed full compatibility with the available EU protocols and contributed to the harmonisation efforts by EU-wide projects such as ESBIO, COPHES, and DEMOCOPHES.

3.7.9. Denmark

3.7.9.1. Danish HBM studies

Initiator: The Department of Growth and Reproduction at the University Hospital in Copenhagen have analysed urine samples from four Danish cohort during the past 6 years, compiling a considerable amount of data that may be comparable to ongoing surveys, e.g., NHANES and GerES. Thus, the department presents data on more than 3600 Danish children (Frederiksen et al., 2014).

Study design/Duration/Population/Recruitment: A collective overview of 4 different cohort studies from the period 2006-2012 of various Danish study populations (a total of 3,625 subjects) on human urinary excretion of non-persistent environmental chemicals has been published as a review (Frederiksen et al., 2014). Different recruitment strategies for the different studies are also discussed in this review (Frederiksen et al., 2014).

Investigated chemicals/Matrices: Urine samples were collected as spot samples except for an adult cohort with 24 h urines, and the list of substances measured in the urine samples from the four Danish populations have been published (Frederiksen et al., 2014). Briefly, the following substances were analysed: **bisphenol A**, **phenols** (Benzophenone-3, Butyl paraben, Ethyl paraben, Methyl paraben, Propyl paraben, 4-tert-octylphenol, Triclosan), and **phthalate metabolites** (MBzP, MiBP, MnBP, MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, MECPP/5cx-MEPP, MNP/MINP, MCPP, MEP, MOP).

Analytical methods: All urine samples were deconjugated by enzymatic hydrolysis and then the total (free and deconjugated) content of 13–16 phthalate metabolites, 9 phenols, and 7 parabens were measured by different isotope dilution-LC–MS/MS methods.

Results/Interpretations/Investigation to exposure sources: The urinary levels of phthalate metabolites, phenols, and parabens in Danish mother-child pairs (Frederiksen et al., 2013) as well as the summary of results from various cohorts (Frederiksen et al., 2014) have been published. Briefly, nearly everyone in the Danish population were exposed to the six most common phthalates (DEP, DiBP, DnBP, BBzP, DEHP and DiNP), bisphenol A, triclosan, benzophenone-3, and at least two of the parabens (methyl parabens and n-propyl parabens). The exposure to other non-persistent chemicals was also widespread. The excretion of DnBP and DEHP has decreased over time, which perhaps reflects a more restrictive use of these chemicals in ordinary consumer products. Despite the decreasing time trend observed for excretion of DnBP and DEHP metabolites, the daily exposure estimated on subgroups from the presented cohorts showed that the highest exposed section of the Danish population was still highly exposed to DnBP and DEHP with values near or above the tolerable daily intake.

Only a few European and American studies have reported biomonitoring data on other phenols and parabens. In general, low levels of triclosan, chlorophenols, phenylphenols, and the parabens were measured in the Danish cohorts compared with Spanish children and pregnant women, French pregnant women, and Americans from the general populations. Benzophenone-3 was measured in comparable levels in Denmark to levels in French and Spanish children and pregnant women while it was about 5-fold higher among Americans (Frederiksen et al., 2014). Questionnaires provide some information regarding exposure sources.

Policy support: The phthalates measurements observed from the various studies are currently used for negotiations by the Danish EPA to ban four phthalates in EU.

3.7.9.2. The Danish National Birth Cohort Study (DNBC)

Initiator/Funding source: The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this Foundation. Additional support for the DNBC is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustinus Foundation, and the Health Foundation (Andersen & Olsen, 2011; Olsen et al., 2001).

Study design/Duration: The DNBC is a conception-to-death-cohort, characterised by repetitive prospective data collections, a broad subject coverage, and active linkage to routinely collected health data in registers, of which the most important are the Danish National Patient Register and the Register of Causes of Death. Pregnant women were enrolled in the study between 1995 and 2002, preferably in the first trimester of pregnancy, but recruitment was allowed until week 24 of gestation.

At the first visit at the GP, a blood sample was taken to the study biobank after oral consent. The sample was stored with personal identification if written consent was received by mail. A second blood sample was taken by the GP in the second trimester, and a blood sample from the child (umbilical cord) was taken by midwives shortly after delivery. Data on lifestyle factors (including a FFQ) and environmental exposures were collected by medical questionnaires, computer-assisted interviews (CATI), and, more recently, web-based questionnaires. DNBC used two mailed questionnaires and 2 CATIs during pregnancy. After the delivery, CATIs at 6 and 18 months and

mailed or web-based questionnaires in the 7 years of follow-up were conducted. In the 11th year of follow-up, only web-based questionnaires are used (Andersen & Olsen, 2011).

Study population/Recruitment: A total of 100,418 pregnancies (women living in Denmark; aged 15-44) were enrolled in the study, and of these 92,670 resulted in the birth of a single live-born child and 2,080 women gave birth to twins or triplets. Written information about the cohort was provided to the women by general practitioners (GP) at the first antenatal visit, and the women enrolled in the cohort gave consent to participate in four telephone interviews, to have blood samples taken and stored in a biobank, and to have her and her offspring's data linked to routinely collected health data. Overall, the women gave consent that the data could be used for research purposes "with the aim of improving health for future children and mothers" and that they accepted to be contacted for further data collection rounds in the future (Andersen & Olsen, 2011; Olsen et al., 2001).

Investigated chemicals/Matrices: Maternal blood and umbilical blood samples were collected in the DNBC study, and, so far, measurement analyses of **fluorocarbons** (namely, PFOS and PFOA) have been conducted in maternal blood samples.

Results/Interpretations: Using blood samples stored in the DNBC's biobank, it was possible to measure levels of PFOS and PFOA in 1,400 maternal blood samples taken early in pregnancy. The analyses showed that maternal PFOA levels in early pregnancy were associated with smaller abdominal circumference and birth length, and higher levels of PFOA were associated with lower placental weight and head circumference. Maternal PFOS levels were not significantly associated with any of the fetal growth indicators (Fei et al., 2008).

Investigation of exposure sources: Completed FFQs allowed further studies of determining chemical exposure to food consumption and occupational exposures (e.g. those of laboratory technicians, green house workers, shift work).

Communication to scientific community/public: Multiple scientific articles have been published using DNBC cohort. Data from DNBC is only available to scientific researchers in Denmark or to those who are collaborating with a Danish researcher, and access to data could be acquired via a request to the board of DNBC.

Policy support: An advantage of using the DNBC cohort is that extensive health information is already available. This opens for a number of studies on possible health effects of both nutrients and environmental contaminants which is currently ongoing at the ages of 11 years and planned for the ages of 14 years of the enrolled children.

3.7.10. Sweden (First-time healthy mothers in Uppsala)

Sweden has a long history of environmental monitoring, with a health related environmental monitoring programme coordinated by the environmental protection agency since 1993. HBM data are used as indicators for environmental quality. A number of times series have been performed on lead in children, methylmercury from fish intake in pregnant women, Cadmium for smokers and POPs (PCB, dioxins/furans, pesticides and phthalates) in human milk. In this study we evaluate a cross-sectional survey that was performed in the city of Uppsala.

Initiator/Funding source: The study was performed by the Institute of Environmental Medicine at the Karolinska Institute and funded by the Swedish Environmental Protection Agency and VINNOVA, which is the Swedish Governmental Agency for Innovation Systems (Bjorklund et al., 2012).

Study design/Duration/Population/Recruitment: A cross-sectional design was chosen to recruit pregnant primiparous women, living in the Uppsala County. Recruitment took place from 1996-2006 as sub-projects in smaller periods, which are published as separate papers (Bjorklund et al., 2012; Darnerud et al., 2010; Glynn et al., 2007; Karrman et al., 2007; Lignell et al., 2009). First-time mothers giving birth at Uppsala University Hospital during the first week of the month and on different days according to a randomisation protocol were asked to voluntarily participate. From fall 1996 to spring 1999, pregnant and primiparous women (n = 405) living in Uppsala County, who were in late pregnancy (week 32–34), were asked to participate in the study (Glynn et al., 2007). Of these women, 211 (52%) agreed to donate maternal milk for chemical analysis. During 4 different sampling periods (April 2000-March 2001, March 2002-February 2003, January-December 2004, and 2006), primiparous mothers were randomly recruited among women who delivered at Uppsala University Hospital. At each sampling period, 30–32 women (46–63% of all women who were asked) participated in the study. At the end, a total of 335 women were recruited from 1996 to 2006.

Investigated chemicals/Matrices/Analytical methods: Breast milk samples were collected, and the following substances were measured directly in the samples: **BFRs** (PBDE 47, 99, 100, 153), **dioxins** (2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8-HpCDD, OctaCDD), **furans** (2,3,7,8-TCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8-HpCDF, OctaCDF), **metals** (Ag, Al, As, B, Ba, Be, Ca, Cd, Co, Cr, Cs, Cu, Fe, Hg, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, Rb, S, Sb, Se, Sn, Sr, Tl, W, U, V, Zn), and **PCBs** (PCB 28, 105, 118, 126, 138, 153, 156, 157, 167, 169, 180). GC/ECNI-MS was used for measuring POPs, and ICP-MS was used for measuring metals.

Results/Interpretations: The results have been published as scientific articles (Bjorklund et al., 2012; Darnerud et al., 2010; Glynn et al., 2007; Karrman et al., 2007; Lignell et al., 2009). A detailed table with concentrations of POPs in maternal milk is available in (Lignell et al., 2009). Declining rates of POPs over time has been reported, and a detailed table with concentrations of elements has been provided in (Bjorklund et al., 2012). Briefly, concentrations of 3 PCB congeners (PCB 52, 77, 101), 2 furans (1,2,3,7,8,9-HxCDF, 1,2,3,4,7,8,9-HpCDF), BDE-154, and HBCD were below the LOQ in most milk samples. PCB 153 showed the highest mean concentration in maternal milk lipids of all of the compounds studied. Among the PCDD/Fs, 1,2,3,4,6,7,8-HpCDD and OctaCDD showed the highest mean concentrations (16 and 79 pg/g lipid, respectively). However, the congeners that contributed most to the PCDD/FTEQ concentrations were 2,3,7,8-TCDD; 1,2,3,7,8-PeCDD; 1,2,3,6,7,8-HxCDD and 2,3,4,7,8-PeCDF in total of 87% (range 75–93%). The mean concentrations of the remaining PCDD/Fs (1,2,3,4,7,8-HxCDD; 1,2,3,7,8,9-HxCDD; 2,3,7,8-TCDF; 1,2,3,7,8-PeCDF; 1,2,3,4,7,8-HxCDF; 1,2,3,6,7,8-HxCDF; 2,3,4,6,7,8-HxCDF; 1,2,3,4,6,7,8-HpCDF and Octa CDF) varied between 0.21 and 2.1 pg/g lipids. Among the PBDEs, BDE-47 showed the highest mean concentration. The mean levels of the PBDE-congeners were lower than most mono-and di-ortho PCBs. For metals, the major findings were related to macronutrients (Ca, K, Mg, P, and Na) and micro nutrients (Cu, Al, Fe, and Se).

The levels of PCBs and PCDD/Fs in maternal milk samples from Uppsala County in Sweden have decreased during the last 10 years while the levels of PBDEs do not show any consistent trend. The different trends among the PBDEs point to the importance of analysing trends of individual congeners. It is also important to consider age of the mothers when temporal trends of POPs are examined since there is a trend among Swedish women of having the first child at older ages.

Investigation of exposure sources/Reference values: The study participants answered a questionnaire with information regarding some dietary habits, e.g. fish intake, to determine possible exposure sources, and reference values for some analysed substances have been established.

3.7.11. Finland (Effects of nationwide addition of selenium to fertilizers)

Initiator/Funding source: The supplementation of fertilizers with sodium selenate in Finland is a nationwide experiment aimed at increasing the Se status of both animals and humans. The window for optimal intake of Se is narrow with the risk of deficiency at very low and of toxicity at excessive levels. Systematic monitoring of the Se status of the population is necessary for safety reasons and also for research purposes (Alfthan et al., 2011). In this monitoring programme, sampling of cereals, basic foodstuffs, feeds, fertilizers, soils, and human tissues has been carried out annually since 1985 by 4 governmental research organizations and is still ongoing.

Study design/Duration: A small longitudinal cohort study was performed where the plasma Se concentration of the same healthy adults has been monitored systematically since 1985 in urban Helsinki and rural Leppävirta. Subjects using Se supplements were excluded, and the intake was solely from foods. All subjects filled in a questionnaire regarding their health status and use of dietary supplements (Se) on each blood sampling occasion. An annual blood sample was drawn into a vacuum tube and plasma, and whole blood samples were stored at –20°C before analysis (within 6 months).

Study population/Recruitment: Plasma samples have been obtained annually from healthy subjects in urban Helsinki (n = 30–35) since 1984, and both plasma and whole blood samples from rural Leppävirta (n = 35–45) since 1985. Their ages in the year 2000 ranged from 26 to 62 years in Helsinki and from 25 to 77 years in Leppävirta. The inclusion criteria for the study are good health status and exclusion of the use of Se-containing supplements. Participation is voluntary. The participants in Helsinki were members of staff of the National Public Health Institute, while those residing in Leppävirta were mostly the same subjects recruited in 1985 for the purposes of following their Se status.

Investigated chemicals/Matrices/Analytical methods/Investigation of exposure sources: Plasma and toenail samples were collected to directly measure the levels of selenium via ET-AAS. The precision between series was 4.4%, and the accuracy was on average within 5% of external quality-assurance plasma standards. In addition, sampling of foods has been done four times per year, and the measurements are complementary to the feed measurements of grains, meat, milk and soil.

Results/Interpretations: A number of publications and findings have been mentioned in the latest review (Alfthan et al., 2014). The mean plasma Se concentration ranged between 0.75 µmol/L and 1.23 µmol/L in the first half of the 1980s. Before Se supplementation of fertilizers started, the mean plasma Se concentration was 0.89 µmol/L, and it reached its highest mean level four years later at 1.5 µmol/L. After the decrease in the amount of fertilizer Se in 1990, plasma Se decreased to a low mean level of 1.10 µmol/L in 1999. This level was still above the general plasma Se value in Europe but lower than that found in Canada or the USA. In the 2010s, the mean plasma Se level has reached a level of 1.4 µmol/L. Toenail Se concentration reflects the integrated intake of Se over a period of 6 to 12 months. The mean toenail Se concentration of adults from 2 separate studies increased from the pre-supplementation level of 0.45 mg/kg to 0.72 mg/kg in 1995. Liver Se is mobile and reflects dietary Se intake over a time period of several weeks (Alfthan et al., 2014).

The mean human plasma Se concentration increased from 0.89 µmol/L to a general level of 1.40 µmol/L that can be considered to be an optimal status. The absence of Se-deficiency diseases and a reference population have made conclusions on the impact on human health difficult. However, the rates of cardiovascular diseases and cancers have remained similar during the pre- and post-supplementation, indicating medical and life-style factors to be much stronger determinants than Se. The nationwide supplementation of fertilizers with sodium selenate is shown to be effective and safe in increasing the Se intake of the whole population as supplementation of fertilizers with selenate has

increased the Se concentration of all major food groups. Plasma Se concentrations of people has increased by 70%. The Se intake surpasses current dietary recommendations. Also, the health of animals has improved.

Reference values/Policy support: Follow-up studies regarding beneficial (lower cardiovascular risk) and eventual adverse effects of selenium supplementation are still ongoing. Thus, it is risky to set the measured concentrations of plasma Se above 1.0 µmol/L as the reference value. The selenium supplementation is governmental.

3.7.12. Norway

3.7.12.1. The Tromsø cohort study

Initiator/Funding source: The Tromsø cohort study was supported by the Northern Norway Regional Health Authority, the Fram Centre, the Research Council of Norway, and the EU project ArcRisk (http://www.arcrisk.eu) (Nøst et al., 2014).

Study design/Duration: The objectives of this longitudinal study were to determine the following: (1) serum PFAS time trends on an individual level, (2) relative compositions and correlations between different PFASs, and (3) assess selected PFAS concentrations with respect to time (calendar year), age, and birth cohort (age-period-cohort) effects. Birth year and body mass index information was extracted from questionnaires, and blood samples (repeated measurements from the same subjects) were collected. The study started in 1979 and went until 2007.

Study population/Recruitment: Five repeated population surveys took place in the municipality of Tromsø in Northern Norway, in 1979, 1986–1987, 1994–1995, 2001, and 2007–2008. Of 60 randomly selected men, 53 had sufficient sample volumes in ≥ 3 sampling years (11 missing samples were randomly distributed across sampling years). In total, the study comprised 254 serum samples from 53 men. The median ages of the first (1979) and last (2007-2008) sampling periods were 43 and 71, respectively. Participation was voluntary, and all participants provided informed consent.

Investigated chemicals/Matrices: Blood samples were collected, and the following substances were measured: **fluorocarbons** (PFDA, PFNA, PFUdA, PFHpA, PFHxS, PFNA, PFOA, PFOS, PFOSA), **organochlorine pesticides** (o,p'-DDT, p,p'-DDT, p,p'-DDE and o,p'-DDE as metabolite of DDT, oxychlordane, trans-Nonachlor, HCB, α-HCH, β-HCH, γ-HCH, Mirex), and **PCBs** (PCB 28, 47/49, 52, 99, 101, 105, 118, 123, 128, 138, 141, 149, 153, 156, 157, 167, 170, 180, 183, 187, 189, 194).

Analytical methods: HCHs, chlordanes, and mirex were measured via GC-MS in selected ion monitoring and negative chemical ionisation modes. DDTs and PCBs were measured via GC-MS/MS with electron ionisation. PFASs were measured via UPLC-triple quadrupole mass spectrometry.

Results/Interpretations: The findings of the levels of POPs and PFASs over 5 sampling periods have been published (Nøst et al., 2013; 2014). The median decreases in summed serum POP concentrations (lipid-adjusted) in 1986, 1994, 2001, and 2007 relative to 1979 were -22%, -52%, -54%, and -68%, respectively. There were observable substantial declines in all POP groups with the exception of chlordanes. The results suggest substantial intra-individual declines in serum concentrations of legacy POPs from 1979 to 2007 in men from Northern Norway. These changes are consistent with reduced environmental exposure during these 30 years and highlight the relation between historic emissions and POP concentrations measured in humans. A longitudinal decrease in concentrations with age was evident for all birth cohorts (Nøst et al., 2013).

The median concentrations of PFOS and PFOA increased 5-fold from 1979 to 2001 and decreased by 26% and 23%, respectively, from 2001 to 2007. The concentrations of PFOS and PFOA peaked during 1994-2001 and 2001, respectively, whereas PFHxS increased to 2001 but did not demonstrate a decrease between 2001 and 2007. PFNA, PFDA, and PFUnDA displayed increasing trends throughout the entire study period (1979-2007). Although PFOS comprised dominating proportions of PFAS burdens during these years, the contributions from PFOA and PFHxS were also considerable. The concentration changes of 10 PFASs in the repeated measurements from 1979 to 2007 demonstrated divergent time trends between the different PFASs. The temporal trends of PFASs in human serum during these 30 years reflect the overall trends in historic production and use, although global transport mechanisms and bioaccumulation potential of the different PFASs together with a varying extent of consumer exposure influenced the observed trends. Sampling year was the strongest descriptor of PFOA, PFUnDA and PFOS concentrations, and the calendar-year trends were apparent for all birth year quartiles. Discrepancies between the trends in this current longitudinal study and previous cross-sectional studies were observed and presumably reflect the different study designs and population characteristics (Nøst et al., 2014).

Investigation of exposure sources/Reference values: Estimates of average and high fish consumption in the Norwegian population were used to model the POPs concentrations as a result of fish consumption (Nøst et al., 2013), and the findings of this longitudinal cohort study serve as reference values for comparing findings from previous sampling periods.

3.7.12.2. The Norwegian Mother and Child Cohort Study (MoBa)

Initiator/Funding source: The Norwegian Mother and Child Cohort Study (MoBa) is a study of the aetiology of diseases among mothers and their children. It was initiated by researchers at the Medical Birth Registry of Norway (MBRN) and at the National Institute of Public Health, which later merged with other institutions and renamed themselves as the Norwegian Institute of Public Health (NIPH), and the study was supported by the Norwegian Ministry of Health and the Ministry of Education and Research, USA's NIH/NIEHS and NINDS, and the Norwegian Research Council/FUGE. Sub-projects involving additional data collection and analysis must have separate funding. (Magnus et al., 2006). (www.fhi.no/moba-en)

Study design/Duration: The MoBa cohort is a longitudinal prospective population-based pregnancy cohort study. Recruitment of participants went from 1999 – 2008, and data acquisition and analysis are still ongoing as of 2014. Prior to the delivery of the child, participants were given a series of self-administered questionnaires to acquire information on their medical histories, mental health, lifestyle habits, exposures in the workplace and at home, and health status or lifestyle changes during pregnancy. The paternal questionnaire focussed on the medical history, lifestyle habits, and exposures at work. Then when the child was 6-months-old, a questionnaire was then given to the participants to acquire data on the child's health and nutrition as well as the mother's health and well-being. The last follow-up of the child has been planned when the child reaches 7 years of age (Magnus et al., 2006). Regarding dietary intake, both FFQs and food diaries (e.g. 4-day weighed food diary) were utilised (Brantsaeter et al., 2008).

Study population/Recruitment: A total of 108,000 children, 90,700 mothers, and 71,500 fathers were recruited from all over Norway. Pregnant women beginning at the 17th week of pregnancy, who attended routine examination, along with the fathers were recruited by postal invitations. All participants gave informed consent and voluntarily took part in the study (Magnus et al., 2006).

Investigated chemicals/Matrices: Blood and urine samples were collected from the mothers during pregnancy (and blood samples from the father) and from the mothers and children (umbilical cord

blood) at birth. From 2008 to 2016, the MoBa study intends to collect teeth samples from the participating children (Tvinnereim et al., 2012). The following substances were measured in biological samples in this study: mercapturic acid derivatives (in urine) and haemoglobin adducts (in blood) of **acrylamide/glycidamide**, **bisphenol A**, **cotinine** (as a biomarker of tobacco smoke exposure), **fluorocarbons** (PFDeA/PFDA, PFOA, PFNA, PFOS, PFUA/PFUdA, PFHxS, PFHpS), **organophosphate pesticide** (3,5,6-trichloropyridinol (metabolite of chlorpyrifos), **organophosphate metabolites** [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for DAP)], and **phthalate metabolites** [MBzP (for BBzP), MiBP (for DiBP), MnBP (for DnBP), MEP (for DEP), 7oxo-MMeOP, 7OH-MMeOP (for DiNP), MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, MECPP/5cx-MEPP, MCMHP (for DEHP), MMP (for DMP), MOP, MCPP (for DOP)].

Analytical methods: All fluorocarbons were measured via either LC coupled to a triple quadrupole mass spectrometer (Starling et al., 2014) or HPLC-MS/MS for PFOS and PFOA (Whitworth et al., 2012). Urinary acrylamide/glycidamide metabolites were measured using LC-triple quadruple MS with positive electrospray ionization mode using multiple reaction monitoring (Brantsaeter et al., 2008), and haemoglobin adducts of acrylamide/glycidamide were measured by applying the 'adduct FIRE' procedure then analysed via LC-MS (Duarte-Salles et al., 2013b). Phthalate metabolites, 3,5,6-trichloropyridinol, organophosphate metabolites, and BPA were all measured either by GC-MS/MS or reversed-phase HPLC-MS/MS (Ye et al., 2009). Plasma cotinine was measured via LC-MS/MS (Kvalvik et al., 2012).

Results/Interpretations: Several studies reported negative associations between maternal exposures to Hg, dioxins and PCBs, or benzo(a)pyrene (all determined via reported dietary intake during pregnancy) and birth weight (Duarte-Salles et al., 2013a; Papadopoulou et al., 2013; Vejrup et al., 2014).

Maternal exposure to acrylamide: A relationship between the dietary intake of crisp bread and potato crisps with increased urinary acrylamide metabolites was reported (Brantsaeter et al., 2008). Furthermore, acrylamide intake during pregnancy was negatively associated with foetal growth (Duarte-Salles et al., 2013b).

Maternal exposure to PFCs: The maternal levels (via blood samples from mothers) and foetal levels (via cord blood) of PFCs are significantly correlated (Gutzkow et al., 2012). The adjusted birth weight z scores were slightly lower among infants born to mothers in the highest quartiles of PFCs compared with infants born to mothers in the lowest quartiles. PFOS and PFOA were each associated with decreased adjusted odds of preterm birth although the sample sizes were small (Whitworth et al., 2012).

Maternal exposure of pesticides, phthalates, and BPA: Daily intakes were estimated from urinary data and compared with reference doses (RfDs) and daily tolerable intakes (TDIs). The MoBa women had a higher mean BPA concentration (4.50 µg/L) than the pregnant women in the Generation R Study in the Netherlands and in the USA's NHANES. The mean concentration of total DAP metabolites (24.20 µg/L) in MoBa women was higher than that in NHANES women but lower than that in Generation R women. MEP was the dominant phthalate metabolite in all three studies with the mean concentrations of greater than 300 µg/L. The MoBa and Generation R women had higher mean concentrations of MnBP and MiBP than the NHANES women. The estimated average daily intakes of BPA, chlorpyrifos/chlorpyrfosmethyl and phthalates in MoBa (and the other two studies) were below the RfDs and TDIs. The higher levels of metabolites in the MoBa participants may have been from intake via pesticide residues in food (organophosphates), consumption of canned food, especially fish/seafood (BPA), and use of personal care products (selected phthalates) (Ye et al., 2009).

Communication to scientific community/public: Multiple scientific articles have been published using MoBa cohort. Data from MoBa is only available to scientific researchers in Norway or to those who are collaborating with a Norwegian researcher, and access to data could be acquired via a request to NIPH.

Investigation of exposure sources: Completed FFQs allowed further studies of determining chemical exposure to food consumption. In addition, a few external sub-studies had correlated maternal chemical exposure to the estimated levels of Hg, dioxins, and PCBs, or acrylamide in food (Brantsaeter et al., 2008; Papadopoulou et al., 2013; Vejrup et al., 2014), and a positive association was reported between smoking and plasma cotinine levels (Kvalvik et al., 2012).

Policy support: One of the duties of the NIPH is to have an overview of the health status of the Norwegian population and factors influencing public health. Therefore, a human environmental biomonitoring program has recently been established and will use the MoBa as a basis for recruitment. An advantage of using the MoBa cohort is that extensive health information is already available. This opens for a number of studies on possible health effects of both nutrients and environmental contaminants.

3.7.13. Arctic Monitoring and Assessment Programme (AMAP)

Initiator/Funding source/Duration: Since 1997, the AMAP has produced integrated assessment reports on the status of and trends in environmental POPs in the Arctic ecosystem (Bonefeld-Jorgensen, 2010). Three reports on biomonitoring of POPs and their health risks for Arctic populations were published in 1998, 2002, and 2009, and the programme is ongoing.

Study design: AMAP's current objective is "providing reliable and sufficient information on the status of, and threats to, the Arctic environment, and providing scientific advice on actions to be taken in order to support Arctic governments in their efforts to take remedial and preventive actions relating to contaminants." Long-term monitoring and trend analysis of contaminant levels in Arctic populations is a crucial component of this objective. Blood is the medium of choice for biological monitoring of contaminants as it accurately reflects the body burden of metals as well as organic contaminants, and is universally available from all members of a population. For lipophilic compounds (which include most POPs), blood levels (expressed on a lipid basis) are well-correlated with levels in other compartments such as stored fat and breast milk. To ensure the comparability of data obtained from different countries, it is required to obtain an adequate number of preserved blood specimens and other samples. (www.amap.no)

Study population: A reported study focused on adult Inuits (aged 18-50, randomly selected from the national register) has been published (Bonefeld-Jorgensen, 2004). There are other AMAP studies that have selected pregnant women.

Investigated chemicals/Matrices: Serum samples were collected, and the following POPs were directly measured in the samples: **BFRs** (PBDE 47, 99, 100, 153), **fluorocarbons** (PFHxS, PFOA, PFOS), **metals** (Pb, Hg, Se), and **PCBs** (PCB 28, 52, 99, 101, 105, 114, 118, 123, 128, 138, 153, 156, 157, 167, 170, 180, 183, 187, 189).

Analytical methods: POPs were measured in serum by HPLC along with fatty acids and the xenobiotic hormone disrupting potential as determined by the hormone receptor transactivation of the luciferase reporter gene expression.

Results/Interpretations: The median values of PCBs, POPs, and metals (Hg, Pb, Se) found in human sera from Greenland have been published (Bonefeld-Jorgensen, 2010), and several studies linking to health effects have been published e.g. semen quality and breast cancer. For mercury, a specific conclusion has been issued:

"What is the impact of mercury contamination on human health in the Arctic? (AMAP Assessment 2011: Mercury in the Arctic)

Some Arctic human populations, especially some indigenous communities that consume large quantities of certain species of freshwater fish or marine mammal tissues for their traditional/local food, receive high dietary exposure to mercury. This raises concerns about human health effects, such as effects on brain development, and effects on the reproductive, immune and cardiovascular systems.

Exposure at current levels in the Arctic can have adverse impacts on human health, particularly for the developing fetus and children. Pregnant women, mothers and children are critical groups for monitoring and measures to reduce dietary exposure.

There has been an overall decline in the proportion of Arctic people that exceed (USA and Canadian) blood mercury guidelines, but a significant proportion of people including women of child-bearing age from communities in the eastern Canadian Arctic and Greenland still exceed these guidelines. Dietary advice has been effective in reducing mercury exposure in some critical groups, but such advice needs to be carefully formulated to balance risks and benefits of traditional/local food consumption.

The general dietary transition from traditional/local to more 'western' diets is also reducing mercury exposure, but at the same time is raising risks of other conditions or diseases associated with a western diet and lifestyle (such as obesity, diabetes, and heart disease). Since traditional/local foods low in mercury are not always available to Arctic indigenous people, the achievement of declining mercury levels in the environment is imperative to allow for the safe promotion of traditional/local food consumption."

Investigation of exposure sources: For Greenland, the AMAP collected food intake via a semi quantitative food questionnaire featuring of 60 food items, namely 35 local Greenland food products (e.g. meats, fish, birds, berries) and 25 Danish imported foods (e.g. breads, fruits, vegetables). Frequency categories range from once a year to several times a day. Standard (i.e. not individually reported) portion sizes were used to estimate dietary intake of food (Deutch et al., 2004).

The AMAP also has extensive focus on environmental exposures including wildlife and climate issuing reports frequently on these issues, available from the AMAP website. The latest reports are the following:

- AMAP, 2013. AMAP Assessment 2013: Arctic Ocean Acidification. Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway. viii + 99 pp.
- AMAP, 2011. Snow, Water, Ice and Permafrost in the Arctic (SWIPA): Climate Change and the Cryosphere. Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway. xii + 538 pp.
- AMAP, 2011. AMAP Assessment 2011: Mercury in the Arctic. Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway. xiv + 193 pp.
- AMAP, 2010. AMAP Assessment 2009: Radioactivity in the Arctic. Arctic Monitoring and Assessment Programme (AMAP), Oslo, Norway. xii + 92 pp.pp.

- AMAP, 2010. AMAP Assessment 2009 - Persistent Organic Pollutants (POPs) in the Arctic. Science of the Total Environment Special Issue. 408:2851-3051. Elsevier, 2010.
- The AMAP study has been mentioned in all reports to link environmental exposures, wildlife and human health.

3.7.14. Canada [Canadian Health Measures Survey (CHMS)]

Initiator/Funding source: Statistics Canada, in partnership with Health Canada and the Public Health Agency of Canada, launched CHMS to collect health and wellness data and biological specimens on a nationally representative sample of Canadians.

Study design/Duration: CHMS is a cross-sectional survey that started in 2007 and is carried out in 2-year cycles. The first *Report on Human Biomonitoring of Environmental Chemicals in Canada* (Cycle 1) was published in August 2010, reporting collected data from March 2007 to February 2009. The second *Report on Human Biomonitoring of Environmental Chemicals in Canada* (Cycle 2) was published in April 2013, reporting collected data from August 2009 to November 2011. CHMS intends to continue further with Cycle 3 of the survey. Home interviews would be conducted, and health questionnaires as well as a semi-quantitative FFQ would be administered at that point. The FFQ would collect data on frequency consumption (i.e. number of times per day/week/month/year) of food groups such as meat and fish, grains, fruits and vegetables, dairy products, dietary fats, water and soft drinks. After the initial data collection, the participants would report to one of the 18 collection sites for direct health measures and sample collection. Furthermore, indoor air (measured in Cycle 2) and tap water (to be measured in Cycle 3) would be measured for exposure of contaminants, namely fluoride and VOCs.

Study population/Recruitment: The 2006 Canadian Census was used as the frame to select dwellings. Dwellings with known household composition at the time of the 2006 Census were stratified by age of household residents into the six age-group strata corresponding to the CHMS cycle 2. Within each collection site, a simple random sample of dwellings was selected in each stratum. Statistics Canada mailed an advance letter and brochure to households that were selected. Each selected dwelling was then contacted and asked to provide a list of current household members; this list was used to select the survey participants. One or two people were selected, depending on the household composition. To meet the objective of producing reliable estimates at the national level by age group and sex, the study required a minimum sample of at least 5,700 participants. People aged 3 to 79 residing in the 10 provinces and 3 territories were targeted. People living on reserves or in other Aboriginal settlements in the provinces, residents of institutions, full-time members of the Canadian Forces, persons living in certain remote areas, and persons living in areas with a low population density were excluded. All participants gave informed consent, and the participation is voluntary.

Investigated chemicals/Matrices/Analytical methods: Urine and blood (whole blood and plasma) were used for substance measurements. For cycle 1 of the CHMS, the following groups of substances were measured: **metals**, **chlorophenols**, **bisphenol A**, **cotinine**, **PFAS**, **pesticides**, and **phthalate metabolites**. For cycle 2, the same substances as cycle 1 along with additional substances (e.g. PCP, triclosan, etc.) and substance groups (**benzene and PAH metabolites**) were measured. To summarise, the following substances were measured in CHMS: **bisphenol A**, **BFRs** (PBDE 17, 28, 47, 99, 100, 153, PBB 153), **carbamate pesticides** (carbofuranphenol, 2-isopropoxyphenol), **chlorophenols** (2,4-DCP, 2,5-DCP, 2,4,5-DCP, 2,4,6-DCP, PCP), **cotinine** (as a biomarker of tobacco smoke exposure), **fluorocarbons** (PFBuS, PFDeA/PFDA, PFDoA, PFOA, PFOS, PFUA/PFUdA), **metals** [Sb, As (including total, inorganic As such as As(III)/As(V)/MMA/DMA, and organic As such as arsenobetaine and arsenocholine), Cd, Cs, Co, Cu, Fl, Pb, Mn, Hg (total & inorganic), Mo, Ni, Se, Ag,

Tl, W, U, V, Zn], **organochlorine pesticides** (Aldrin, p,p'-DDT, p,p'-DDE as a metabolite of DDT, Oxychlordane, trans-Nonachlor, HCB, β-HCH, γ-HCH, Mirex), **organophosphate metabolites** [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for DAP)], **PAH metabolites** [(3-Hydroxybenzo(a)pyrene (for benzo[a]pyrene), 2-Hydroxyfluorene, 3-Hydroxyfluorene, 9-Hydroxyfluorene (for fluorene), 1-Hydroxyphenanthrene, 2-Hydroxyphenanthrene, 3-Hydroxyphenanthrene, 4-Hydroxyphenanthrene, 9-Hydroxyphenanthrene (for phenanthrene), 1-Hydroxypyrene (for pyrene), 1-Hydroxynaphthalene (1-Naphthol), 2-Hydroxynaphthalene (2-Naphthol) (for naphthalene)], **PCBs** (PCB 28, 52, 101, 138, 153, 180), **phenols** (Triclosan), **phthalate metabolites** [MBzP (for BBzP), MiBP (for DiBP), MnBP (for DnBP), MEP (for DEP), MiNP (for DiNP), MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP (for DEHP), MMP (for DMP), MOP, MCPP (for DOP), MCHP (for DCHP)], and **pyrethroid metabolites** [F-PBA (for cyfluthrin), Br_2CA (for deltamethrin), cis-Cl_2CA, trans-Cl_2CA, 3-PBA (for cypermethrin, deltamethrin, and permethrin)].

Please refer to the second *Report on Human Biomonitoring of Environmental Chemicals in Canada* for the complete list of measured substances and their analytical methods (Health Canada, 2013). Also, small amounts of blood and urine from consenting participants are frozen and stored anonymously in a biobank at the National Microbiology Laboratory in Winnipeg for use in future health studies (http://www.statcan.gc.ca/eng/survey/household/5071g).

Results/Interpretations/Reference values: Table 32 shows the matrices and the geometric mean levels of the tested substances in CHMS. A detailed summary of the analyses of the tested substances in CHMS could be found in the first or the second *Report on Human Biomonitoring of Environmental Chemicals in Canada*. This report includes temporal data for substances measured in both cycle 1 (2007–2009) and cycle 2 (2009–2011) and baseline data for substances introduced to the survey in cycle 2. The concentrations found for the tested substances from CHMS Cycle 1 are subsequently used as reference values for future CHMS cycle surveys. In addition, the data from newly-added chemicals in CHMS Cycle 2 would also be used as reference values. The values are published in the first and the second *Report on Human Biomonitoring of Environmental Chemicals in Canada*. Results from future cycles of CHMS can then be compared with the baseline data from cycle 1 and cycle 2 in order to begin to examine trends in Canadians' exposures to selected environmental chemicals.

Results/Interpretations/Communication to public: The second *Report on Human Biomonitoring of Environmental Chemicals in Canada* is accessible online. A strategy was developed to communicate results to survey participants with the expert opinion of CHMS Laboratory Advisory Committee, the Physician Advisory Committee, l'Institut national de santé publique du Québec, and Health Canada's Research Ethics Board. Environmental metals (e.g. Pb, Hg, and Cd) were actively reported to participants. Participants could receive all other test results upon request to Statistics Canada. CHMS provides data access to analysts and researchers using Research Data Centres, where they are located in universities across the country and staffed by Statistics Canada employees. Furthermore, the CHMS data could also be made available to scientists upon request by contacting Statistics Canada at info@statcan.gc.ca for additional scientific analysis.

Investigation of exposure sources/Policy support: CHMS cycle 2 included indoor air measurements of VOCs, and in the upcoming Cycle 3, household tap water samples are to be analysed for fluoride and VOCs.

The CHMS is a major component of the monitoring initiatives developed under the Chemicals Management Plan (CMP), launched by the Government of Canada in 2006. The goal of CMP is to further enhance its role in protecting Canadians and their environment from exposure to chemicals. The CMP supports a number of additional research, monitoring and assessment activities to help

Canadians better understand their exposure and the potential effects on human health. These activities include biomonitoring studies targeting vulnerable populations (such as the MIREC study), environmental monitoring studies, and research to support biomonitoring. Health Canada also partners with Aboriginal Affairs and Northern Development Canada's Northern Contaminants Programme to undertake health research and biomonitoring in Canada's northern populations. Furthermore, the CHMS data could help the development and implementations of health policies such as the need of public health actions towards substances of concern and raising public awareness about exposures and possible health effects relating substances of concern.

3.7.15. United States of America (USA) [National Health and Nutrition Examination Survey (NHANES)]

Initiator/Funding sources: NHANES is a programme of studies designed to assess the health and nutritional status of adults and children in the USA. It is a major programme of the National Center for Health Statistics (NCHS) and is a part of the Centers for Disease Control and Prevention (CDC), who has the responsibility for producing vital and health statistics.

Study design/Duration: NHANES is a cross-sectional study that began in the early 1960s and started with measurements of environmental chemicals in 1976. The survey has been conducted as a series of surveys focusing on different population groups or health topics. The historical surveys are referred to as NHANES I, NHANES II (1976–1980), Hispanic HANES (1982–1984) and NHANES III (1988–1994). In 1999, the survey became a continuous yearly programme that has adaptable components on a variety of health and nutrition measurements to meet emerging needs. NHANES is currently ongoing.

There are two main parts to the survey: (1) health interviews conducted in the participants' homes and (2) health measurements performed in specially-designed and equipped mobile centres. All participants visit the physician. Dietary interviews and body measurements are included for everyone. For dietary interviews, food intake data collection is thoroughly conducted with the "Automated Multiple-Pass Method," which is a 5-step dietary interview involving 24-hr recalls (Moshfegh et al., 2008). For the body measurements, all but the very young will have a blood sample taken and a dental screening. Depending upon the age of the participant, the rest of the examination includes tests and procedures to assess the various aspects of health. In general, the older the individual, the more extensive the examination.

Study population: The sample for the survey is selected to represent the American population (non-institutionalised civilians) of all ages, and NHANES examines a nationally representative sample of at least 10,000 persons from 30 localities over a 2-year period. Participants are selected through a complex statistical process using the most current Census information. Briefly, NHANES divides the USA into communities. The communities are divided into neighbourhoods, which are selected at random for each survey. From each neighbourhood, housing units are further selected at random. Selected households are approached by the study interviewers, who screen the residents to determine their eligibility for the survey. Participants are selected based on age, gender, and ethnic background. Oversampling of minority populations (e.g. Hispanics, low income residents, etc.) occur in NHANES to better understand the possible risk factors and exposures to specific chemicals. The study population includes pregnant women. The minimum age for participation is 2 months, but urine samples are not collected from participants less than 6 years of age. Blood samples for most environmental chemical measurements are collected from participants 12 years and older; however, because of the small amount of blood required, lead, cadmium and mercury are measured in all participants providing a 9-ml blood sample (most of the blood is used for nutritional and clinical testing) and who are at least 1 year of age. For a similar reason, cotinine is measured in everyone 3

years of age and older; they are asked to provide 22 ml of blood. The participants, or their parents, also complete an extensive questionnaire on demographics and health behaviours and undergo a complete physical and medical examination. The participants represent a national probability sample; thus, the results can be extrapolated to include the entire US population.

Recruitment: Participants receive free measurements of various health status parameters (e.g. bone density) that would normally not be covered during routine physical exams. A report of medical findings is given to each participant. Also, all participants receive cash remuneration, and NHANES reimburse participants for transportation and baby/elder care.

Investigated chemicals/Matrices: The chemical measurements are conducted on a random one-third subset of the NHANES participants.

Blood (serum and plasma) and urine samples were used for analysis, and the following substances had been analysed at least once in NHANES: **acrylamide and its metabolite glycidamide**, **BFRs** (PBDE 17, 28, 47, 66, 85, 99, 100, 153, 154, 183, BDE 209, PBB 153), **bisphenol A**, **carbamate pesticides** (Carbofuranphenol, 2-isopropoxyphenol), **chlorophenols** (2,4-DCP, 2,5-DCP, 2,4,5-DCP, 2,4,6-DCP, PCP), **cotinine** (as a biomarker of tobacco smoke exposure), **dioxins** (1,2,3,4,6,7,8-HpBDD, 1,2,3,4,7,8-HxBDD, 1,2,3,6,7,8-HxBDD, 1,2,3,7,8,9-HxBDD, 1,2,3,7,8-PeBDD, 2,3,7,8-TBDD, 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD), **fluorocarbons** (PFBuS, PFDeA/PFDA, PFDoA, PFHpA, PFHxS, PFNA, PFOA, PFOS, PFOSA, Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFUA/PFUdA), **furans** (1,2,3,4,6,7,8-HpBDF, 1,2,3,4,7,8-HxBDF, 1,2,3,7,8-PeBDF, 2,3,4,7,8-PeBDF, 2,3,7,8-TBDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF), **herbicides** (2,4-D, 2,4,5-T), **metals** [Sb, As including inorganic As such as As(III)/As(V)/MMA and DMA and organic As such as arsenobetaine, arsenocholine and trimethylarsine oxide, Ba, Cd, Cs, Co, Cu, Pb, Mn, Hg (total/ethyl and methyl species/inorganic), Mo, Se, Sr, Tl, Sn, W, U, Zn), **mycotoxins** (Aflatoxin B1), **NNAL** (metabolite of NNK), **organochlorine pesticides** (aldrin, dieldrin, endrin, heptachlor epoxide, o,p'-DDT, p,p'-DDT, p,p'-DDE as a metabolite of DDT, oxychlordane, trans-nonachlor, HCB, β-HCH, γ-HCH, mirex), **organophosphate pesticides** [3,5,6-trichloropyridinol (metabolite of chlorpyrifos), Acephate, Dimethoate, Malathion diacid (metabolite for malathion), Methamidophos, Omethoate, Oxypyrimidine (metabolite for diazinon), Paranitrophenol (metabolite for methyl parathion)], **organophosphate metabolites** [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for DAP)], **PAH metabolites** [2-Hydroxyfluorene, 3-Hydroxyfluorene, 9-Hydroxyfluorene (for fluorene), 1-Hydroxyphenanthrene, 2-Hydroxyphenanthrene, 3-Hydroxyphenanthrene, 4-Hydroxyphenanthrene (for phenanthrene), 1-Hydroxypyrene (for pyrene), 1-Hydroxynaphthalene (1-Naphthol), 2-Hydroxynaphthalene (2-Naphthol) (for naphthalene)], **PCBs** (PCB 28, 44, 49, 52, 66, 74, 81, 87, 99, 101, 105, 110, 114, 118, 123, 126, 128, 138, 146, 149, 151, 153, 156, 157, 167, 169, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 199, 203, 206, 209), **perchlorate**, **phenols** (Benzophenone-3, Butyl paraben, Ethyl paraben, Methyl paraben, Propyl paraben, 4-tert-octylphenol, Triclosan), **phthalate metabolites** [MBzP (for BBzP), MiBP (for DiBP), MnBP (for DnBP), MiNP, MCOP (for DiNP), MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, MECPP/5cx-MEPP (for DEHP), MMP (for DMP), MCPP (for DOP), MCHP (for DCHP), MCNP (for DiDP)], **pyrethroids and their metabolites** [permethrin, F-PBA (for cyfluthrin), Br_2CA (for deltamethrin), trans-Cl_2CA, 3-PBA (for cypermethrin, deltamethrin, and permethrin)].

The complete list of chemicals and their results could be found on the CDC's website (http://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Laboratory). As of July 2014,

the latest published NHANES data is from the sample collection during 2011-2012. The following chemicals were analysed in previous NHANES surveys:

- Aflatoxin B1 from NHANES 1999-2000
- 2003-2004:
    - Acrylamide & glycidamide
    - Aldrin, dieldrin, endrin, heptachlor epoxide (Organochlorine Pesticides)
    - Carbofuranphenol, 2-Isopropoxyphenol (Urinary Current Use Pesticides)
    - Dioxins & furans (Dioxins, Furans, and coplanar PCBs)
- 2005-2006
    - 2,4,5-trichlorophenol, 2,4,6-trichlorophenol (Environmental Pesticides)
    - Acephate, Dimethoate, Methamidophos, Omethoate (Urinary Carbamates and Organophosphorus Pesticides)
- 2007-2008
    - Urinary Organophosphate Insecticides: Dialkyl Phosphate Metabolites
    - Urinary Pyrethroids, Herbicides, and Organophosphate (OP) Metabolites
    - NHANES pesticides from 2007-2008
    - PCBs (Non-dioxin-like Polychlorinated Biphenyls and mono-ortho-substituted PCBs)
    - Brominated flame retardants

Analytical methods: The analytical methods of the tested substances could be found in detail in the data files presented under "Laboratory Data" of the NHANES website.

Results/Interpretations/Reference values: Table 33 shows the matrices and the geometric mean levels of the tested substances in NHANES.

According to CDC, NHANES' data has stimulated important policy changes and further research such as the following:

- Blood lead data were instrumental in developing policy to eliminate lead from gasoline and in food and soft drink cans. Recent survey data indicate the policy has been even more effective than originally envisioned, with a decline in elevated blood lead levels of more than 70% since the 1970s.
- Overweight prevalence figures have led to the proliferation of programmes emphasizing diet and exercise, stimulated additional research, and provided a means to track trends in obesity.
- Information collected in this survey will help the Food and Drug Administration decide if there is a need to change vitamin and mineral fortification regulations for the Nation's food supply.

NHANES partners with the EPA and the US Department of Agriculture to study the influence of pollutants in human health and to cooperate in planning and reporting dietary and nutrition information from the survey, respectively.

Communications to participants/scientific community/public: Analyses using NHANES data have been published as an extensive series of articles in scientific and technical journals. For data users and

researchers throughout the world, survey data are also available on the internet (http://www.cdc.gov/nchs/nhanes.htm) and on easy-to-use CD-ROMs. NHANES participants receive a report of their health examination.

Policy support: Primary data users are federal agencies that collaborated in the design and development of the survey. The National Institutes of Health, the Food and Drug Administration, and CDC are among the agencies that rely upon NHANES to provide data essential for the implementation and evaluation of programme activities. The US Department of Agriculture and NCHS cooperate in planning and reporting dietary and nutrition information from the survey.

3.7.16. South Korea

3.7.16.1. The Korea National Health and Nutrition Examination Survey (KNHANES)

Initiator/Funding source/Duration: KNHANES was first established in 1998 based on the Article 16 of the National Health Promotion Act proclaimed in 1995 and is still an ongoing surveillance programme. This surveillance system has been conducted by the Korea Centers for Disease Control and Prevention (KCDC). KNHANES has been financially supported by the Health Promotion Fund of Korea with administrative support from the Ministry of Health and Welfare. Furthermore, this surveillance system is technically supported by major academic societies in Korea based on the memoranda of understanding between KCDC and those academic societies (Kweon et al., 2014).

Study design: KNHANES is a nationwide cross-sectional survey conducted every year and features three components: a health interview, health examination, and nutrition survey. The survey collects detailed information on socioeconomic status, health behaviours, quality of life, healthcare utilisation, anthropometric measures, health measures such as dental, vision, hearing, and bone density, X-ray test results, biochemical profiles using fasting blood serum and urine, food intake, and dietary behaviours. The nutrition survey addresses dietary behaviours, food frequency and food intake and is conducted using the face-to-face interview method, see (Kweon et al., 2014) for more details.

Study population/Recruitment: Since 2008, about 10,000 individuals were surveyed every year. The target population comprises non-institutionalised Korean citizens (males and females) aged 1 year and over residing in Korea. The participants were recruited based on a multi-stage clustered probability design. For example, in the 2011 survey, 192 primary sampling units (PSUs) were drawn from approximately 200 000 geographically defined PSUs for the whole country. A PSU consisted of an average of 60 households, and 20 final target households were sampled for each PSU using systematic sampling.

Investigated chemicals/Matrices: Urine and blood samples were collected from participants aged 10 years and over. Aside from testing for various markers of organ functions, **cotinine** (as a biomarker of tobacco smoke exposure) and **heavy metals** (Hg, Pb, Cd, Mn, As, and Zn) were measured.

Analytical methods: All metals except for mercury were measured using AAS. Mercury was measured using a Direct Mercury Analyser (DMA-80), and urinary cotinine was measured by GC-MS.

Results/Interpretations: The levels of urinary As and cotinine as well as blood Mn, Hg, Cd, and Pb have been reported in several scientific articles (Jung et al., 2012; Koh et al., 2014; Park & Lee, 2013; Shin et al., 2012). The results are summarised in Table 34.

Blood Hg levels in the high consumption groups compared to the low consumption groups were elevated by about 20% with seafood and alcohol and by about 9-14% with seaweeds, green

vegetables, fruits and tea, whereas rice had no effect on Hg levels. Urinary As levels were markedly increased with consumption of rice, seafood and seaweed, whereas they were moderately increased with consumption of grains, green and white vegetables, fruits, coffee, and alcohol. The remaining food categories tended to minimally lower these levels. Thus, the typical Asian diet (high in rice, seafood, vegetables, alcoholic beverages, and tea) may be associated with greater blood Hg and urinary As levels (Park & Lee, 2013).

Blood Mn levels were significantly lower in the diabetes group compared with the non-diabetes group and the renal dysfunction group compared with those with normal renal function. There was no significant association between blood manganese levels and the presence of ischemic heart disease or stroke. (Koh et al., 2014).

The increase of serum Cd in blood was associated with the increase in the prevalence of hypertension after adjusting for age, education, income, alcohol, smoking, and BMI. The increase in blood Cd concentration was also associated with the increase of both systolic and diastolic blood pressure. Although higher fish intakes were significantly associated with higher blood Hg concentration, fish intakes did not affect either blood Cd or Pb concentration, and there was no evidence of a clear relationship between cardiovascular disease and frequency of fish consumption (Shin et al., 2012).

Urinary cotinine levels according to KNHANES 2007-2010 were highest for male active smokers. The difference between urinary cotinine levels for males and females was statistically significant. Urinary cotinine concentration is a useful biomarker for discriminating non-smokers from current smokers but is not useful in distinguishing between passive smoke exposure groups and non-exposure groups (Jung et al., 2012).

Investigation of exposure sources/Reference values: One study demonstrated associations between blood mercury levels and the consumption of seafood, vegetables, fruits, and alcohol. Furthermore, urinary arsenic levels were also increased with the consumption of rice and seafood (Park & Lee, 2013). Also, the levels of cotinine as a biomarker of tobacco smoke exposure between Korean smokers and non-smokers was analysed (Jung et al., 2012). Reference values for blood lead, cadmium, and mercury have been reported (Son et al., 2009).

Communication to participants/scientific community/public: KNHANES reports are released annually and are available to the public at the end of the year free of charge. KCDC is in the process of preparing an English version of their homepage to be finished by the end of 2014. A growing number of scientific publications has used KHANES data. The data were also used in international comparison studies. Recent publications on inequalities in non-communicable diseases and the global burden of metabolic risk factors used several rounds of KNHANES data and provided comparable health statistics. KCDC has provided annual workshops for data users to promote the more proficient use of the data. For example, between 2011 and 2012, the workshops were held three times with 400-800 researchers attending each workshop.

Policy support: KNHANES data are widely used by governmental organizations and researchers. The Korean Government has periodically revised national health plans and recently established the National Health Plan 2020 (HP 2020). KNHANES has supported health statistics on more than half of target indicators for HP 2020 goals. KNHANES has been used for the development of Korean standards regarding health and nutrition, such as the Dietary Reference Intakes for Koreans and will be used for the 2017 Growth Charts for Korean infants, children and adolescents.

3.7.16.2. Korea National Survey for Environmental Pollutants in the Human Body (KorSEP)

Initiator/Funding source/Duration: In order to address the concern regarding environmental pollution, the Ministry of the Environment in Korea has made efforts to measure the levels of environmental pollutants in the human body across the population and conducted regular surveillance to identify human exposure to toxic substances from the environment. The first survey (KorSEP I) was initiated as part of the KNHANES in 2005, and KorSEP II was conducted from April 2007 to December 2007. KorSEP III was designed in 2008 by the National Institute of Environmental Research (NIER) in Korea to assess the general population exposure to environmental pollutants (Lee et al., 2012).

Study design: KorSEP is a national cross-sectional study surveying Korean adults throughout the country. The study consists of questionnaire-based interviews [for data collection regarding sociodemographic information, socioeconomic data, family history, indoor and outdoor environments, life-style (i.e., exposure to smoking, alcohol and drug consumption, and physical activity), occupational history and dietary information] and sample collection.

Study population/Recruitment: KorSEP III in 2008 comprised 5087 Korean adults (males and females; non-institutionalised civilians) aged 20 or older from 193 areas in South Korea. Similar to KNHANES, the participants were recruited using a stratified multistage probability sampling design. In KorSEP III, 193 sampling units were randomly selected from the 264,183 primary sampling units in order to represent the overall Korean population (Lee et al., 2012). The participants voluntarily chose to partake in the survey. No financial rewards were offered, but the social impact of the study was explained.

Investigated chemicals/Matrices: Blood and urine samples were collected, and the following substances were measured: **bisphenol A**, **cotinine** (as a biomarker of tobacco smoke exposure), **metals** [As (namely inorganic As, MMA and DMA combined), Cd, Pb, Mn, Hg], **PAH metabolites** [(1-Hydroxypyrene (for pyrene), 2-Hydroxynaphthalene (2-Naphthol) (for naphthalene)], **phthalate metabolites** [MBzP (for BBzP), MiBP (for DiBP), MnBP (for DnBP), MiNP(for DiNP), MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP (for DEHP), MOP (for DOP), MCHP (for DCHP)], and **pyrethroid metabolite** [3-PBA (for cypermethrin, deltamethrin, and permethrin)].

Analytical methods: Pb, Mn, and Cd were measured by GF-AAS. As levels were determined by HG-AAS with a muffle furnace atomiser. Hg is measured directly using Direct Mercury Analyser 80 (DMA-80) equipped with a cold vapour generator. Phthalate metabolites were measured using HPLC. 1-hydroxypyrene and 2-naphthol were measured by HPLC-fluorescence after enzymatic hydrolysis. Cotinine was measured by GC-MS.

Results/Interpretations: Findings from the KorSEP III study have been published as scientific articles. Table 35, Table 36 and Table 37 report the findings of KorSEP III (Lee et al., 2012; Lee et al., 2011; Sul et al., 2012).

The levels of 1-hydroxypyrene, 2-naphthol, and cotinine were very similar between Korea and Germany; however, these levels were slightly higher than the levels in the USA (Sul et al., 2012). The levels of phthalate metabolites tended to be higher than the levels found in the USA NHANES survey but lower than the levels found in the Germany GerES IV survey. Urinary levels of phthalates were observed to be higher among subjects with older age, females, subjects with higher body mass index, and subjects with lower income (Lee et al., 2011). The levels of arsenic (particularly inorganic As, MMA, and DMA) from this study had been reported to be higher than those from NHANES, GerES, and Eastern Europe (Lee et al., 2012).

Investigation of exposure sources: Statistical analyses had been performed comparing the levels of heavy metals and several lifestyle factors such as fish consumption and smoking, and the higher levels of blood Hg and urinary As could be linked by the greater seafood consumption among the Korean population. (Lee et al., 2012). In addition, reference values for heavy metals, PAH metabolites, and cotinine have been determined and reported (Lee et al., 2012; Sul et al., 2012).

Policy support: Based on the KorSEP I-III findings, the Ministry of the Environment in Korea continued with the survey of Korean residents and conducted the Korea National Environmental Health Survey such as the KorEHS-C study (described next in detail). Analysis of the biomonitoring data from the Korean population provides useful information regarding one Asian population for use in international comparisons in environmental health research and other scientific areas.

3.7.16.3. Korean Environmental Health Survey in Children and Adolescents (KorEHS-C)

Initiator/Funding sources/Duration: KorEHS-C is a pilot HBM study initiated at the Dankook University in Cheonan, Korea and is financially supported by the Korean NIER. The recruitment phase of this study was conducted between December 2011 and May 2012. The exposure analysis was reported in June 2013 (Ha et al., 2013).

Study design: KorEHS-C is a cross-sectional study, which the parents/guardians and children were given multiple questionnaires for assessment of environmental exposure, food contamination exposure, and health status. Blood and urine samples were collected from the participants for measurement of various biomarkers of exposure.

Study population/Recruitment: From December 2011 to May 2012, a total of 351 children and adolescents (199 males and 152 females; age: 6-19) were recruited from Asan (rural) and Incheon (industrial) areas for this pilot survey. The schools were selected with the support of the Office of Education of each region. Students were asked to participate in the survey, and the teachers distributed consent forms and information brochures to the parents/guardians of the students. Those who participate would receive a gift voucher of 5,000 KRW (approximately 3.58 €) as an incentive.

Investigated chemicals/Matrices/Analytical methods: Blood and urine samples were collected from each participant. **Metals** (Pb, Hg, and Cd) were measured in blood. **Bisphenol A**, **cotinine** (as a biomarker of tobacco smoke exposure), and **phthalate metabolites** [MnBP (for DnBP), MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP (for DEHP)] were measured in urine. Pb and Cd were analysed via AAS, and Hg was analysed via CV-AAS. Phthalate metabolites and BPA were measured using HPLC-MS/MS. Cotinine levels were determined via ELISA.

Results/Interpretations/Communication: The levels of metals (Pb, Hg, and Cd) in blood and of BPA, phthalate metabolites, and cotinine in urine found in the KorEHS-C study have been reported (Ha et al., 2013). The results of this study would be reported to the individual participants and their schools after the survey is finished.

The blood Pb level was significantly higher in male children, children in urban areas, and children with less educated parents compared to those of subjects who were female, lived in rural areas, and had higher educated parents, respectively. The level of blood lead showed a decreasing (but not statistically significant) trend according to increase in age. The geometric mean level of Pb in blood was lower than that measured in Korean children (average age=6 years) in 2005 (1.8 µg/dL) or in German children (aged 3 to 14) years in 2003-2006 (3.5 µg/dL) but was similar to that of US children (aged 6-11) in 2003-2004 (1.25 µg/dL). The decrease in blood lead level with age and the higher levels in boys than in girls amongst children are well-known findings. The finding of a higher level of

blood lead in children with lower SES is also consistent with the findings in German children, US children, and Korean adults.

The blood Cd and Hg levels were not different between gender and area of residence after adjustment for covariates. In the higher cotinine group, the levels of Cd and Hg were higher than in the lower cotinine group. The Cd and Hg levels also increased with age. The median levels of Cd and Hg in blood were much higher than those of subjects in Germany and US. The main source of exposure to Cd and Hg is dietary intake in Korea. Rice accounts for about 23% of the total daily Cd intake, and the rest comes from seafood and vegetables. The main source of organic Hg is fish consumption, and most people in the Korean peninsula eat fish frequently.

Urinary median levels of BPA were lower than those in Germany and the US while those of phthalate metabolites were generally similar to levels in those countries. The level of BPA was the highest in the youngest children and the second highest in the oldest group, which is a similar finding in other countries. The BPA level was higher in groups with higher cotinine level than in groups with lower cotinine level in the current subjects, although there was no statistical significance.

All three kinds of phthalate metabolites showed significant decreasing trends with age even after adjustment for covariates. Significant decreasing trends in metabolites of phthalates by increasing age are consistent findings in Germany and in the US. In urban areas, the level of MEHHP was significantly higher than in rural areas.

The level of urinary cotinine was the lowest in middle school students while the highest levels were found in high school students. Thirty-nine students (17%) were reported to be active smokers, which 29 of them (74%) are high school students. The level of cotinine was significantly higher in children and adolescents whose parental educational level was lower. Parental educational level was reported as a good index of the socioeconomic position of Korean children as there was a relationship between parental education level and unequal environmental exposure to tobacco smoking and health inequality (Ha et al., 2013).

Investigation of exposure sources: The KorEHS-C research group intends to use this observed data (Phase 1) and proceed to Phase 2 of the study, which is to conduct an in-depth investigation to indicate the major exposure routes and to study the relationship between certain hazardous environmental factors and health outcomes, particularly in the high-risk target groups.

Policy support: The Environmental Health Act (EHA), implemented on March 22, 2009, requires special regulations and countermeasures in order to reduce and prevent environmental exposure in the "Susceptible Population," namely pregnant women and children, including infants and toddlers and calls for the generation of scientific evidence (Articles 14 and 15 of the EHA). The prevention and eradication of environment-related diseases is the main goal of the environmental sector among various government-designated policy goals of the current administration (Ha et al., 2013). KorEHS-C could help support the EHA and supply scientific data of environmental exposure among children in Korea.

3.7.16.4 . The Mothers and Children's Environmental Health (MOCEH) Study

Initiator/Funding sources/Duration: The MOCEH study started as an initiative of the National Environmental Health Action Plan (NEHAP), developed by the Korea Ministry of Environment, and it is funded by the Ministry of Environment (Kim et al., 2009). The recruitment for the MOCEH study began in 2006 and continued until 2010. The researchers intend to perform follow-up studies on the children up to 5 years of age.

Study design: The MOCEH study is a prospective hospital- and community-based cohort study designed to investigate the effects of pre- and postnatal environmental exposures on growth, development, and health from early foetal life into young adulthood. A questionnaire is administered to collect socio-demographic information, relevant data about the subject's biological, medical, and obstetric history, information regarding drug usage, vaccinations, or complications during pregnancy, breastfeeding, nutrition, and environmental exposure. The air quality inside and outside of each participant's home is assessed. Maternal blood is collected at 20 weeks of gestation. At birth, cord blood and a piece of umbilical cord are collected. Blood samples are not taken from the children until they are 3 years of age. Urine samples are collected from the mother at less than 20 weeks of gestation and from the child at 6, 12, 24, 36 months, and 5 years of age. Breast milk sample is taken at the end of the first feeding on the third day of delivery. Also, dietary information is collected from the mother prior and during pregnancy. Every 6 months after birth, mothers are asked about their child's diet during a 48h recall interview. A FFQ will be administered when the children are 3 and 5 years of age. Assessment of outcome (i.e. birth outcomes, growth and development, neurocognitive development, and allergies/asthma in children) would be conducted (Kim et al., 2009).

Study population/Recruitment: A total of 1,209 mothers (and 1,169 fathers) were recruited between 2006 and 2010 from the following different communities: (1) metropolitan Seoul, (2) industrial Ulsan, and (3) medium-sized urban Cheonan. Mothers who plan to move out of the residential areas of interest within 1 year from the date of screening and who are cognitively impaired are excluded from the study (Kim et al., 2009). Pregnant women in their first trimester were approached for recruitment at obstetric clinics in Seoul, Cheonan, and Ulsan. Eligible women were invited to participate through posters on the walls of the clinics and by examining obstetric doctors.

Investigated chemicals/Matrices/Analytical methods: Maternal and cord blood, urine, and breast milk samples from mothers as well as blood and urine samples from children were collected. **Bisphenol A**, **cotinine** (as a biomarker of tobacco smoke exposure), **PAH metabolites** [1-Hydroxypyrene (for pyrene), 2-Hydroxynaphthalene (2-Naphthol) (for naphthalene)], and **phthalate metabolites** [MnBP (for DnBP), MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP (for DEHP)] were measured in the urine. **Metals** (Pb, Hg, and Cd) were measured in the blood. Pb and Cd were analysed via AAS, and Hg was analysed via CV-AAS. Phthalate metabolites were measured using HPLC-MS/MS. PAH metabolites were analysed by HPLC-fluorescence detection. BPA was measured by HPLC-isotope dilution-MS/MS.

Results/Interpretations: A number of findings from the MOCEH Study has been published as peer-reviewed scientific articles and summarised below.

Phthalates metabolites: The association between prenatal phthalate exposure and the Mental and Psychomotor Developmental Indices (MDI and PDI, respectively) of the Bayley Scales of Infant Development was explored. MDI was inversely associated with the natural log concentrations of MEHHP and MEOHP, and PDI was inversely associated with MEHHP. In males, MDI was inversely associated with MEHHP, MEOHP, and MBP; PDI was inversely associated with MEHHP, MEOHP, and MBP. No significant linear associations were observed for females. The results suggest that prenatal exposure to phthalates may be inversely associated with the MDI and PDI of infants, particularly males, at 6 months." (Kim et al., 2011b)

PAH metabolites: Urinary levels of 2-naphthol, 1-hydroxypyrene, and malondialdehyde (MDA; a biomarker of oxidative stress) were analysed in 715 pregnant women at 12–28 weeks of gestation. The dietary antioxidant intake during pregnancy was estimated using the 24-h recall method. Urinary MDA level was positively correlated with the 2-naphthol and 1-hydroxypyrene levels. Urinary 1-

hydroxypyrene level was positively associated with the MDA level, which only existed in pregnant women with either low fruit and vegetable or vitamin C intake. These results suggest that an adequate maternal intake of fruit, vegetables and vitamin C is beneficial to the defence against the oxidative stress associated with exposure to PAHs in pregnant women." (Kim et al., 2011a)

BPA: Urinary BPA concentrations were shown to be higher in women with a higher income level. Univariate regression analysis revealed a significant association between BPA levels and birth weight. This relationship was more pronounced in male neonates. Also, prenatal exposure to BPA was associated with an increase of ponderal index in total, especially in female neonates (Lee et al., 2014).

Metals (Cd, Pb, and Hg): The blood Pb and Cd levels were measured in 884 mothers during their early and late pregnancy. The geometric mean of the maternal blood concentration was 1.36 mg/dL [90th percentile (P90) = 2.13; range = 0.26–9.10] for Pb and 1.42 mg/L (P90 = 2.16; range = 0.03–9.87) for Cd during the early pregnancy period and 1.27 mg/dL (P90 = 2.10; range = 0.12–4.28) for Pb and 1.52 mg/L for Cd (P90 = 2.10; range = 0.43–3.73) during the late pregnancy period. The prenatal Pb and Cd concentrations during the early pregnancy period showed no association with the adjusted MDI or PDI scores. The Pb levels during the late pregnancy period were inversely associated with the MDI score but not with the PDI score. The prenatal Cd levels during the late pregnancy period showed no association with the MDI or PDI score. These results suggest that there is a synergistic effect modification between Pb and Cd during the late pregnancy period. These findings suggest that there is dose-dependent interaction between prenatal exposure to Pb and prenatal exposure to Cd (Kim et al., 2013b).

Blood Hg data was analysed based on serum folate status at two gestational time points (mid and late pregnancy, n = 1105 and 841, respectively), and a negative association between serum folate and blood Hg concentrations in pregnant Korean women was found (Kim et al., 2013a).

Policy support: The MOCEH Study Group established a database of longitudinal measures and a repository of both environmental and biological specimens that would allow future assessments to address important issues concerning clinical and public health outcomes.

3.7.17. Japan

3.7.17.1. The Tohoku Study of Child Development

Initiator/Funding source: This study began at the Tohoku University in Sendai, Japan and was supported by several grants from the Japan Ministry of Health, Labour and Welfare, from the Ministry of Education, Culture, Sports, Science and Technology, from the Japan Public Health Association, and from the Ministry of the Environment (Nakai et al., 2009).

Study design/Duration: The Tohoku Study was a perspective cohort study investigating the effects of perinatal exposures to methyl mercury and POPs on neurobehavioral development among Japanese children. The recruitment period occurred between January 2001 and September 2003. The latest findings of this study were reported in 2010.

Study population/Recruitment: A total of 687 healthy pregnant women were recruited in Sendai, Japan between January 2001 to September 2003, and after recruitment, 599 eligible mother-neonate pairs (e.g. no in vitro fertilisation, no severe diseases or abnormalities from both the mother and infant, etc.) were registered in the cohort study (Nakai et al., 2004). Healthy pregnant women were recruited at the obstetrical wards of two hospitals in Sendai with their informed consent.

The participants were given several types of questionnaires to acquire the following information: educational background, occupation, income, smoking habit, alcohol consumption, hair treatments, dental treatment, and importantly, fish/seafood intake and nutrition status. For food intake, a detailed FFQ (e.g. amounts of consumption of 13 seafood types) was given to the participants, see (Suzuki et al., 2010) for a more detailed description.

Blood samples were collected from the mothers at 28 weeks of pregnancy. Blood samples from the umbilical cord, placenta, and the cord tissue were collected after the delivery. Hair samples were also collected from the mothers after delivery, and breast milk samples were collected one month after delivery. Neurodevelopment assessment (e.g. Bayley Scale of Infant Development, the Kyoto Scale of Psychological Development, and the Fagan Test of Infant Intelligence) on children was performed.

Investigated chemicals/Matrices: Maternal blood, cord blood, placenta, breast milk, and maternal hair samples were collected, and the following substances were measured: **bisphenol A**, **dioxins** (1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD), **furans** (1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF), **metals** (Cd, Pb, Hg/MeHg, Se), **organochlorine pesticides** (Dieldrin, Heptachlor epoxide, p,p'-DDT, p,p'-DDE as a metabolite of DDT, trans-Nonachlor, HCB, β-HCH, Mirex), and **PCBs** (all 209 PCB congeners).

Analytical methods: Cd and Pb were determined by GF-AAS and ICP-MS, respectively. Total Hg was measured via CV-AAS followed by GC-ECD. Level of Se was measured fluorometrically. PCBs were analysed by HRGC/HRMS using the isotope dilution method. Dioxins were assessed using the Chemically Activated LUciferase gene eXpression (CALUX) assay, which uses a patented recombinant mouse cell line that contains luciferase reporter gene under the control of dioxin-responsive elements. The amount of light generated by the luciferase is directly related to dioxin TEQ value.

Results/Interpretations: Several findings from the Tohoku Study have been published as peer-reviewed scientific articles (Nakamura et al., 2008; Suzuki et al., 2010). Total Hg reported in maternal hair and detectable levels of dioxins, furans, and PCBs in breast milk, maternal blood, and cord blood have been reported in several scientific articles (Suzuki et al., 2010). A negative relationship between the maternal hair mercury level (median, 1.96 μg/g) and the motor cluster of Neonatal Behavioural Assessment Scale was observed. The ∑PCB level in cord blood (45.5 ng/g-lipid) was negatively correlated with the motor cluster, but this association was attenuated after adjusting for mercury and the confounders. Briefly, prenatal exposure to MeHg adversely affects neonatal neurobehavioral function, but the neurobehavioral effect of prenatal exposure to PCBs remains unclear (Suzuki et al., 2010).

The concentrations of PCDD/DFs, DL-PCBs, and PCBs in breast milk, maternal blood and cord blood, obtained from the participants registered in a birth cohort study in Tohoku, Japan, were measured. The PCBs concentrations were in the order of breast milk > maternal blood > cord blood. TEQ concentrations and PCBs were negatively associated with parity, and maternal age was positively associated with PCBs. However, the associations with BMI and fish intake during pregnancy were not significant. The results suggest that parity is an important factor affecting the concentrations of dioxins and PCBs in these specimens (Nakamura et al., 2008).

Investigation of exposure sources/Reference values: Several studies have associated the exposure of methyl mercury and PCBs to fish consumption (Iwasaki et al., 2003; Mato et al., 2007). According to

the 2002 *Annual Report on Health and Welfare* from the Japan Ministry of Health, Labour and Welfare, more than 80% of dioxin exposure comes from consumption of fish and shellfish. No reference value has been reported in this study.

Investigation of exposure sources/Policy support: The Tohoku Study offers some of the first reports on the neurobehavioral effects of prenatal exposure to methyl mercury and PCBs in Japanese neonates. These findings could address some of the questions policy makers might have regarding health effects from exposure to methyl mercury and other substances.

3.7.17.2. The Hokkaido Study on Environment and Children's Health

Initiator/Funding sources/Duration: The Hokkaido Study began at the Hokkaido University in Sapporo, Japan and was supported by several grants from the Japan Ministry of Health, Labour and Welfare, from the Ministry of Education, Culture, Sports, Science and Technology, and from the Japan Society for the Promotion of Science (Kishi et al., 2011). It began in 2002 and is currently ongoing.

Study design: Two perspective cohort studies are conducted: the Toho hospital cohort with one obstetric hospital in Sapporo and the Hokkaido large-scale cohort with 37 hospitals and clinics in Hokkaido prefecture. In the Toho cohort, a baseline questionnaire was given to obtain information regarding demographics, dietary habits, and chemical exposure in the daily life, as well as alcohol consumption, caffeine intake, and income. Medical records regarding pregnancy and birth were obtained. Maternal blood samples were collected during late pregnancy stage, and cord blood and placenta were taken immediately after birth. Maternal hair samples were collected within 5 days after delivery, and breast milk from mothers was collected within 4 weeks after birth. Chemical exposure analysis was conducted, and the neurodevelopment in the children was assessed. A follow-up questionnaire was used at 18, 42, and 84 months of age to obtain information regarding allergy prevalence, dietary habits, and smoking history of mother and father. In the Hokkaido large-scale cohort, a baseline questionnaire was given to obtain information regarding demographics, medical history, and dietary supplement intake during pregnancy, as well as chemical exposure at work. Birth records were obtained from the responsible obstetricians. Maternal blood samples were collected three times: between 6-14 weeks of gestation, during the third trimester, and at delivery. Maternal serum samples were tested for folic acid level and plasma cotinine concentration. Cord blood was taken immediately after birth. Follow-up questionnaires were given at 4, 12, 24, and 48 months to obtain information vaccination history, dietary habits, parental smoking history, and allergy prevalence (Kishi et al., 2011).

Study population/Recruitment: The recruitment for the Toho hospital cohort was conducted from July 2002 to October 2005. The Toho cohort recruited participating pregnant women who intended to deliver at the Toho hospital. Of 1796 potentially eligible women, 514 agreed to participate. The subjects were women who enrolled at 23–35 weeks of gestation and delivered at the Toho hospital. All the subjects were resident in Sapporo City or surrounding areas. The Hokkaido large-scale cohort recruited participating women in early pregnancy (<13 weeks of gestational age) that visited one of associated hospitals or clinics in the study area for prenatal health care at the maternity unit. From February 2003 to the end of 2009, 16,306 mothers were registered in this cohort. These two cohorts did not show significant differences in the characteristics of mothers and infants, and both cohorts will follow its participants up to school age.

Investigated chemicals/Matrices: Maternal blood, cord blood, breast milk, and maternal hair samples were collected for analysis, and the following substances were measured: **bisphenol A**, **cotinine** (as a biomarker of tobacco smoke exposure), **dioxins** (1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD,

1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD), **fluorocarbons** (PFOA, PFOS), **furans** (1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF), **metals** (Cd, Pb, MeHg), **PCBs** (PCB 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189), and **phthalate metabolites** (MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, MECPP/5cx-MEPP for DEHP). Additional biochemical measurements were also analysed (Kishi et al., 2011).

Analytical methods: The levels of PCDDs/PCDFs and PCBs in maternal blood and breast milk were measured using HRGC/HRMS. PFOS and PFOA levels in maternal blood, cord blood and breast milk were analysed by LC-MS/MS. Total Hg levels in maternal hair samples were measured by oxygen combustion-gold amalgamation using atomic absorption detection. Maternal serum cotinine concentration in maternal blood was measured using an ELISA.

Results/Interpretations/Communication: PFOS & PFOA concentrations in maternal serum, cotinine concentrations in plasma, and PCDD, PCDF, and PCB concentrations in maternal blood from the Hokkaido Study have been published as peer-reviewed scientific articles. All collected source data are maintained and stored at the Department of Public Health Sciences at Hokkaido University. Inquiries could be made by contacting the primary investigator, Dr. Reiko Kishi.

Among male infants, significant adverse associations with birth weight were found for total PCDDs TEQ level, total PCDDs/PCDFs TEQ level, and total TEQ level. However, among female infants, these significant adverse associations were not found. With regard to individual congeners of PCDDs/PCDFs and DL-PCBs, we found significantly negative association with the levels of 2,3,4,7,8-PeCDF. This suggests that prenatal low-level exposure to PCDDs and PCDFs, especially 2,3,4,7,8-PeCDF, may result in lower birth weight (Konishi et al., 2009).

The associations between the total or individual PCB levels and dioxins in 134 Japanese pregnant women's peripheral blood and the mental or motor development of their 6-month-old infants were evaluated using the second edition of the Bayley Scales of Infant Development. The mean level of total TEQ was 18.8 (4.0-51.2) pg/g lipid in the blood. After adjustment for potential confounding variables, the total TEQ value was shown not to be significantly associated with MDI or PDI. However, the levels of 1 PCDD isomer, total PCDDs, and total PCDDs/ PCDFs were significantly negatively associated with MDI, and the levels of 2 PCDDs and 3 PCDFs were significantly negatively associated with the PDI. The background exposure of several dioxin isomers during the prenatal period might affect the motor development of 6-month-old infants (Nakajima et al., 2006).

Higher levels of PCDFs were associated with a significantly increased risk of otitis media, especially among male infants. Higher levels of 2,3,4,7,8-PeCDF were also associated with a significantly increased risk of otitis media. However, there was a weak association between dioxin-like compound levels and allergic symptoms in infancy. At environmental levels, prenatal exposure to dioxin-like compounds may alter immune function and increase the risk of infections in infancy, especially among males (Miyashita et al., 2011).

PFOS levels were negatively correlated with birth weight. In addition, analyses stratified by sex revealed that PFOS levels negatively correlated with birth weight only in female infants. However, no correlation between PFOA levels and birth weight was observed. This indicates that in utero exposure to relatively low levels of PFOS was negatively correlated with birth weight (Washino et al., 2009).

The exposure source of serum cotinine was investigated among smokers, smoke-exposed non-smokers, and unexposed non-smokers. Based on self-reports, the 5,128 pregnant women were classified into three groups: 650 smokers, 728 ex-smokers and 3750 non-smokers, and cotinine levels in maternal blood samples were analysed. Using the receiver operating characteristic curve, plasma cotinine cut-off value of 11.48 ng/mL was established for separating smokers from non-smokers, resulting in a smoking prevalence of 14%. A cotinine cut-off value of 0.21 ng/mL for discriminating exposed and unexposed non-smokers resulted in a 63% prevalence of exposure to tobacco smoke among non-smokers. Cotinine biomarker analysis proved accurate in validating self-reported smoking information in the subjects. Lower validity of SHS exposure suggests a need to confirm questionnaire information with biochemical analysis (Sasaki et al., 2011).

Policy support: The Hokkaido Study provides findings that could address some of the questions policy makers might have regarding health effects from exposure to POPs in mothers and children.

3.7.17.3. Japan Environmental and Children's Study (JECS)

Initiator/Funding source: The Japan Advisory Board on Children's Environmental Health, established by the Ministry of the Environment (MOE), proposed a large-scale birth cohort study in order to evaluate the effects of environmental chemicals on children's health and development. In April 2008, the Working Group of the Epidemiological Research for Children's Environmental Health (later JECS Working Group) was organized and started systematic reviews on existing epidemiological findings regarding health impact of chemical exposures and the roles of potential confounders and effect modifiers, such as other environmental factors, genetic factors, socioeconomic status and lifestyle, in order to develop JECS study design and hypotheses. In March 2010, JECS Working Group published a draft conceptual plan for a large-scale birth cohort study covering all of Japan. The budget for conducting JECS was approved in 2010, and JECS was launched in April 2010 (Kawamoto et al., 2014).

Study design/Duration: JECS is a nation-wide large-scale perspective cohort study. Recruitment period started in January 2011 and ended in March 2014. Environmental exposure analysis began after recruitment period and is currently an ongoing process. Participating children will be followed until they reach 13 years of age. The JECS is expected to continue until 2032, five years after all the participating children reach 13 years of age, allowing through data analysis. Self-administered questionnaires were given to recruited expecting mothers to obtain information regarding socioeconomic status, lifestyle factors, and physical environment. Medical records from the expecting mothers are to be obtained. Maternal blood and urine samples are to be collected during the first and second trimesters while the partners' blood samples are to be collected only once. At birth, maternal hair and blood samples as well as the cord blood and child's dried blood spot are to be collected. One month after birth, a follow-up questionnaire will be answered, and samples of breast milk from the mothers are to be collected. Thereafter, questionnaires are sent out every 6 months. Pending on approval from the Ethics committee, blood and urine samples of selected children will begin when they reach 2 years of age (Kawamoto et al., 2014).

Study population/Recruitment: The Center for JECS makes contact with as many expecting mothers who reside in the study areas as possible. Either or both of the recruitment protocols are applied: 1) recruitment at the time of first prenatal examination at cooperating health care providers and/or 2) recruitment at local government offices issuing pregnancy journals, namely Mother-Child Health Handbooks. Due to the nature of recruitment at health care providers or local government facilities, the recruitment process is not completely random. Therefore, the Center for JECS attempts to recruit as many eligible expecting mothers in the study areas as possible. The eligibility criteria for participants (expecting mothers) are as follows: 1) They should reside in the study areas at the time of

the recruitment and are expected to reside continually in Japan for the foreseeable future, 2) expected delivery date should be between 1 August 2011 and mid-2014, and 3) they should be capable to participate in the study without difficulty. A total of 100,000 pregnant women is the targeted number of enrolment for the study. Partners are also recruited, but their participation is not mandatory. Recruitment period was between January 2011 and March 2014. To ensure generalizability and ability to extrapolate the results to the Japanese population, 15 Regional Centers are selected to cover diverse geographical areas within Japan (Kawamoto et al., 2014).

Investigated chemicals/Matrices: Blood (maternal, cord, and possibly children) and urine (maternal and possibly children) samples will be tested for various substances. JECS intends to analyse the following substances: **acrylamide**, **BFRs** (PBDE 17, 28, 47, 66, 85, 99, 100, 119, 126, 153, 154, 183, 196, 197, BDE 209, HBCDDs, TBBPA, 2,4,6-TBP, HBB, PBB153), **bisphenol A**, **chlorophenols** (2,4-DCP, 2,5-DCP, 2,4,5-DCP, 2,4,6-DCP, PCP), **cotinine** (as a biomarker of tobacco smoke exposure), **dioxins** (1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD), **fluorocarbons** (PFNA, PFOA, PFOS), **furans** (1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF), **herbicides** (2,4-D, 2,4,5-T), **metals** (As, Cd, Pb, Hg), **organochlorine pesticides** (Aldrin, Dieldrin, Endrin, Heptachlor, o,p'-DDT, p,p'-DDT, DDE as a metabolite of DDT, Oxychlordane, HCB, α-HCH, β-HCH, γ-HCH, Mirex), **organophosphate pesticides** (Acephate, Methamidophos), **organophosphate metabolites** [DEP, DMP, DETP, DMTP, DEDTP, DMDTP (for DAP)], **PAH metabolites** [3-Hydroxybenzo[a]pyrene (for benzo[a]pyrene), 2-Hydroxyfluorene, 3-Hydroxyfluorene, 9-Hydroxyfluorene (for fluorene), 1-Hydroxyphenanthrene, 2-Hydroxyphenanthrene, 3-Hydroxyphenanthrene, 4-Hydroxyphenanthrene, 9-Hydroxyphenanthrene, 4-Phenanthrene (for phenanthrene), 1-Hydroxypyrene (for pyrene), 1-Hydroxynaphthalene (1-Naphthol), 2-Hydroxynaphthalene (2-Naphthol) (for naphthalene)], **PCBs** (PCB 28, 44, 49, 52, 66, 74, 77, 81, 87, 99, 101, 105, 110, 114, 118, 123, 126, 128, 138, 146, 149, 151, 153, 156, 157, 167, 169, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 199, 203, 206, 209), **phenols** (Butyl paraben, Ethyl paraben, Methyl paraben, Propyl paraben, Triclosan), **phthalate metabolites** [MBzP (for BBzP), MiBP (for DiBP), MnBP (for DnBP), MEP (for DEP), MiNP, MCOP (for DiNP), MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, MECPP/5cx-MEPP (for DEHP), MMP (for DMP), MOP, MCPP (for DOP), MCHP (for DCHP), MCNP (for DiDP), MHCNH (for DINCH)], and **pyrethroid metabolites** [F-PBA (for cyfluthrin), Br_2CA (for deltamethrin), cis-Cl_2CA, trans-Cl_2CA, 3-PBA (for cypermethrin, deltamethrin, and permethrin)]. In addition, 8-OHdG is to be measured as a biomarker of oxidative DNA damage. The complete list of compounds to be analysed has been published (Kawamoto et al., 2014).

Results/Interpretations/Reference values: As the analysis of the listed chemicals is currently ongoing, no results, analytical methods, or reference values has been reported yet.

Investigation of exposure sources: The JECS intends to conduct some environmental measurements (mainly indoor air monitoring) during home visits. Indoor air pollutants, including volatile organic compounds, aldehydes, nitrogen oxides, and fine particulate matters will be measured. Other parameters such as noise levels, temperature, and humidity will also be recorded. Furthermore, there are about 1,500 ambient air quality monitoring stations and about 500 roadside air quality monitoring stations throughout Japan, where levels of five classical air pollutants, carbon monoxide, suspended particulate matter, sulphur dioxide, nitrogen dioxide, and photochemical oxidants are monitored continuously. Twenty other hazardous air pollutants are also monitored at over 300 sights. Exposure to classical and hazardous air pollutants will be estimated from the monitoring station data using atmospheric simulation models.

Communication to participants/scientific community/public: JECS provides information that could allow additional adjunct studies from the Japan National Center, Medical Support Center, or Regional Centers to be conducted. The Center for JECS expects chemical analysis of bio-specimens to start after the completion of the recruitment in early 2014. Reports associating environmental factors and birth abnormalities are to be published within the next few years.

Policy support: JECS aims to provide the foundation for policy making to safeguard the environment for the next generations (i.e. children). The ultimate goal of JECS is "to identify environmental factors that affect children's health and development in order to help decision makers design better chemical risk management strategies."

3.7.18. China (National Monitoring on POPs in human milk of China)

Initiator/Funding source: This monitoring programme was initiated by the National Institute of Nutrition and Food Safety of the Chinese Center for Disease Control and Prevention (China CDC). The study was based on the WHO-coordinated Fourth Survey of Breast Milk for Persistent Organic Pollutants in cooperation with the UNEP. The study was carried out in conjunction with the 2007 Chinese Total Diet Study and was financially supported by the National Science and Technology Support Programme of China, the National Nature Science Foundation of China, and the Chinese Ministry of Health (Li et al., 2009).

Study design/Duration: This cross-sectional study was developed based on the 'Guidelines for Developing a National Protocol' of the Fourth WHO-coordinated survey of Human Milk for Persistent Organic Pollutants in Cooperation with UNEP with some modifications. The collection period was held from July to November 2007, and the latest publication regarding this study was published at the beginning of 2012. A written questionnaire was completed to record the content of the face-to-face interview for each mother. The information included date of birth, place of birth, residence record, dietary habits, consumption of animal-origin food including aquatic food, meat, egg and milk, occupation before pregnancy, and the indoor using of DDT at home. According to the questionnaires, none of the mothers smoked, and none used DDT in their home. The participating mothers provided the samples at the local contact places, where collection was supervised. At least 50 mL of milk was collected from each mother. The samples were collected directly to the pre-washed collecting jars and were stored at -20°C until analysis.

Study population/Recruitment: A total of 1,237 primiparous mothers (age range: 18-35; mean: 25.6) voluntarily participated in the study, which the collection period occurred during the second half of 2007. The participants came from 12 provinces (Fujian, Guangxi, Hebei, Heilongjiang, Henan, Hubei, Jiangxi, Liaoning, Ningxia, Shanghai, Shanxi, and Sichuan), which accounts for about 50% of the total population of China. In each province, one urban site and two rural sites were selected for sampling. In each urban area, 50 donors were selected, and in each rural area, 30 donors were selected (Li et al., 2009).

Investigated chemicals/Matrices: Breast milk samples were collected and analysed for levels of the following substances: **BFRs** (PBDE 47, 99, 100, 153, 154, 183, HBCDDs, TBBPA), **dioxins** (1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD), **fluorocarbons** (PFDeA/PFDA, PFHxS, PFNA, PFOS, PFOA, PFUA/PFUdA), **furans** (1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF), **organochlorine pesticides** (Aldrin, Dieldrin, Endrin, Heptachlor, Heptachlor epoxide, o,p'-DDT, p,p'-DDT, DDE as a metabolite for DDT, Oxychlordane, trans-

Nonachlor, HCB, α-HCH, β-HCH, γ-HCH, Mirex), and **PCBs** (PCB 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189).

Analytical methods: The pesticide POPs were measured via GC-ECD & GC-LRMS with isotope dilution. The marker PCBs were measured by GC-HRMS or GC-LRMS with isotope dilution. The PCDDs, PCDFs, and DL-PCBs are analysed by GC-HRMS with isotope dilution. The PBDEs were measured by GC-HRMS or GC-LRMS with isotope dilution. PFCs were measured by UPLC-triple quadruple mass spectrometry, and HBCD (α, β, γ) were measured by LC-MS/MS with isotope dilution.

Results/Interpretations/Communication: Some of the results have been already published as peer-reviewed articles and have been presented to the United Nations Environment Programme (Wu).

The TEQs concentrations (for PCBs and dioxins/furans) of pooled samples in 12 provinces has been first published in 2009 (Li et al., 2009). Subsequently, the levels of PFCs (Liu et al., 2010) and of various organochlorine pesticides (Zhou et al., 2011) in breast milk samples from China have been reported. Positive correlations were found between total-TEQ level in human milk and the consumption of aquatic food and meat. However, both the TEQ body burden of the sample population and estimated daily TEQ intake of breast-feeding infants were lower than those of developed countries. Continuous surveillance on PCDD/Fs and DL-PCBs levels in human milk is needed to correctly evaluate both the environmental impact and human health risk in China (Li et al., 2009).

PFOS and PFOA were the predominant PFCs found in all the samples tested. A large variation in geographical distribution was observed for PFCs in human milk. High concentrations of PFOA were found in human milk from Shanghai. The estimated dietary intake (EDI) for PFOA (88.4 ng/kg/d) for Shanghai was close to the tolerable daily intake (100 ng/kg/d) proposed by the German Federal Institute for Risk Assessment and the Drinking Water Commission. The results suggest both mothers and infants have a high exposure to PFCs in the Shanghai region. The potential health impact of postnatal exposure through breastfeeding to infants should therefore be comprehensively evaluated (Liu et al., 2010).

DDTs were the most prevalent agent of the organochlorine pesticides, followed by HCHs and HCB, whereas levels of chlordane compounds, drins and mirex were lower. The relatively lower DDE/DDT ratio in the Fujian rural area suggested more recent exposure to DDT than in other areas. The mean level of DDTs in breast milk from the southern China was higher than those from northern China ($p < 0.05$). A positive correlation was observed between DDT levels in human milk and consumption of animal-origin food, suggesting that this parameter could play an important part in influencing organochlorine pesticide (OCP) burdens in lactating women. The mean estimated daily intakes of different OCPs for breastfed infants were lower than the tolerable daily intake (Zhou et al., 2011).

Investigation of exposure sources/Policy support: The China CDC intends to measure the levels of pollutants in the food in order to correlate to the HBM results and to evaluate their findings in order to set up the national maximum levels of pollutants in food. Therefore, the national food safety standards for pollutants could be improved.

3.7.19. European research programmes including HBM

Using the European Commission's Community Research and Development Information Service (CORDIS) portal, several European research programs including HBM analyses and information about food intake are identified and described below.

3.7.19.1. Consortium to Perform Human Biomonitoring on an European Scale (COPHES)/Demonstration of a Study to Coordinate and Perform Human Biomonitoring on an European Scale (DEMOCOPHES)

Initiator/Funding source: Project no 244237 under FP7

Duration: 2009-2013

Study design: In 2009, European scientists and stakeholders from 35 institutions in 27 European countries began work towards setting up a European-wide human biomonitoring framework. Funded by the EU's Seventh Framework Programme, COPHES developed harmonised protocols allowing the collection of comparable HBM data throughout Europe. Its twin project, the feasibility study DEMOCOPHES, was launched one year later to test this hypothesis and to gain information on levels and major determinants of exposure in Europe as well as to establish protocols for the translation of HBM results into concrete policy recommendations.

Study population/Recruitment: Participants in this study were children aged 6-11 years and their mothers aged 45 years and under. Fieldworkers in the participating countries collected hair and urine samples from a total of 3688 volunteers, half from urban areas and half from rural areas. Mothers provided details via a questionnaire on their living environment, nutrition (mainly exposure-related food intake), smoking behaviour, and other information that could help to explain the levels of the biomarkers measured in hair and urine.

Investigated chemicals/Matrices: Using biomarkers and questionnaire data, research teams in Belgium, Cyprus, Czech Republic, Denmark, Germany, Hungary, Ireland, Luxembourg, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom studied exposure to mercury, cadmium, tobacco smoke, and some phthalates and their possible associations to lifestyle. Bisphenol A was added as an additional substance for a group of 6 countries. The national teams translated the European common protocol, which describes in detail how to implement the study. Without compromising the comparability of the results, small adaptations were allowed to suit cultural differences and sometimes specific national needs. Before starting the study, ethics authorities in each country approved the necessary documents (Becker et al., 2014; Casteleyn et al., in press; Fiddicke et al., 2014). The study measured biomarkers in human hair and urine from around 120 mother-child pairs in the 17 participating countries, in total almost 4000 samples.

Analytical methods: The laboratories analysing the samples were selected through a strict quality assurance process, comprising Interlaboratory Comparison Investigations (ICI) and External Quality Assessment Schemes (EQUAS) which is described by (Esteban et al., 2014; Schindler et al., 2014). Some countries such as Denmark extended the basic scenario with supplementary measurements (Mørck et al., 2014).

Results/Interpretations: COPHES/DEMOCOPHES results demonstrate that harmonisation is possible, but further capacity building is needed to establish the networks and infrastructure in EU countries. These results are the first step towards EU-wide databases on the distribution of the chemical burden in the population, which will allow to follow levels in the population and evaluate the effectiveness of regulatory measures such as a ban on certain chemicals or smoking regulations. At the same time, improved comparability of European HBM data in the future will allow cross boundary evaluation of gradients in human exposure throughout Europe and it will facilitate the elaboration of guidance values and the identification of potential high exposure populations or subpopulations and may help to target measures.

Investigation of exposure sources: From the questionnaire filled in by the mothers, sources such as food intake, lifestyle and habitation have been identified. External sources have also been surveyed (Smolders et al., 2014).

Reference values: Values found in participating countries could be considered as reference values when the limitations of a non-representative sample are taken account.

Communication to participants/scientific community/public: This is the first time that we have information on the distribution of chemicals in 17 EU countries, which are comparable between the countries and with international data. Protocol considerations, national and common results are published, some in a special volume of Environmental Research. Special emphasis related to policy implications of COPHES/DEMOCOPHES has been published (Joas et al., 2014).

Policy support: DEMOCOPHES was supported by the Life+ program financing 50% of the national expenses and the other 50% financed by national authorities.

3.7.19.2. Environmental Cancer Risk, Nutrition and Individual Susceptibility (ECNIS)

Initiator/Funding source: Project no 266198 under FP6 and FP7

Duration: 2005-2013

Study design: A major approach employed in ECNIS research is the use of biomarkers of carcinogenesis. Biomarkers of carcinogenesis are usually substances which can be measured in body fluids or tissues and provide information about a person's exposure to carcinogens or about cellular damage caused by carcinogens far earlier than the appearance of clinical disease. Furthermore, genetic polymorphisms can serve as biomarkers of individual susceptibility to carcinogenesis. ECNIS research also addresses the mechanisms by which chemicals alter cellular processes to cause cancer and the way in which food components intervene in these mechanisms. It also aims to improve cancer risk assessment, and to address important socio-ethical issues arising from the use of biomarker technology.

Study population/Recruitment: The ECNIS Network consisted of 24 partners, which represent a multi-disciplinary team of nearly 200 scientists, including toxicologists, epidemiologists, food and nutrition scientists, chemists and molecular biologists. Coming from 13 European countries, the ECNIS partner institutions represent regions and populations with diverse climates, pollution levels and dietary habits, thus providing unique opportunities for the assessment of the impact on cancer risk of environmental exposures and dietary patterns over a wide range of variation, and enabling population studies on a pan-European scale. This diverse and wide membership also provides opportunities for the optimal utilization of the large number of cohorts and human tissue sample banks that exists throughout Europe.

Investigated chemicals/Matrices: The vision of ECNIS was the creation of a dynamic research network which will work to decrease cancer incidence by

- identifying chemicals or other factors in the environment and food which cause cancer,
- elucidating the mechanisms by which dietary and lifestyle patterns increase or decrease cancer risk,
- facilitating the development of new foods with cancer-preventive properties,
- discovering genetic (hereditary) factors which make individuals more or less susceptible to cancer, and
- formulating improved approaches to the risk assessment of carcinogens.

Analytical methods: ECNIS fostered collaboration between research groups with data on biomarkers of exposures to carcinogens and cancer risk.

Results/Interpretations: The biomarkers have been further validated.

Investigation of exposure sources: Environmental and occupational exposures as well as lifestyle including food intake have been recorded for the study subjects included in the ECNIS database. However, the information is at different levels of detail since only the data from the original studies is taken into account.

Reference values: No reference value has been established as the ECNIS overall project is analytical and descriptive.

Communication to participants/scientific community/public: The ECNIS website (http://www.ecnis.org/) offers background information to the public. ECNIS hosted a number of workshops and issued 7 special reports as well as a high number of scientific publications. Also, help desk facilities for ethics approval has been issued.

Policy support: The ECNIS study has been promoting European HBM as later materialized in the COPHES/DEMOCOPHES project.

3.7.19.3. EnviroGenomarkers – Genomics Biomarkers of Environmental Health

Initiator/Funding source: Project no 226756 under FP7

Duration: 2009-2013

Study design: Small/medium-scale collaborative research project

Study population/Recruitment: Existing biobanks in Europe and beyond, containing stored biosamples from millions subjects, represent an enormous investment and a precious resource for environmental health studies. However, the experience with their potential to benefit from –omics technologies is very limited to date. By utilising some of Europe's major existing biobanks and including systematic technical validation of the application of –omics on their samples, the EnviroGenomarkers project helps open the way to the exploitation of this important resource.

Investigated chemicals/Matrices: Currently, human biomonitoring is based on the measurement of chemicals or their metabolites in human tissues and provides information only on the level of population exposure to environmental chemicals. The combination of such data on chemical-specific

biomarkers of exposure with –omics data provides the opportunity to link exposure information with biological data measured on the same human biosample.

Analytical methods: The EnviroGenomarkers project, by combining the analysis of human blood samples for a number of high-priority chemicals of great interest for population biomonitoring programmes with the –omics-based assessment of the same biosamples, is taking a step into the future and represents the next day in human biomonitoring activities.

Results/Interpretations: Omics technologies provide exciting opportunities to develop a new breed of biomarkers of environmental health which, in contrast to traditional ones, allow the use of the same generic methodology (e.g., microarrays) for the detection of cellular responses to different categories of chemicals and types of toxicity and provide mechanistic information at an unprecedented scale. In fact the prospect of simultaneously obtaining, in human biosamples, a global picture of the functional state of the cell at the levels of DNA, RNA, proteins and metabolites, which can be integrated into a holistic view of the perturbation of cellular pathways by the environment, provides a paradigm shift for environmental biomarker research and molecular epidemiology.

Investigation of exposure sources: Environmental and occupational exposures as well as lifestyle including food intake have been recorded for the study subjects included in the cohorts. However, the information is at different levels of detail since only the data from the original studies is taken into account.

Reference values: EnviroGenomarkers project constitutes an effort in establishing this new paradigm of omics and since it is still under development no reference values have been obtained.

Communication to participants/scientific community/public: Results are being published in scientific journals (Chadeau-Hyam et al., 2014) and are displayed on the project's website (http://www.envirogenomarkers.net/).

Policy support: Omics is considered in a number of EU projects as a tool of holistic exposure assessment.

3.7.19.4. Integrated Assessment of Health Risks from Environmental Stressors in Europe (INTARESE)

Initiator/Funding source: Project under FP6

Duration: 2005-2010

Study design: A five-year integrated project

Study population/Recruitment: The project brought together a team of internationally renowned scientists in the areas of epidemiology, environmental science and biosciences to collaborate on developing and applying new, integrated approaches to the assessment of environmental health risks and consequences, in support of European policy on environmental health. The INTARESE approach was based on the principle that environmental health issues are not stand-alone issues but the result of interdependent decisions and events and can affect human health in many different interacting ways.

Investigated chemicals/Matrices: The project describes a number of models taking exposure and uptake into account.

Analytical methods: Mathematical modelling

Results/Interpretations: INTARESE achieved its objectives and developed the concept and methodology of integrated environmental health impact assessment, produced an extensive series of case studies and combined these findings in an on-line Integrated Environmental Health Impact Assessment System (IEHIAS), which provides guidance on integrated assessment, gives access to key data sources, models and methodologies, a large number of worked examples, and gateways to open platforms.

Investigation of exposure sources: Included in the models

Reference values: Not applicable as the project has only developed models.

Communication to participants/scientific community/public: More information about the project can be found on the INTARESE's website (http://www.intarese.org/). A series of Technical Briefs was published to provide more specific information on the different aspects and approaches taken as well as the achievements of the project.

3.7.19.5. Expert Team to Support Biomonitoring in Europe (ESBIO)

Initiator/Funding source: Project no 22580 under FP6

Duration: 2005-2008

Study design: The research team created an extended inventory of European HBM activities, past and present, incorporating self-registration and including information relevant to researchers and stakeholders alike. In addition, the investigators focused on rules and practices related to ethical conduct, providing recommendations regarding protocols, biobanking issues, special concerns with respect to the participation of children and harmonisation of overall procedures on a European level.

Finally, the team provided an Excel tool for socioeconomic optimisation of future HBM projects providing the total necessary project budget based on user inputs.

Study population/Recruitment: Data included people and laboratories involved in certain projects and entities with expertise in specific analytical areas.

Investigated chemicals/Matrices/Reference values: A number of chemicals and matrices were represented with reference to the included studies, investigating different exposures and in different setups, primarily focused on children. No reference values could be stated.

Communication to participants/scientific community/public: A number of reports and publications were issued.

Policy support: In summary, the ESBIO project made significant progress in developing protocols and tools for coordinating HBM research efforts on a European level, in particular as related to children. Better coordination among EU countries has the potential to elucidate important findings that might otherwise be buried without shared data and shared methods, resulting in better health for EU citizens via more effective policies and regulations.

3.7.19.6. Public Health Impact of Long-Term, Low-Level Mixed Element Exposure in Susceptible Population Strata (PHIME)

Initiator/Funding source: Project no 244237 under FP6

Duration: 2006-2011

Study design: PHIME had 39 partners in 22 countries, mainly in Europe but also in Morocco, Ecuador, China, the Seychelles, and Bangladesh.

The background was a renewed interest in toxic metals, due to a growing awareness that the exposure in the general population in Europe and elsewhere is at levels with potential to cause toxic effects in susceptible individuals. Such exposures may have a role in the aetiology of common clinical diseases, as well as sub-clinical effects, which may be serious for the society. The impact of toxic metal (particularly cadmium, mercury, lead and manganese) exposure through foods on diseases of public health concern (nervous and cardiovascular systems, osteoporosis/fractures, kidneys, diabetes) was studied. Benefits of exposures to essential elements (selenium, zinc)/other dietary components (fatty acids, fibre), and some aspects of risk/benefit relationships have been described.

Study population/Recruitment: Some studies utilize unique biobank material. Occupational exposures were studied as models. Mother-child cohorts were also included.

Investigated chemicals/Matrices: From mother-new-born pairs, maternal hair, cord blood, maternal and child's urine, or meconium was collected at birth. Rarely, breast milk samples at 3-6 months post-delivery were collected.

Analytical methods: Analyses were only performed centrally to assure comparability.

Results/Interpretations: A wealth of important, novel information was produced. For example, the exposure to lead and cadmium seems to be fairly similar in many European countries, with the exception of particularly polluted areas. The exposure to mercury differs, according to varying fish intake and dental practice. The exposure to lead and mercury is decreasing, while cadmium does not show such a favourable time trend. The tissue concentrations of "catalytic converter elements" platinum, palladium and rhodium are much lower than previously thought.

The toxic effects of methylmercury in fish on the central nervous system of foetuses and on the myocardium of adults are markedly modified by nutrition, notably intake of long-chain n-3 polyunsaturated fatty acids, which also occurs mainly through fish. Arsenic and manganese, ingested mainly through drinking water and food, affect development and health of foetuses, infants and children. Lead exposure is toxic to children's central nervous system at very low exposures.

Data cast doubt on the urinary excretion of low-molecular weight proteins as a biomarker of cadmium risk to the kidney at low exposure, but, at the same time, there is now evidence of low-level cadmium exposure causing toxic bone effects, with decrease of bone mineral density, increase of osteoporosis and fractures. Preventive actions against cadmium urgently are needed, in light of the continuous exposure world-wide.

Gene-environment interaction is important in metal toxicity. Thus, the metabolism (toxicokinetics) of mercury, arsenic, lead and cadmium was shown to be modified by genetics, as is toxicodynamics of arsenic, lead, cadmium and manganese. This should be considered in risk assessment, as the risk may vary between individuals, and between populations with different gene frequencies.

Investigation of exposure sources: The exposure sources were identified through questionnaires.

Reference values: Background levels of the analysed metals from different study populations have been established.

Communication to participants/scientific community/public: Information about PHIME can be found online (http://www.med.lu.se/labmedlund/amm/forskning/haelsorisker_av_metaller/phime). A number of workshops have been arranged, and the project has a large publication record.

Policy support: Taken together, the scientific results contributed by PHIME have brought new, important insights to the health impact from metals, as a basis for risk assessment and prevention.

3.7.19.7. Newborns and Genotoxic Exposure Risks (NewGeneris)

Initiator/Funding source: Project under FP6

Duration: 2005-2010

Study design: Integrated project

Study population/Recruitment: NewGeneris, with more than a hundred researchers from 25 European Institutions, studied approximately 2,000 pregnant women located in five European cohorts - UK (BiB), Spain (INMA), Denmark (DKbiobank), Norway (BraMijlo/BraMat), Greece (Rhea), collecting information on their diet and associated intake of toxic chemicals of interest, measuring changes ("biomarkers") which reflect exposure to such chemicals or their early biological effects, in both the blood of the mothers and of the foetus (umbilical cord blood collected at delivery). The project also collected information on birth outcomes (e.g. length of gestation, weight, head circumference and other physical characteristics of the baby at birth). A genome-wide association study (GWAS) on genetic variation was conducted to look for associations between specific mutations and the biomarkers or birth effects being measured.

Investigated chemicals/Matrices: Blood samples from newborns (cord blood) and their mothers were collected at birth and processed for further analysis. Following classes of chemicals have been investigated: **acrylamide**, **alcohol**, **dioxins**, **DNA reactive aldehydes**, **heterocyclic amines**, **mycotoxins** (aflatoxin and deoxynivalenol), **nitrosamines**, **PAHs** such as benzo[a]pyrene, and **PCBs**.

Analytical methods: Red blood cells were analyses for haemoglobin adducts of acrylamide, glycidamide and ethylene oxide. Micronuclei was analysed in lymphocytes. DNA was extracted from white blood cells and analysed for PAH adducts and plasma was analysed for compounds with dioxin-like activity.

Results/Interpretations: Main achievements of NewGeneris include the following:

1. Establishment of new mother-child cohorts and subcohorts

2. Construction of a database on dietary intakes, biomarkers of exposure and effect, and birth outcomes with data of more than 2000 mother-child pairs

3. Development of methodology for assessment of dietary exposure of pregnant women to chemicals from FFQs, characterisation of geographic variation of intakes and main dietary sources of exposure in European regions

4. Measurement of biomarkers of exposure and/or early effects (DNA adducts and oxidative damage, gene expression profiles, micronuclei, proteomics) in approx. 1200 mother-child pairs

5. Genome-wide SNP analysis on approx. 780 cord blood samples

6. In vitro studies of a) placental perfusion and b) effects on sperm

7. Integrative evaluation of the above data for exposure-biomarker-effect relationships

Investigation of exposure sources: Questionnaires including FFQ gave estimates of exposures to compounds such as acrylamide, dioxins, and nitrose compounds.

Reference values: Background levels in the five countries involved have been reported.

Communication to participants/scientific community/public: Information about NewGeneris can be found online (http://www.newgeneris.org/). A number of workshops were hosted with reports, and scientific publications are still being issued. The first overall analysis has been published as a scientific article (Pedersen et al., 2012).

Policy support: NewGeneris developed ethical practices to handle personal data and samples with strict rules (ethical permits, information sheets, informed consent) according to European standards.

3.7.19.8. EXPOsOMICs

Initiator/Funding source: EU-funded Project under FP 7

Duration: 2013-2018

Study design: This integrated project will provide better understanding by developing a personal exposure monitoring (PEM) system (including sensors, smartphones, geo-referencing, satellites) and collect data on individual external exposome as well as analysing biological samples (internal markers of external exposures) using multiple "omics" technologies. The search for relationships between external exposures (as measured by PEM, which has not previously been used in large scale studies) and global profiles of molecular features (as measured by omics) in the same individuals constitutes a novel advance towards the development of "next generation exposure assessment" for environmental chemicals and their mixtures. The linkage with disease risks opens the way to what are defined here as 'exposome-wide association studies' (EWAS).

DBPs in air and water and/or in biological samples such as exhaled breath (e.g. trihalomethanes) and urine (haloacetic acids) from study subjects have been examined. In addition to exposure measurements that include toxicity tests in water samples, bio-samples will be collected from subsets of subjects for the measurement of omics and other intermediate markers (e.g. blood micronuclei, urine mutagenicity).

Study population/Recruitment: The EXPOsOMICS project aims to develop a new approach to assess environmental exposures, primarily focusing on air pollution and water contaminants. Using 'omics' techniques, the collected exposure data can be linked to biochemical and molecular changes in our body. The results will help to improve our understanding on how these pollutants influence the risk of developing chronic diseases.

Investigated chemicals/Matrices: Air and water pollution in selected blood samples

Analytical methods: **Metabolomics** (molecules involved in cellular metabolism), **adductomics** (in EXPOsOMICS: set of compounds that bind to human serum albumin), **transcriptomics** (the set of all RNA molecules, including mRNA, rRNA, tRNA, and other non-coding RNA), **proteomics** (the entire set of proteins produced or modified by an organism or system), and **epigenomics** (the complete set of epigenetic modifications on the genetic material of a cell) are to be investigated. Disinfection by-products (DBP) (trihalomethanes, haloacetic acids, mutagen X, chloramines, and haloacetonitriles) constitute ubiquitous pollutants in drinking water. Traditionally, only trihalomethanes are measured in drinking water.

Results/Interpretations: Not available as the study is currently ongoing, but the ultimate goal is to use the new tools in risk assessment and in the estimation of the burden of environmental disease.

Investigation of exposure sources: Focus is on air pollution and water quality.

Reference values: May be obtained from the project

Communication to participants/scientific community/public: Information on the EXPOsOMICS project can be found online (http://www.exposomicsproject.eu), and the use of omics-based biomarkers has been reviewed (Vineis et al., 2013).

Policy support: The omics tool is considered most promising.

3.7.19.9. The Human Early Life Exposome (HELIX)

Initiator/Funding source: Project under FP7

Duration: 2013-2018

Study design: Integrated project HELIX, a project of 13 partner institutions, will measure environmental exposures of up to 32,000 mother–child pairs and their consequent impact on the growth, development, and health of the children.

Study population/Recruitment: HELIX will use data from six ongoing, prospective European birth cohorts of mothers and children living in Spain, France, the United Kingdom, Norway, Greece, and Lithuania. Large amounts of health data already have been collected, which HELIX investigators will pool. They also plan to collect extensive biomarker data for a subset of 1,200 mother–child pairs.

Investigated chemicals/Matrices: External exposure measures for food, water, air pollution, pesticides, noise, and ultraviolet (UV) radiation will be integrated with molecular markers from metabolomic, proteomic, transcriptomic, and other "omics" studies. Then the investigators will estimate the burden of childhood disease from multiple environmental exposures.

Analytical methods: In six existing prospective birth cohort studies in Europe, HELIX will estimate prenatal and postnatal exposure to a broad range of chemical and physical exposures: persistent and non-persistent organic chemicals, metals, pesticides, environmental tobacco smoke, water contaminants, air pollutants, noise, UV radiation, and contact with green spaces. Exposure models will be developed for the full cohorts totalling 32,000 mother-child pairs and biomarkers will be measured in a subset of 1,200. Nested repeat-sampling panel studies (N=150) will collect data on biomarker

variability and use smartphone-linked sensors to assess individual mobility, physical activity, and personal exposure to air pollutants and UV radiation.

Results/Interpretations: The HELIX project will run for 4.5 years and has not produced results yet as of 2014.

Investigation of exposure sources: Among the innovative tools created specifically for HELIX is ExpoApp, a mobile application for tracking participants' activity levels. ExpoApp uses GPS and a smartphone's built-in accelerometer to track a person's location and measure physical activity every 10 seconds. Participants will wear ExpoApp-enabled smartphones for a week, along with air pollution and UV monitors. The data will be used to calculate the amount of air inhaled and an individual's exposure to air pollutants.

Reference values: To be determined

Communication to participants/scientific community/public: Background information about HELIX is available online (http://www.projecthelix.eu) and has also been scientifically published (Vrijheid et al., 2014).

Policy support: The project will qualify the use of omics in exposure characterisation.

3.7.19.10. Health and Environment-wide Associations based on Large Population Surveys (HEALS)

Initiator/Funding source: EU project funds

Duration: 2013-2019

Study design: Integrated project of 29 partners form a truly multi-disciplinary consortium and cover the wide range of expertise necessary for developing the integrated approach to the exposome, including environmental exposure monitoring and modelling, biological monitoring, -omics genetics and epigenetics, bioinformatics and data-mining, epidemiology, toxicology, and software programming as well as its impact on health. Geographically, the participants cover all main regions of Europe.

Study population/Recruitment: HEALS aims at integrating, in an innovative approach, a comprehensive array of novel technologies, data analysis, and modelling tools that support efficiently exposome studies.

Investigated chemicals/Matrices: Assessing individual exposure to environmental stressors and predicting health outcomes imply that both environmental exposures and epigenetic variations can be measured simultaneously and reliably. For the first time, HEALS will try to reverse the paradigm of "nature versus nurture" and adopt one defined by complex and dynamic interactions between DNA sequence, epigenetic DNA modifications, gene expression and environmental factors that all com-bine to influence disease phenotypes.

Analytical methods: To be determined

Results/Interpretations: Ongoing

Investigation of exposure sources: Various methods to be determined

Reference values: RVs are to be expected from the end of this study.

Communication to participants/scientific community/public: Brief description about the HEALS project can be found online (http://www.imp.lodz.pl/upload/projekty/heals.pdf).

Policy support: HEALS introduces the integrated approach to health risk assessment. The external exposome will be derived by data and model fusion using algorithms for mining existing environmental monitoring datasets and ubiquitous sensing using geo-localized sensors and mobile phones and the coupling of these data with agent-based models.

4. Discussion

This chapter covers the evaluation of the study results in terms of a comparative analysis of the reviewed HBM programmes with an emphasis on similarities and differences which may impact on the added value that HBM can provide to risk assessment in food safety areas, a review of results from HBM studies, in terms of an identification of potential emerging chemicals or chemical classes and possibly higher exposed sub-groups or specific vulnerable groups of a population from HBM investigations, with a particular focus on the exposure to foods, an inventory of validated biomarkers of exposure to chemicals that can be found in the diet identified through HBM, and other issues considered relevant for EFSA's risk assessment activities, such as emerging biomarker and method developments or a short discussion about political challenges and obstacles in the European Union.

4.1. Comparative analysis of the reviewed national HBM programmes

This chapter provides a comparative analysis of the similarities and differences among the 37 previous or currently existing national HBM programmes, which are described in detail in chapter 3.7.

1. Funding: All national studies and programmes were funded by the respective government. Population representative studies were in general (Germany, Flanders, France, Spain, Italy, Canada, the USA, Korea Japan, China, Czech Republic, Slovenia, Austria, Finland, and Norway) coordinated and managed by their respective governmental centres (e.g. German Environmental Agency, Flemish Centre of Expertise for Environment and Health, etc.).

Other more local studies and cohort studies (Korea's Kor-EHS C, Japan's Tohoku and Hokkaido University cohort study, Sweden's Uppsala study, and Denmark's HBM review study) were coordinated and managed by renowned Universities such as Dankook University (Cheonan, Korea), Tohoku University (Sendai, Japan), Hokkaido University (Sapporo, Japan), Karolinska Institute (Stockholm, Sweden), and University Hospital in Copenhagen (Denmark), respectively.

The different EU-wide HBM research projects were funded by European Commission's Research Programmes (FP6 and FP7), whereas the feasibility study DEMOCOPHES, which tested the European wide COPHES protocol received co-funding from Life+.

2. Duration of the programmes: NHANES programme started with first measurements of environmental chemicals in 1971 and since 1999 is performed continuously with chemicals being monitored in one third of the study population at 2 year intervals. HBM programmes for Germany (ESBHum and GerES), Finland (selenium surveillance), and Norway (The Tromsø cohort) have existed for more than 28 years. However, except of NHANES these aforementioned HBM programmes do not occur yearly but have multiple sampling periods spanned over the years. Eleven out of the 37 reviewed HBM programmes are relatively new, with a study duration period of less than 5 years. The duration of the EU funded research projects ranged from 3 to 8 years.

3. Study design: 21 out of the 37 reviewed HBM programmes are cross-sectional studies (Germany's GerES, Flanders' FLEHS, France's ENNS and ESTEBAN, Spain's BIOAMBIENT.ES, Italy's PROBE, Czech Republic's CZ-HBM, Slovenia's HBM programme, Austria's Pollutants in Humans, Sweden's Mothers in Uppsala, Denmark's HBM Review, AMAP, Canada's CHMS, USA's NHANES, Korea's KNHANES, KorSEP, and Kor-EHS-C, China's POPs in Human Milk, EU's DEMOCOPHES, NewGeneris, and EXPOsOMICS).

10 of the investigated studies are based on longitudinal cohort studies (France's ELFE, Denmark's DNBC, Finland's Selenium Study, Norway's Tromsø cohort and MoBa study, Korea's MOCEH, Japan's Tohoku Study, Hokkaido Study, and JECS, and EU's HELIX). ESBHum in Germany is a biobank that is used for retrospective trend analyses for chemical levels when needed. Most of the EU-wide HBM research projects (e.g. ECNIS, EnviroGenomarkers, and PHIME) utilised existing databanks, tissue sample banks, and cohort studies to further develop new biomarkers or assessment methods of environmental exposures.

Table 12 and Figure 7 indicate the frequency (i.e. recurring vs. one-time) of the reviewed HBM programmes, showing that majority of the HBM programmes (27 out of 37 or 73% of the reviewed programmes) has only occurred once. However, it should be mentioned that 6 of these one-time programmes are longitudinal and are currently ongoing as of 2014.

Table 12 Reviewed HBM programmes sorted by frequency

Frequency	HBM
Recurring (n = 10)	ESBHum/GerES (Germany), FLEHS (Flanders), ENNS (France), CZ-HBM (Czech Republic), Slovenia HBM, AMAP, CHMS (Canada), NHANES (USA), KNHANES (South Korea)
One-time (n = 27)	ELFE[(a)]/ESTEBAN[(a)] (France), BIOAMBIENT.ES (Spain), PROBE (Italy), Pollutants in humans (Austria), Danish HBM/DNBC[(a)] (Denmark), Mothers in Uppsala (Sweden), Selenium supplement monitoring[(a)] (Finland), Tromsø cohort (Norway), KorSEP/Kor-EHS C/MOCEH[(a)] (South Korea), Tohoku/Hokkaido/JECS[(a)] (Japan), POPs in human milk (China), (DEMO)COPHES/ECNIS/EnviroGenomarkers/INTARESE/ESBIO/PHIME/NewGeneris/EXPOsOMICs/HELIX/HEALS (EU)

(a): Longitudinal study that is currently ongoing as of 2014.

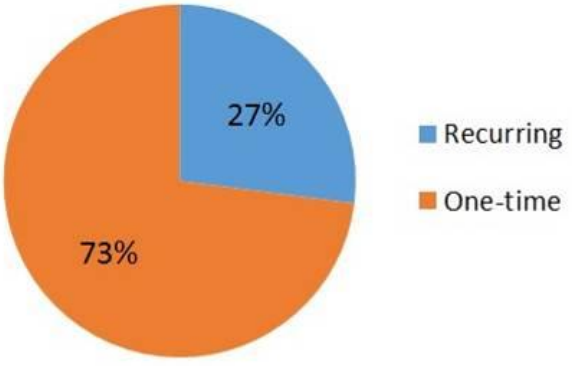

Figure 7 The frequency pattern of the reviewed HBM programmes

4. Size and type of the study population: Norway's MoBa cohort study and Denmark's DNBC study have the biggest study population with over 100,000 participants (mothers, fathers, and children).

12 of the investigated programmes (Flanders' FLEHS, France's ENNS, ELFE, and ESTEBAN programmes, Denmark's DNBC, Norway's MoBa, Canada's CHMS, the USA's NHANES, South Korea's KNHANES and KorSEP programmes, Japan's JECS, and EU's HELIX) have study populations of more than 4,000 participants per recruitment period.

8 programmes (Germany's GerES, Spain's BIOAMBIENT.ES, Italy's PROBE, Denmark's HBM programme, Korea's MOCEH, China's POPs in Human Milk Study, and EU's DEMOCOPHES and NewGeneris) have study populations between 1000 to 4000 participants per recruitment period.

9 programmes (Germany's ESBHum, Slovenia's HBM programme, Austria's Pollutants in Humans Study, Sweden's Mothers in Uppsala Study, Norway's Tromsø cohort, Finland's Selenium Study, Korea's Kor-EHS-C, and Japan's Tohoku Study and Hokkaido Study) have study populations of less than 1000 participants per recruitment period.

Concerning different age groups in the study population most but not all of the investigated HBM programmes cover one than one age group. In particular the European cross sectional surveys aim at a full coverage of all age groups similar to NHANES, but except Germany and France did not yet arrive at such a broad coverage. Overall, slightly more than half of the investigated programmes focus on the adult population, and another 40% address mothers and new-born. Whereas roughly one quarter each are cover (also) other age groups such as children (age 3-13), adolescents (age 14-17) or the elder generation (age >50).

Figure 8 and Table 13 show the targeted study populations of the reviewed HBM studies.

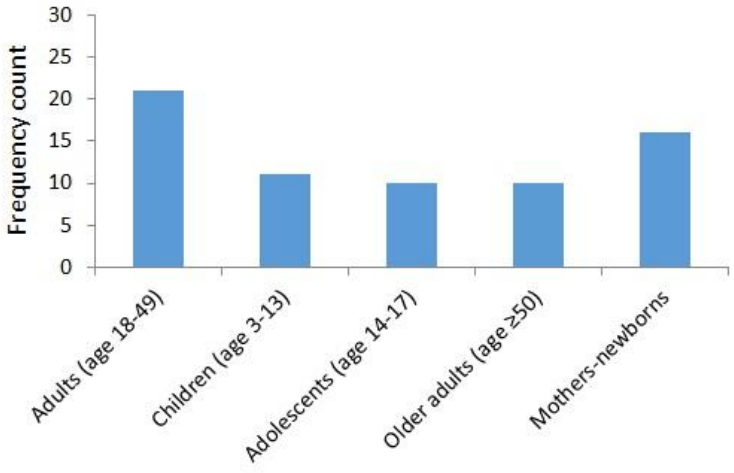

Figure 8 The overview of the population groups targeted in the reviewed HBM programmes

Table 13 An overview of the targeted study populations in the reviewed HBM studies

	Germany		Flanders	France			Spain	Italy	Czech Rep	Slovenia	Austria	Denmark		Sweden	Finland	Norway		AMAP	Canada	USA	South Korea				Japan			China	EU			**TOTAL**
	ESBHum	GerES	FLEHS	ENNS	ELFE	ESTEBAN	BIOAMBIENT:ES	PROBE	CZ-HBM	National HBM	Pollutants in human	Danish HBMs	DNBC	Mothers in Uppsala	Selenium supp.	Tromsø cohort	MoBa	AMAP	CHMS	NHANES	KNHANES	KorSEP	Kor-EHS C	MOCEH	Tohoku	Hokkaido	JECS	POPs in milk	DEMOCOPHES	NewGeneris	HELIX	
Adults (age 18-49)	x	x	x	x		x	x	x	x	x	x	x			x	x	x	x	x	x	x	x		x			x					21
Children (age 3-13)		x		x		x			x	x	x								x	x	x		x						x			11
Adolescents (age 14-17)		x	x	x		x	x				x								x	x	x		x									10
Older adults (age ≥50)		x	x	x		x		x	x	x									x	x	x											10
Mothers-Newborns			x		x				x	x		x	x	x			x							x	x	x	x	x	x	x	x	16

5. Recruitment strategy: The participants for all of the HBM studies were volunteers and gave informed consent. For 9 programmes (Germany's GerES, Flanders' FLEHS, France's ENNS and ESTEBAN programmes, Canada's CHMS, the USA's NHANES, South Korea's KNHANES, Austria's Pollutants in Humans, and Sweden's Mothers in Uppsala), participants were randomly chosen.

12 programmes (Germany's ESBHum, France's ELFE, Spain's BIOAMBIENT.ES, Italy's PROBE, Czech Republic's CZ-HBM, Norway's MoBa, Finland's Selenium Study, Korea's Kor-EHS-C and MOCEH programmes, and Japan's Tohoku Study, Hokkaido Study, and JECS) recruited their participants mainly with information sessions or flyers.

For mother-child cohorts recruitment was generally done via maternity wards or by obstetricians.

The EU-wide HBM research projects mainly used existing cohort studies and databases. DEMOCOPHES however, did full recruitment according to the COPHES study protocol mostly via schools.

Only for a number of the investigated studies there was information about small incentives for participation. For Germany's ongoing GerES V, a 20 € allowance is given as a token of gratitude. For Flanders' FLEHS, participants receive incentives (baby cape with logo of the study for the newborns; cinema tickets or book voucher for the adolescents; book voucher for adults) after study completion. For Spain's BIOAMBIENT.ES, a small token USB drive was given to the participants. For the USA's NHANES, the participants receive cash remuneration, compensation for transportation, baby/elder care, and a free medical report. For Korea's Kor-EHS-C, participants received a gift voucher of 5,000 KRW (approximately 3.58 €). In DEMOCOPHES study participants received small gifts but no money was paid.

6. Analysed substances and substance groups: With the majority of the longer-existing programmes, the number of chemical analyses increased considerably over time. With the USA's NHANES, for example, the number of measured analytes has increased from 27 (in 1999) to almost 300 today.

More than 65% of the investigated HBM programmes analysed various congeners and totals for dioxins/furans and PCBs, as well as selected heavy metals (namely As and Hg).

For dioxins, furans and PCBs, the levels of multiple congeners were mainly measured and summed up as totals depending on the analytical method. For example, the Flanders' FLEHS and Japan's Tohoku Study measured total dioxin and furan levels only using the CALUX assay, and levels of indicator PCBs (e.g. PCB 138, 153 and 180) were measured together and reported as sums. One observed exception is the Japanese Hokkaido Study, where mainly 2,3,4,7,8-PeCDF (furan) was found to have a negative association with birth weight (Konishi et al., 2009).

For most metals, no differentiation between different species was made. However, Flanders' FLEHS, France's ENNS, Canada's CHMS and USA's NHANES have measured different species of arsenic such as inorganic As(III), As(V), MMA, DMA as well as organic arsenobetaine, arsenocholine, and trimethylarsine oxide. In the FLEHS study, it was observed that levels of inorganic arsenic (more toxic form) were higher in participants living near an industrial plant than control participants (Vrijens et al., 2014).

For mercury measurement, MeHg in hair is the primary species used in the investigated HBM programmes, such as Flanders' FLEHS, Spain's BIOAMBIENT.ES, Austria's Pollutants in Humans study, USA's NHANES and Japan's Tohoku and Hokkaido studies. For NHANES, additional Hg species such as inorganic Hg and ethylmercury have also been measured.

Cotinine (as biomarker for environmental tobacco smoke exposure), organochlorine pesticides, phenols, various phthalates, perfluorinated compounds (PFCs), polybrominated diphenyl ethers (PBDEs) and polyaromatic hydrocarbons (PAHs) have been measured in more than 25% of the investigated studies.

Organophosphates, pyrethroids, and chlorinated phenols were analysed in 20% of the programmes, whereas acrylamide and carbamates were seldom measured.

Mycotoxins, fungus-specific IgE, selected fungicides, perchlorate, nitrosamine and alkaloids have only been measured in single HBM programmes. At the European level, mycotoxins were only measured in France's ESTEBAN and in the EU-based research project NewGeneris. Fungicides (e.g. chlorothalonil and trifloxystrobin) were measured only in France's ESTEBAN and Germany's GerES. Perchlorate and nitrosamine were not measured in any of the European HBM Programmes.

Substance groups that were included in the literature search as substances of interest for EFSA but were not measured in any of the selected HBM programmes comprise the following: monochloropropane-ester (3-MCPD), mycotoxins other than aflatoxin and deoxynivalenol, alkaloids other than nicotine, mineral oil hydrocarbons (MOHs), pyrethroids, triazoles, neonicotinoids and other pesticides in current use, as well as smoke flavourings, BADGE, sweeteners and enzymes.

Figure 9 and Table 14 provide an overview of the analysed substances among the reviewed HBM programmes and studies. Table 15 and Table 16 list the substances that have been analysed in only 1 or 2 HBM programmes and have never been analysed, respectively.

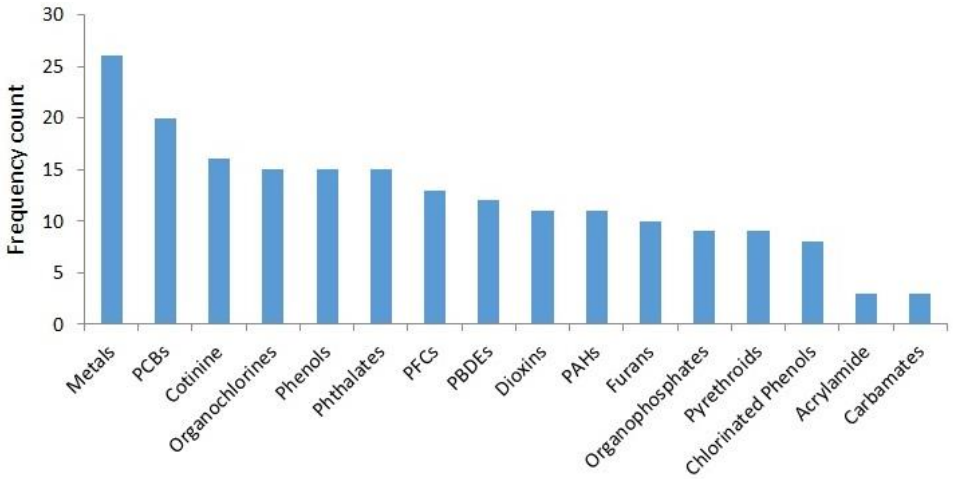

Figure 9 The overview of the substances analysed in the reviewed HBM programmes

Table 14 Overview of analysed substances (sorted by chemical groups)

	Germany		Flanders	France			Spain	Italy	Czech Rep	Slovenia	Austria	Denmark		Sweden	Finland	Norway		AMAP	Canada	USA	South Korea				Japan			China	Europe			
	ESBHum	GerES	FLEHS	ENNS	ELFE	ESTEBAN	BIOAMBIENT:ES	PROBE	CZ-HBM	National HBM	Pollutants in human	Danish HBMs	DNBC	Mothers in Uppsala	Selenium supp.	Tromsø cohort	MoBa	AMAP	CHMS	NHANES	KNHANES	KorSEP	Kor-EHS C	MOCEH	Toholu	Hokkaido	JECS	POPs in milk	(DEMO)COPHES	PHIME	NewGeneris	**TOTAL**
Metals	x	x	x	x	x	x	x	x	x	x	x			x	x			x	x	x	x	x	x	x	x	x		x	x	x	26
PCBs	x	x	x	x	x	x	x		x	x				x		x		x	x	x					x	x	x	x		x	x	20
Cotinine		x	x		x	x	x		x								x		x	x	x	x	x	x		x	x		x			16
Organochlorines	x	x	x	x		x	x		x							x			x	x					x		x	x		x	x	15
Phenols	x	x	x		x	x					x	x							x	x		x	x	x		x	x		x			15
Phthalates	x		x		x	x					x	x					x		x	x		x	x	x		x	x		x			15
PFCs	x		x		x	x							x			x	x	x	x	x						x	x	x				13
PBDEs			x		x	x	x			x	x			x				x	x	x							x	x				12
Dioxins			x		x	x				x				x						x					x	x	x	x			x	11
PAHs		x	x			x	x												x	x		x		x			x	x			x	11
Furans			x		x	x				x				x						x					x	x	x	x				10
Organophosphates		x	x	x	x	x											x		x	x							x					9
Pyrethroids		x	x	x	x	x													x	x		x					x					9
Chlorinated Phenols	x	x	x	x	x	x													x	x												8
Acrylamide																	x			x											x	3
Carbamates					x														x	x												3

Table 15 Substances that have only been or are to be analysed in 1 or 2 HBM programmes

	Class of substances	Substance of interest	HBM Programme
Analysed in 2 HBM programmes			
	Mycotoxins	Total aflatoxin	France's ESTEBAN EU's NewGeneris
Analysed in 1 HBM programme			
	Mycotoxins	Aflatoxin B1	USA's NHANES [(a)]
		Deoxynivalenol	EU's NewGeneris
	Perchlorate	Perchlorate	USA's NHANES
	Alkaloids	Nicotine	Germany's GerES
	Nitrosamine	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonol (NNAL)	USA's NHANES
	Fungus-specific IgE	*Penicillium (notatum) chrysogenum, Aspergillus versicolor, Alternaria alternata, Wallemia sebi, Eurotium spp*	Germany's GerES
	Fungicide	Chlorothalonil	France's ESTEBAN
		Trifloxystrobin	Germany's GerES

(a): The last NHANES measurement for aflatoxin B1-lysine (albumin adduct) occurred in 1999-2000.

Table 16 Substances that have not been analysed in any HBM programmes

Class/type of substances	Substances of interest
3-Monochloropropane-1,2 Diol Ester (3-MCPD)	3-MCPD
Mycotoxins	Ochratoxin A, patulin, Zearalenone, Fumonisin B1 or B2, T-2 toxin, HT-2 toxin
Mineral oil hydrocarbons	Mineral oil saturated hydrocarbons, Mineral oil aromatic hydrocarbons, Naphthenes, Paraffins
Alkaloids	Piperine, cocaine, scopolamine, niacin, dopamine, mescaline, tubocuarine, capsicain, ephedrine, serotonin, ergotamine, caffeine, quinine, theobromine
Regulated chemical substances	Smoke flavourings, BADGE, sweeteners, enzymes
Pyrethroids	Acrinathrin, beta-cyfluthrin, bifenthrin, lambda-cyhalothrin, esfenvalerate, tefluthrin
Triazoles	Bromuconazole, Cyproconazole, Epoxiconazole, Fenbuconazole, Fluquinconazole, Flusilazole, Metconazole, Myclobutanil, Propiconazole
Neonicotinoids	Imidacloprid
Pesticides	8-Hydroxyquinoline incl. oxyquinoleine, Abamectin (aka avermectin), Aclonifen, Amitrole (aminotriazole), Azimsulfuron, Benfluralin, Bifenox, Bitertanol, Carbendazim, Carfentrazone-ethyl, Chloridazon (aka pyrazone), Chlorothalonil, Chlorotoluron (unstated stereochemistry), Copper compounds (Bordeaux mixture, Copper hydroxide, Copper oxide, Copper oxychloride), Cyprodinil, Diclofop, Difenacoum, Diflufenican, Dimethachlor, Dimethenamid-P, Dimethoate, Dimoxystrobin, Diquat (dibromide), Diuron, Ethofumesate, Ethoprophos, Famoxadone, Fenamiphos (aka phenamiphos), Fenbutatin oxide, Fenpropimorph, Fipronil, Flufenacet (formerly fluthiamide), Flumioxazine, Fluometuron, Fluxapyroxad, Formetanate, Fuberidazole, Haloxyfop-P (Haloxyfop-R), Imazamox, Imazaquin, Imazosulfuron, Ioxynil, Linuron, Lufenuron, Metam (incl. -potassium and -sodium), Methiocarb (aka mercaptodimethur), Methomyl, Methoxyfenozide, Methyl nonyl ketone, Metribuzin, Metsulfuron-methyl, Molinate, Napropamide, Oxadiazon, Oxyfluorfen, Paclobutrazol, Pencycuron, Pendimethalin, Pirimicarb, Prochloraz, Prosulfocarb, Pyraclostrobin, Quinoclamine, Quinoxyfen, Quizalofop-P-tefuryl, Spirodiclofen, Sulcotrione, Tebufenpyrad, Terbuthylazine, Tralkoxydim, Triazoxide,

7. Biological matrices: Blood is the most commonly analysed matrix taken (67% of the studies), followed by urine (57% of the studies) and scalp hair (35% of the studies).

9 studies (France's ELFE, Korea's MOCEH, Japan's Tohoku Study, Hokkaido Study, and JECS, China's POPs in Human Milk Study, Czech Republic's CZ-HBM, Slovenia's HBM Programme, and Sweden's Mothers in Uppsala Study) analysed also breast milk samples.

Other 9 studies (Germany's ESBHum, Flanders' FLEHS, Korea's MOCEH, Japan's Tohoku Study, Hokkaido Study, and JECS, and EU's DEMOCOPHES, PHIME, and NewGeneris) analysed various samples of mother-child pairs (i.e., maternal blood, cord blood, maternal and child's urines, child's hair, placenta, amniotic fluid).

Pubic hair, saliva, teeth and toe nails were less common biological materials in the investigated studies. Germany's ESBHum had analysed pubic hair and saliva until 2004, and Finland's Selenium Study analysed selenium in toenails. Norway's MoBa began collecting teeth samples from the participating children while Czech Republic's CZ-HBM analysed lead levels in teeth samples.

Figure 10 provides an overview of the biological matrices that had been analysed in the reviewed HBM programmes.

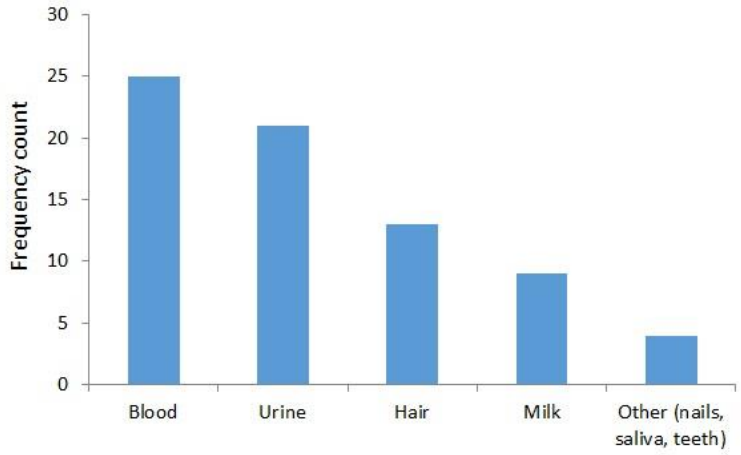

Figure 10 The overview of the biological matrices analysed in the reviewed HBM programmes

8. Analytical methods: For most of the substances (in particular for all organic substances), different types of gas or liquid chromatography followed by mass spectometry (GC-MS or LC-MS, respectively) is the most commonly used analytical method. Among the reviewed HBM programmes, GC-MS (including GC-MSD) and LC-MS (including HPLC-MS and UPLC-MS) had been utilised 59 and 53 times, respectively, to measure substances in different matrices. Other utilised methods include gas chromatography-electron capture detector (GC-ECD), enzyme-linked immunosorbent assay (ELISA), LC-UV detection, chemiluminesce and ion chromatography-mass spectrometry (IC-MS). Congeners within a substance class (e.g. PCBs, dioxins, furans, PBDEs) are always measured with the same analytical method among themselves in a HBM programme. For dioxins and furans, the CALUX assay has been used innovative approach for high throughput quantification in Flander's FLEHS and Japan's Tohoku Study for cost and time reasons. For metals except mercury, inductively-coupled plasma-mass spectrometry (ICP-MS) is the most commonly used method, followed by atomic absorption spectrometry (AAS). An overview of the frequency count of the analytical methods used among the reviewed HBM programmes (except methods used for measuring mercury) is provided in Figure 11.

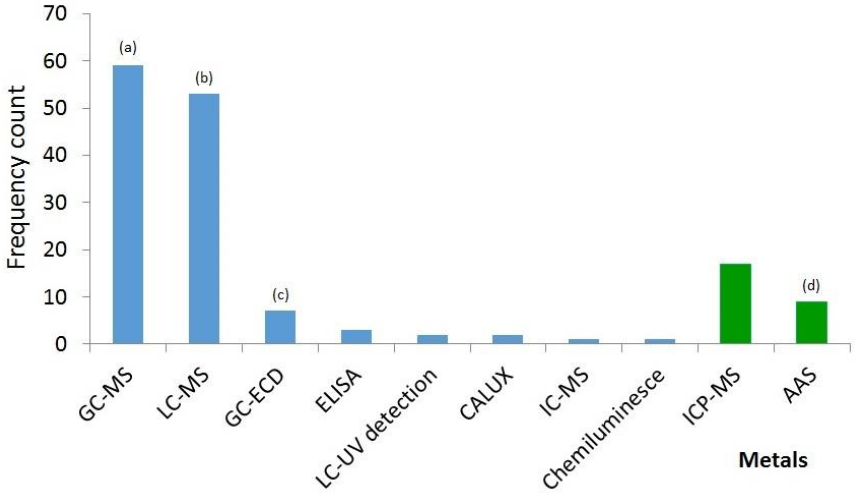

Figure 11 The overview of the analytical methods used to measure the reviewed substances among the reviewed HBM programmes. Methods used for measurement of metals (except mercury) are marked in green while methods used for measurement of the other remaining compounds are marked in blue. (a): Count includes GC-MS and GC-MSD. (b): Count includes LC-MS, HPLC-MS and UPLC-MS. (c): Count includes GC-ECD and GC-ECD-MS. (d): Count includes ET- and GF-AAS.

The detection for mercury is varied across the different HBM studies. France's ENNS, Canada's CHMS, the USA's NHANES, Spain's BIOAMBIENT.ES (for blood and urine), Italy's PROBE, and Austria's Pollutants in Humans Study measured mercury via ICP-MS. Germany's ESBHum and GerES studies, Japan's Tohoku Study, Korea's MOCEH and Kor-EHS-C studies, Slovenia's HBM Programme (for urine) on the other hand measured mercury via cold-vapour AAS. Spain's BIOAMBIENT.ES (for hair), Korea's KNHANES and KorSEP studies, Czech Republic's CZ-HBM and Slovenia's HBM programme (for hair and blood) measured mercury via a direct mercury analyser. Flanders' FLEHS and AMAP measured mercury via atomic fluorescence spectroscopy (AFS) and HPLC, respectively. Figure 12 depicts the frequency count of various analytical methods used among the HBM programmes for the measurement of mercury in various matrices.

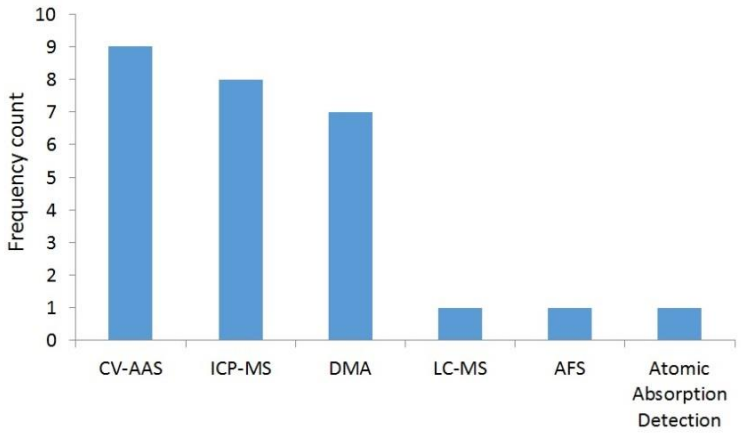

Figure 12 The overview of the analytical methods used to measure mercury among the reviewed HBM programmes

A detailed overview of the analytical methods used for measuring different classes of substances in various biological matrices (i.e. blood, urine, hair, and milk) is provided in Table 38 in Appendix B.

9. Biomarkers of exposure: Many of the investigated chemicals (i.e., metals, dioxins, furans, PCBs, PBDEs, etc.) were directly measured as the parent compounds in the matrices. On the other hand metabolites are measured as biomarkers of exposure for phthalates, polyaromatic hydrocarbons, organophosphate pesticides, organochlorine pesticides (mainly DDE for DDT), pyrethroid pesticides, and tobacco smoke (mainly cotinine) in all HBM studies.

Glycidamide and NNAL were used as metabolic biomarkers of acrylamide and of nitrosamine exposure in the USA's NHANES, whereas the Norwegian MoBa study analysed both urinary acrylamide/glycidamide metabolites and haemoglobin adducts of acrylamide/glycidamide in the blood.

In the Flanders' FLEHS and Japan's JECS, 8-OHdG is envisaged to be analysed as a first biomarker of oxidative DNA damage.

10. Dissemination of information: The most commonly used method to disseminate information regarding HBM studies is via peer-reviewed scientific articles. However, several HBM studies (e.g., Germany's GerES, France's ENNS, Italy's PROBE, Canada's CHMS, the USA's NHANES, and Austria's Pollutants in Humans Study) have released the findings as governmental reports, which are available for public to access online. Germany's ESBHum published all the findings on their study programme's website. Several programmes (e.g., Germany's GerES, Flanders' FLEHS, France's ENNS, Spain's BIOAMBIENT.ES, the USA's NHANES, and Czech Republic's CZ-HBM) have stated that the result findings would be communicated to the participants.

11. Policy impacts: The HBM programs from Germany, Flanders, France, Italy, Canada, the USA, South Korea (particularly KNHANES and KorSEP), China, Czech Republic, and Slovenia have direct influences on policy-making of their respective governments. In addition, several European countries (e.g., Denmark, Austria, and Spain) have participated in the COPHES/DEMOCOPHES project.

12. Biobanking:

Biobanks may store wide array of biospecimens including blood, saliva, plasma and can play an important role in biomedical research and retrospective anaylsis of human tissues e.g. for the absence or presence of contaminants. Biobanks may catalog specimens using age, gender, blood type, and ethnicity or genetic traits. Some samples are also categorized according to environmental factors such as whether the donor had been exposed to substance that can affect human health.

In biomedical research researchers access biobanks when they are in need of specimen with similar traits for their research studies. The ability to seek out very specific collections of biospecimens is how biobanks serve as an essential resource for scientists worldwide.

However, there are important ethical and data protection issues which need to be taken into account. The protection of individual rights and the privacy of individuals is a primary concern in the management of any biobank. Therefore samples are normally codes with any biographical data of the donor being removed and the sample being identifiable only by a unique code.

The Declaration of Helsinki states that all biobanks must take donated materials via a process of informed consent; research investigators must provide potential subjects with a clear appreciation and

understanding of the facts, implications, and future consequences of submitting biological samples to a biobank.

An important aspect besides a thorough wording to the inform consent are thorough sample handling and transport condition, which prevent an external contamination of the sample from the storage device or the degradation of the biomarker during storage time, to enable for future use.

As harmonised standards for data management and biobanking are a prerequisite for comparable European wide interpretation and potential reanalysis, it is considered crucial for future European HBM to establish guidance on these aspects and to establish one central data repository, which can virtually or physically be linked to national data bases. Based on current experiences and due to privacy issues a central European biobank does not seem to be feasible at this stage of time. But EU efforts could develop guidance for sample preparation for storage and biobank management in the light of retrospective analysis of chemical substances.

Whereas there are quite a number of biobanks in the European Union, that store samples from clinical trials or public health surveys, there is not widespread use of biobanking in environmental HBM so far.

Among the reviewed programmes, only ESBHum (Germany), DNBC (Denmark) and CHMS (Canada) store the collected biological samples to create biobanks. In addition, samples have been stored in national biobanks in the course of DEMOCOPHES based on the COPHES protocol.

13. Accompanying activities to investigate exposure source: The investigated HBM programmes in general did not take environmental samples together with HBM except of house dust (Germany) and tap water measurements in Germany, Canada and France, as well as selective food monitoring in Czech Republic, Finland and Germany. For 60% of the investigated HBM programmes however, there was information about other measures (questionnaire or correlation with environmental and health registry data) taken to identify potential sources. Correlation of internal exposure to dietary intake has been mainly performed by data collection of food consumption.

In this context it is important to note that in 2009, EFSA published a guidance on “General principles for the collection of national food consumption data in the view of a pan-European dietary survey” and launched a pan-European Food Consumption Survey, also known as “What’s on the Menu in Europe” ("EU Menu") survey, for which two EU pilot studies developed and tested procedures and tools.

The PILOT-PANEU project (Ambrus et al., 2013) developed, tested and evaluated the applicability of tools and procedures for conducting a dietary survey with adolescents, adults and elderly people, based on 2 x 24-hr recall.

The Pilot Study for Assessment of Nutrient Intake and Food Consumption among Kids in Europe (PANCAKE) developed, tested, and evaluated tools and procedures for an EU Menu among infants, toddlers, children (up to ten years), and breastfeeding women. The tools included age-group specific food diaries, EPIC-Soft software for data entry, validated picture books for portion size estimation, a web repository for the picture series, a questionnaire on background characteristics, a food propensity questionnaire, a data entry tool, and evaluation questionnaires (Ocké et al., 2012). Based on these pilot studies and two methodological projects, EFSA has updated the former guidance document in 2014 to cover the EU Menu methodology to facilitate the collection of more harmonised food consumption data from all EU Member States by the year 2020. (EFSA, 2014)

The up-dated guidance recommends collection of information on food consumption by means of two non-consecutive 24-hour food diaries using computer assisted personal or telephone interview (CAPI/CATI). The reported foods should be described according to the EFSA FoodEx2 food classification system. A short food propensity questionnaire should be used to collect information on the consumption of some less frequently eaten foods and consumption frequencies of food supplements. Information on the weight and height of participants and physical activity levels should also be collected in the survey.

In addition there exist other froms of questionnaires. Food-frequency questionnaire (FFQ) has been defined as a questionnaire in which the respondent is presented with a list of foods and is required to say how often each is eaten in broad terms such as x times per day/per week/per month, etc. Foods chosen are usually chosen for the specific purposes of a study and may not assess total diet (Margetts & Nelson, 1997). In addition, family and dietary habits questionnaires have been developed for specific age groups with a process of involving careful selection of items, pilot studies for setting scales, and testing reliability with many steps as thoroughly described in (Bjelland et al., 2014).

Out of the 37 reviewed HBM programmes (60%) have mentioned the data collection in food consumption. The most common method has been using FFQs (9 out of 22 programmes), followed closely by general study questionnaires including questions about food consumption (8 out of 22 programmes). In COPHES/DEMOCOPHES, a semi-qualitative approach was chosen in obtaining information about exposure-related food intake from the past 4 weeks from sources of drinking water, alcohol, and specified food items (meat, fish, bread, rice, etc.) (Becker et al., 2014).

The only HBM programmes that use a customised 24-hr food recall method according to EFSA recommendations were France's ENNS, Czech Republic's CZ-HBM, and the USA's NHANES. Only 2 programmes use more than 1 method for food consumption: Norway's MoBa using both FFQ & food diary and South Korea's KNHANES using both FFQ and 24-hr recall.

Figure 13 provides an overview of the individual methods used for collecting food consumption data.

Table 17 in addition provides further details on the type of measurement and the food intake questioning.

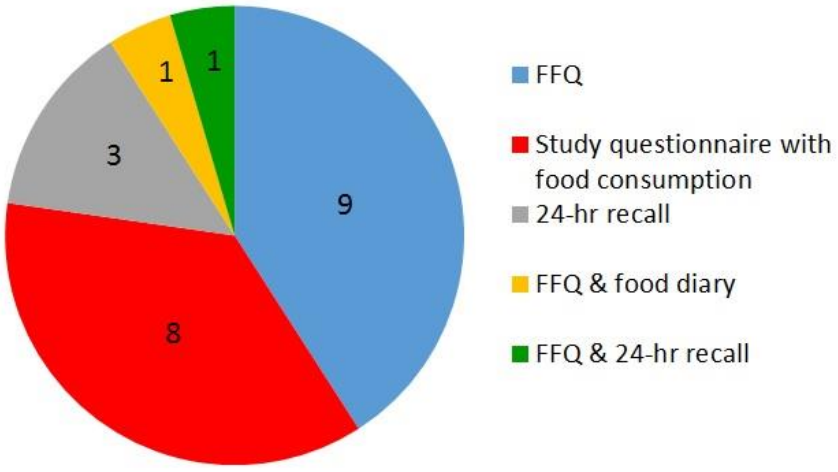

Figure 13 The distribution and count of the methods used for food consumption data collection

Table 17 Food intake measurement and additional monitoring studies for further investigation of chemical exposure due to food intake or due to environment exposure

Country	HBM	Food intake measurement	Findings/activities related to food	Measure in food
Germany	ESBHum	Self-administered questionnaire including nutrition	Collection and analysis of marine specimens (e.g. fish and mussels) for levels of metals, PCBs, pesticides, PAHs, HBCD, etc.	Yes
	GerES	Food frequency questionnaire	FFQ gathered consumption of 50 food groups about food selection of the children. The contribution of the domestic environment to chemical exposure was also assessed by analysing domestic drinking tap water mainly for metals among others.	Yes (water)
France	ELFE	Self-administered questionnaire	The children's environment (e.g. water and ambient air) will be monitored.	Yes (water)
	ENNS	Three 24-hr recall randomly distributed over 15 days	Participants recalled food consumed the day before interview and gave details on amounts through a photography manual with typical portion sizes.	No
Spain	BIOAMBIENT.ES	Short food frequency questionnaire	FFQ with HBM measurements showed a significant association between fish consumption and serum PCB concentrations.	No
Czech Republic	CZ-HBM	Two 24-hr recall	Various food groups (fish, meats, rice, vegetables, etc.) as well as drinking water had been analysed for mercury levels to determine the sources of mercury body burden. Mercury burden in the Czech population appeared low.	Yes
Slovenia	National HBM	Short questionnaire	The study participants answered a questionnaire with information regarding food consumption.	No
Austria	Pollutants in Humans	Food frequency questionnaire	The study participants answered FFQs to gain information regarding food consumption.	No
Denmark	DNBC	Food frequency questionnaire	Completed FFQs allowed further studies of determining chemical exposure to food consumption and occupational exposures (e.g. those of laboratory technicians, green house workers, and shift work).	No

Country	HBM	Food intake measurement	Findings/activities related to food	Measure in food
Sweden	Mothers in Uppsala	Short questionnaire	The study participants answered a questionnaire with information regarding some dietary habits, e.g., fish intake.	No
Finland	Selenium	Self-administered questionnaire	In addition to food intake data collection, sampling of foods for selenium levels has been done four times per year, and the measurements are complementary to the feed measurements of grains, meat, milk and soil.	Yes
Norway	Tromsø cohort	Not reported	Estimates of average and high fish consumption in the Norwegian population were used to model the POPs concentrations as a result of fish consumption.	No
	MoBa	Food frequency questionnaire & 4-day weighed food diary	FFQs, chemical measurements in blood/urine and previous chemical measurements in food revealed correlations of maternal chemical exposure to the estimated levels of Hg, dioxins, and PCBs, or acrylamide in food.	No
AMAP	AMAP	Semiquantitative food frequency questionnaire	FFQ of 60 local (e.g. meats, fish, birds, berries) and imported (e.g. breads, fruits, vegetables) food items. Frequency categories range from once a year to several times a day.	No
Canada	CHMS	Semiquantitative food frequency questionnaire	FFQ collecting data on dietary intake of meat and fish, grains, fruits and vegetables, dairy products, dietary fat, water and soft drinks. Frequency reported as number of times per day, week, month or year. Also, indoor air was measured for levels of VOCs in Cycle 2 of the CHMS. Future cycles to include tap water measurement of fluoride and VOCs.	Yes (water)
USA	NHANES	A customised 24-hr dietary recall	A thorough dietary food collection using the Automated Multiple-Pass Method, a 5-step dietary interview, see (Moshfegh et al., 2008) for more detail.	No
South Korea	KNHANES	Food frequency questionnaire & 24-hr recall	Please refer to (Kweon et al., 2014) for more detail on the food intake data collection. Associations between blood mercury levels and the consumption of seafood, vegetables, fruits, and alcohol have been made. Also, urinary arsenic levels were shown to increase with the consumption of rice and seafood.	No

Country	HBM	Food intake measurement	Findings/activities related to food	Measure in food
	KorSEP	Questionnaire-based interviews to include dietary information	Dietary information and chemical measurements allowed comparison between the levels of heavy metals and several lifestyle factors such as fish consumption and smoking.	No
	MOCEH	Food frequency questionnaire	FFQ will be administered and blood samples will be collected when children are 3 years or older.	No
Japan	Tohoku	Food frequency questionnaire	Refer to (Suzuki et al., 2010) for more detail on the FFQ. Several studies have associated the exposure of methyl mercury and PCBs to fish consumption.	No
EU-wide	(DEMO)COPHES	Questionnaire including exposure-related food intake (e.g. Hg)	There was a highly significant correlation between national levels of fish consumption and mercury in hair.	No
	ECNIS	None	Environmental and occupational exposures as well as lifestyle including food intake have been recorded for the study subjects included in the ECNIS database.	No
	Environ-Genomarkers	None	Environmental and occupational exposures as well as lifestyle including food intake have been recorded for the study subjects included in the cohorts.	No
	PHIME	Questionnaire	Exposure sources were identified through questionnaires.	No
	NewGeneris	Food frequency questionnaire	Questionnaires gave estimates of exposure to acrylamide, dioxins, etc.	No
	EXPOsOMICS	None	DBPs in air and water and/or in biological samples such as exhaled breath (e.g. trihalomethanes) and urine (haloacetic acids) from study subjects have been examined.	Yes (water)

Based on the data collection systems used in the selected HBM programmes, a number of chemicals have been identified to have associations with consumption of specific food (Table 18).

Table 18 Identification of several analysed chemicals in HBM programmes and their associations with specific food consumption

Chemical class	Chemical	Associated food	HBM programme
Metals	Arsenic	Seafood/Fish	FLEHS (Flanders) ENNS (France) KorSEP (South Korea)
		Rice	NHANES (USA)
		Alcohol	ENNS (France)
	Mercury	Seafood/Fish	GerES (Germany) FLEHS (Flanders) CHMS (Canada) NHANES (USA) KorSEP (South Korea) KorEHS-C (South Korea) DEMOCOPHES (EU)
		Alcohol	CHMS (Canada) KNHANES (South Korea)
		Vegetables	KNHANES (South Korea)
	Lead	Alcohol	PROBE (Italy)
	Cadmium	Rice	KorEHS-C (South Korea)
	Manganese	Alcohol	PROBE (Italy)
PCBs	NDL-PCBs	Food of animal origin/Seafood	ENNS (France)
	PCBs in general	Seafood/Fish	BIOAMBIENT.ES (Spain) Tohoku study (Japan)
Organophosphates		Fresh fruits & Fruit juice	GerES (Germany)
Bisphenol A (BPA)		Canned food	DEMOCOPHES (EU)

Beyond the reviewed HBM programmes, some additional studies have linked chemical exposure via dietary intake. In December 2013, very high levels of PFCs such as PFOA, PFOS and PFHxS (exceeding water quality guidelines with orders of magnitude) in groundwater coming from a municipal waterworks in Sweden were detected, possibly exposing the general population to PFAS via drinking water. The groundwater was contaminated with PFCs coming from fire-fighting foams used on a fire drill site situated near the waterworks. Consequently, a small biomonitoring study in children revealed markedly higher serum levels of several PFASs (15 to 50-fold) compared to a nearby control group. These findings are currently followed up in a research program

(http://www.skane.se/sv/Webbplatser/Labmedicin_Skane/Verksamhetsomraden/Arbets--och-miljomedicin/Aktuellt-om-PFAS/ (only in Swedish)).

The Swedish Mammography Cohort, which is excluded for review in this report as it started in 1987 with a follow up in 1997, is a population-based prospective cohort of 30,210 postmenopausal women who were cancer-free at baseline (1987) and completed FFQ at baseline and at the follow-up (1997). Dietary Cd intake based on the questionnaire and Cd content in all foods were estimated. Results from this cohort study showed that average estimated dietary Cd intake was 15 µg/day, which 80% of this intake surprisingly came from cereals, bread, potatoes, roots, and vegetables. Furthermore, Cd intake was significantly associated with increased risk of endometrial cancer in all women (relative risk of 1.39; P_{trend} = 0.019) (Åkesson et al., 2008). Taking this association between dietary Cd intake and risk of endometrial cancer into consideration, it would be advantageous for future HBM programmes to measure chemical levels in food and to correlate these levels with the body burden levels within the general population.

Table 19 provides an example of the contaminants and the known food-related sources where the contaminants could be found (WHO, 2002).

Table 19 Food-related sources of chemicals and contaminants

Contaminant	**Food-related sources**
aldrin, dieldrin, DDT (*p,p'*- and *o,p'*-), TDE (*p, p'*-), DDE (*p,p'*- and *p,o'*-) endosulfan (α, β and sulfate), endrin, HCH (α, β, γ), HCB, heptachlor, heptachlor epoxide, chlordane, PCBs (28, 52, 77, 101, 105, 114, 118, 123, 126, 138, 153, 156, 167, 169, 180 and 189), and dioxins/furans (PCDDs and PCDFs)	whole milk, dried milk, butter, eggs, animal fats and oils, fish, cereals, vegetable fats and oils, human milk
Lead (Pb)	milk, canned/fresh meat, kidney, fish, molluscs, crustaceans, cereals, pulses/beans, legumes, canned/fresh fruit, fruit juice, spices, infant food, drinking water
Cadmium (Cd)	kidney, molluscs, crustaceans, cereals, flour, vegetables
Mercury (Hg)	fish, fish products, mushrooms
Arsenic (As), inorganic	drinking water
Aflatoxins	milk, milk products, maize, cereals, groundnuts, other nuts, spices, dried figs
Ochratoxin A	wheat, cereals, wine
Patulin	apple juice
Fumonisins	maize, wheat
Bisphenol A (BPA)	protective internal epoxy resin coatings of canned foods, polycarbonate tableware, food storage containers, water bottles, and baby bottles

4.1.1. Strengths and limitations of the comparative analysis

Strength of this comparative evaluation are the detailed assessment of analytical methodologies, study populations, study intervals, and analysed matrices. Information on stratification of results by region, gender and age has been taken into account, but is not conclusive in this report.

The strongest weakness is the comparison of reference values, even though much effort has been made to increase comparability. Due to varying test methods and study design, as well as due to lack of information on analytical sensitivity and specifity the given reference values may only be considered as proxies for the dimensions of internal dose.

Other weaknesses relate to public availability of information on communication, recruitment, detailed stratification of results, validation of biomarkers and development in substance coverage. Another limitation is the lack of results from the most recent programmes as well as the omission of a number of studies. Information on LOD/LOQ is generally not listed in this report.

This report hence may not be used directly for risk assessment but may be understood as a detailed screening of the state of HBM in major population based survey in the European Union.

Besides the fact, that detailed information on the type and detail of food frequency questionnaires and of results from environmental monitoring was often not easy to identify, the use of tailormade food intake questionnaires hampers considerably the reliability of the conclusions on food source taken from many of the existing HBM programmes, and increases the uncertainty regarding comparability of results obtained from food questionnaire within countries and between countries. In this context the successful comparability of data on maternal diet from the DNBC study and the MoBa Study through comparison of (i) the methodology used for dietary assessment and (ii) the estimated intake of selected food groups in the two cohorts could serve as a basis for future designs (Olsen et al., 2014), and the up-take of EFSA guidance recommendations needs to be improved.

Regarding duration, frequency and number of substances covered (191), and collection of food intake data by means of 24h recall the American NHANES programme is the most extensive of the investigated HBM programmes. As seen in Table 15, NHANES has measured the exposure levels of a number of chemicals (e.g. perchlorate, nitrosamine, etc.) that no other HBM programme has included. In addition, it covers several classes of chemicals that are seldom or have never been analysed by other programmes but are of interest for EFSA. In the European Union in contrast although strong efforts have been made in recent years there are only few national programmes in Flanders, Germany, France and Sweden aim at least a a surveillance level which can be compared with the USA. 24h recall currently is only used in France's ENNS, and Czech Republic's CZ-HBM.

EFSA has particularly raised concerns of 3-MCPD, mycotoxins, neonicotinoids, triazoles, and pyrethroids and MOHs. A broader inclusion of these chemicals into European HBM programmes would allow appropriate risk management and would facilitate the reduction of exposure of these chemicals.

4.2. Review of HBM study results

This chapter provides a review of results from HBM studies in line with study objective 3. This review focuses on emerging chemicals or chemical classes and possibly higher exposed sub-groups or specific vulnerable groups of a population from HBM investigations, with a particular focus on the exposure to foods and on an inventory of validated biomarkers of exposure to chemicals (e.g. metals,

polycyclic aromatic hydrocarbons (PAHs), phthalates, phenols, polychlorinated compounds, pesticides) that can be found in the diet identified through HBM.

4.2.1. Emerging chemicals and chemical classes as identified in HBM programme

As no definition of "emerging risk" is provided by EC Regulation 178/2002, an operational definition has been developed with reference to the food/feed chain, by the EFSA's SC and adopted by EFSA in 2007 (EFSA, 2007).

According to this definition an emerging risk to human, animal and/or plant health is understood as a risk resulting from a newly identified hazard to which a significant exposure may occur or from an unexpected new or increased significant exposure and/or susceptibility to a known hazard. The term "new" is considered as new scientific evidence, or not regulated in the EU, or not yet addressed by EFSA. Exposure of human beings, animals and/or plants must be present or envisaged for the definition of emerging risk to be met.

An assessment of emerging risk is characterized by the early detection of facts related to that risk derived either from research and/or from monitoring programs or episodic observations.

The evidence supporting the identification of an emerging risk should preferably be in the form of an "indicator" (e.g. measurement and/or observation) and of a trend over time or space. Ideally, an "indicator", should be reliable, sensitive, quantifiable, and should provide the information on the nature of the hazard (agent/process involved) and the source of the risk. For evaluation of an indicator, its relevance and value for predicting problems affecting human health, animal health, animal welfare and/or plant health should be confirmed. Moreover, tools and methods for the detection and measurement of an indicator and for effective monitoring should be in place.

Based on this definition the TECHNICAL REPORT "Towards a methodological framework for emerging risk identification" (Supporting Publications 2012:EN-243) describes the main steps for a simplified framework for emerging risk identification (ERI). ERI systems, aim specifically at identifying risks pro-actively before they have any impact or at an early stage of development. Whilst not specifically designed for ERI, in certain cases early warning systems can be useful in the detection of emerging risks. Some past examples for emerging risks in this meaning are presented in chapter 3.2.2.

Within this chapter, "emerging chemicals" are understood as chemicals that have been taken up by HBM programmes in more recent year because they have been considered a new "emerging" threat.

Within the reviewed HBM programmes, several emerging classes of chemicals have been added to their latest survey cycles. The Japanese JECS, Germany's GerES (GerES V), Flanders' FLEHS (Den Hond et al., 2013), Canada's CHMS (CHMS 3) (http://www.eu-hbm.info/cophes/HealthCanadasBiomonitoringApproachDHaines.pdf) , and the USA's NHANES (survey cycles after 2009) (http://www.cdc.gov/exposurereport/pdf/NER_Chemical_List.pdf) have measured parabens (such as butyl/ethyl/methyl/n-propyl parabens), acrylamide/glycidamide, and perchlorate for the first time, suggesting a need to monitor the exposure of these emerging chemicals and to investigate their possible sources.

Perfluorinated compounds (PFCs) have been reported as another group of "emerging" chemicals. In December 2013, high levels of multiple PFCs (particularly PFOA, PFOS and PFHxS) had been found in serum samples of Swedish children who might be exposed to such PFCs via contaminated drinking

water coming from a municipal waterwork situated near a fire drill site. The average levels found in the serum samples of 1 016 subjects living near this area were 290 ng/mL for PFOS, 256 ng/mL PFHxS and 16 ng/mL for PFOA. Research on the potential health risks from exposure to PFCs is currently ongoing (http://www.skane.se/sv/Webbplatser/Labmedicin_Skane/Verksamhetsomraden/Arbets--och-miljomedicin/Aktuellt-om-PFAS/ (only in Swedish)). In addition, a study had shown all tested drinking water samples from the Rhine-Ruhr area in Germany to be contaminated with PFCs (particularly PFOA at concentrations to 0.5 µg/L), most likely due to waste materials contaminating the soils near the river area (Skutlarek et al., 2006). Subsequently, the Drinking Water Commission of the German Ministry of Health conducted a provisional toxicological assessment of PFOA and PFOS and established a "strictly health-based guidance value for safe lifelong exposure of all population groups" for combined PFOA and PFOS concentrations at 0.3 µg/L (TWK, 2006). The CONTAM Panel of EFSA established TDIs of 150 ng/kg body weight per day and 1.5 µg/kg body weight per day for PFOS and PFOA, respectively (http://www.efsa.europa.eu/en/press/news/contam080721.htm). Although it is currently not clear the health risks associated with exposure to PFCs, PFCs are known to be persistent in the body, therefore warranting further research on the potential health effects associated with the long-term exposure of PFCs.

Parabens are anti-microbial preservatives commonly used in personal care products. Furthermore, two parabens [methylparaben (MeP) and ethylparaben (EtP)] are used for **preservation of certain foods**. The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) published an opinion on the safety of using parabens (additives E 214-219) in foods in 2004. The Panel concluded that a group ADI (Acceptable Daily Intake) of 0-10 mg/kg body weight per day could be established for methyl and ethyl parabens and their sodium salts. However, the panel considered that propyl paraben could not be included in this group ADI due to effects on sperm production observed at a relatively low dose in male juvenile rats, for which no clear NOAEL (No Observed Adverse Effect Level) could be identified. In the meantime there are some of the national HBM programmes have reported human excretion of parabens. For example, excretion of parabens in school children and their mothers in Denmark were lower than reported values in US (Frederiksen et al., 2013).

Acrylamide and its metabolite glycidamide are particular of high interest regarding food safety. The observation of normally-occurring background levels around 0.03 nmol/g globin in non-occupationally exposed persons raised questions about sources of this background level, and formation of **acrylamide during cooking** (especially foods with high carbohydrate content) at elevated temperatures was identified. **Coffee, fried potato products, bread, biscuits and breakfast cereals were further identified as major sources.** A background level of 0.030 nmol/g Hb of the acrylamide adduct was calculated to correspond with an intake of 1.2 µg/kg bodyweight per day, which was higher than the 0.5 µg/kg bodyweight per day calculated from consumption statistics and measured levels of acrylamide in foods (Knudsen & Hansen, 2007). The BE value of 13-130 µg/L urine has been set as HBGV for acrylamide.Clinical symptoms of the peripheral nervous system, irritation of skin, eyes and the respiratory tract, and general discomfort of headache, dizziness and nausea. Acrylamide has been classified as a Group 2A carcinogen (probable carcinogenic to humans) by IARC, and a proxy NOAEL value of 0.51 nmol/g globin was estimated for symptoms of numbness or tingling in feet or legs (Knudsen & Hansen, 2007).

Perchlorate is a man-made chemical that is used to produce rocket fuel, fireworks, flares and explosives and is a naturally occurring chemical. Perchlorate can also be present in bleach and in some fertilizers. **Food areas of concern for Perchlorate contamination are mainly drinking water, but also fruits and vegetables (particularly leafy vegetables/herbs grown in glasshouse)**. In the USA,

an oral RfD of 7 x 10^{-4} mg/kg day has been set whilst the levels in the general population have been monitored in the last round of NHANES with a GM mean of 2.97 µg/L and a P95 of 12.8 µg/L.

DINCH: The commonly used phthalate substitute, 1,2-cyclohexane dicarboxylic acid diisononyl ester (or better known by its trademark name 'Hexamoll DINCH') has not commonly been analysed in HBM programmes (with the USA's NHANES as an exception). In a retrospective analysis of samples from the German Environment Specimen bank, it was observed that almost all the urinary samples of the participants (mainly children) had detectable levels of oxidized DINCH metabolites and that DINCH exposure in children appeared to be 5 times higher than that of adults. This was considered as a consequence of DINCH being introduced into the German market since 2002 and currently being used as a plasticiser substitute for phthalates such as DEHP and DINP besides other in **food contact materials** (Schutze et al., 2013). The AFC Panel of EFSA established a TDI of 1 mg/kg body weight per day for DINCH (EFSA AFC Panel, 2006), and in 2014, the German Commission established HBM-I values of 3.2 and 4.8 mg/L for children and adults, respectively.

Imidacloprid (IMI) has been reported to be applied as an insecticide on crops like apples, tomatoes and sugar beets. It is currently one of the most used **neonicotinoids** as it is distributed in more than 120 countries. Recent studies have reported cellular changes and cytotoxicity in mammalian neurons and human cell lines, respectively, after exposure to IMI (Kimura-Kuroda et al., 2012; Mesnage et al., 2014). This raises the concern of the possible adverse effects in human health and warrants a need to monitor the IMI levels in humans. In 2013, EFSA's Panel on Plant Protection Products and their Residues (PPR) reviewed the open scientific literature on IMI and concluded that IMI shows developmental neurotoxic potential and adverse effect on neuronal development (EFSA PPR Panel, 2013). Although IMI has not been measured in the investigated HBM programmes, a pilot study was conducted in 2013 to measure IMI levels in hair specimens of urban and rural residents in Crete. His study showed that 65.6% of the rural but none in the urban population had positive levels of IMI with 27 ng/mg as the highest detected level among the samples (Kavvalakis et al., 2013). According to European Commission's Directive 08/116, an ADI of 0.06 mg/kg bw per day has been established for IMI (http://ec.europa.eu/food/plant/protection/evaluation/3010_rev_181208.xls).

Pyrethroids: Pyrethroids are insecticides widely used in and around households, including on pets, in mosquito control, and in agriculture. The use of pyrethroids has increased during the past decade with the declining use of organophosphate pesticides. Several national HBM programmes have recently measured levels of pyrethroids via their metabolites. ENNS results show the highest geometric mean levels for all of the pyrethroid metabolites, followed by GerES (although the results are exclusively focused on children), CHMS, and NHANES. In 363 serum samples obtained from non-occupationally exposed adults from Tenerife, Spain, 96.1% had detectable levels of pyrethroids with bifenthrin being the most prevalent type (Burillo-Putze et al., 2014). Another study reported detection of multiple pyrethroids (e.g. lambda-cyhalothrin, bifenthrin, and esfenvalerate) in human breast milk samples which increased along with the increased use of pyrethroids, yet the estimated daily intake values of nursing infants were always below the ADI levels (Corcellas et al., 2012). One study from Germany reported that the pyrethroid exposure of the general population (1 177 inhabitants in the Frankfurt area) is most likely attributable to dietary exposure of pyrethroid (Schettgen et al., 2002).

Paracetamol (or N-acetyl-4-aminophenol, NAAP). Paracetamol is an over-the-counter drug used by many populations and excreted in the urine. Recent studies in Germany and Denmark showed that there is a ubiquitous body burden of NAAP in Danish mothers and children even when paracetamol analgesics had not been recently used. Hence, several unknown sources of NAAP/paracetamol exposure have to exist. An association in NAAP excretion between the mothers and their children could indicate common lifestyle-related exposure (e.g. via food or indoor air sources). However,

association between lifestyle data from questionnaires and levels of NAAP excretion has not been found yet. The knowledge about possible sources of exposure leading to this omnipresent paracetamol excretion is limited, and further investigation is needed (Nielsen et al., 2014).

4.2.2. Exposed sub-groups and vulnerable population groups as identified in HBM programmes

Possibly higher exposed sub-groups or specifically vulnerable groups of a population with higher susceptibility are of special interest in HBM programmes because they are at higher risk of adverse health effect upon exposure of chemicals. Many HBM programmes stratify the data according to various factors in order to determine the potential risk factors of higher body burden. In this chapter, we present the outcomes from HBM investigations, with a particular focus on the exposure to foods.

HBM programmes, such as France's ESTEBAN or the USA's NHANES, collect participants of all ages; hence, age stratification analyses are often conducted to determine the chemical levels among different age groups. In addition, emerging HBM programmes are starting to focus only on specific populations. For example, the German GerES has performed the last 2 survey cycles focusing on children and adolescents, and the French ELFE cohort study intends to follow up on the children in France until adulthood. In Norway, South Korea, and Japan, there are also multiple HBM studies determining the exposure of chemicals in pregnant women and following up on the exposure in their newborns. On the European level, programmes such as NewGeneris and PHIME reported HBM data from birth cohorts, and such data has been included in the HELIX program, providing information about fetal exposures from measurements in cord blood. The first harmonised European cross-sectional survey DEMOCOPHES included school children and their mothers and was able to demonstrate age differences in body burdens.

4.2.2.1. Pregnant women and newborns

Pregnant women and their newborns are particularly populations with high susceptibility risks as chemical exposure in pregnant women could result in prenatal exposure of chemical in newborns via the placenta. Numerous HBM studies have already shown that the prenatal exposure to chemicals in infants could result in some adverse health effects. For example, it was observed from the French ELFE study that pregnant women have a significant exposure to phthalates, reflecting a potential high exposure in the hospitals (Zeman et al., 2013), and findings from the South Korean MOCEH study suggested that prenatal exposure to phthalates may be inversely associated with the neurodevelopment of infants (Kim et al., 2011b). In the Flanders' FLEHS study, a strong correlation for Pb, As, and Tl was found between levels in cord blood and maternal blood, suggesting that these metals are transported to the fetus from the mother (Baeyens et al., 2014), and it appears that prenatal exposure to metals have adverse effects on newborns. The MOCEH study indicated a negative relationship between maternal Pd and Cd levels during late pregnancy period and neurodevelopment (Kim et al., 2013b). The EU-wide DEMOCOPHES project showed elevated levels of methyl mercury in fish eating subgroups of the investigated populations (i.e. mothers), and the Norwegian MoBa cohort study reported negative association between maternal exposure to mercury (via reported dietary intake during pregnancy) and birth weight(Vejrup et al., 2014). The Japanese Tohoku HBM study also reported a negative relationship between maternal hair mercury level and motor abilities of infants (Suzuki et al., 2010).

Aside from phthalates and metals, the MoBa study also showed that maternal exposure to dioxins, PCBs, or benzo(a)pyrene resulted in decreased birth weight (Duarte-Salles et al., 2013a; Papadopoulou et al., 2013), and the Japanese Hokkaido HBM study observed lower birth weight, higher risk of infections in infants, and reduced motor development due to maternal exposure to

PFOS, 2,3,4,7,8-PeCDF, and PCDDs, respectively (Konishi et al., 2009; Miyashita et al., 2011; Nakajima et al., 2006; Washino et al., 2009). Collectively, these studies emphasised the importance to monitor the chemical levels in pregnant women in order to reduce chemical exposure and health risks in newborns.

4.2.2.2. Children

Children are regarded as a population of high risk for health impairment due to behavioural tendencies (e.g. hand-to-mouth contact, crawling, chewing toys), making them more susceptible to chemical exposure, and interest in children's environmental health is increased by rapidly rising rates of chronic disease in children of asthma, cancer, autism, attention-deficit/hyperactivity disorder, birth defects, obesity, and diabetes (Landrigan & Etzel, 2014). Chemicals also have different effects on children than adults because of the ongoing body development in children. The impairment in neurodevelopment due to childhood lead exposure is a well-known example of this disparity (Becker et al., 2008). In 1993, a report of the US National Academy of Sciences (NAS) published a report on pesticides in the diets of infants and children identifying the following four differences between children and adults increasing the susceptibility to pesticides and other toxic chemicals(National Academy of Sciences, 1993):

1. Children have proportionately greater exposures than adults to toxic chemicals on a body weight basis as children have a larger surface to volume ratio and more permeable skin. The respiratory rates are higher and the food intake per kg body weight higher. Further the age related behaviors further magnify their intake from the environment
2. Children's metabolic pathways are immature which may imply longer half-lives in the body of environmental chemicals.
3. Children's extremely rapid but exquisitely delicate developmental processes are easily disrupted which is associated with windows of vulnerability most frequently reported related to fetal development, however persisting throughout childhood.
4. Children have more time than adults to develop chronic diseases that may be triggered by environmental exposures in early life related to diabetes and cardiovascular risk (Barker, 2004).

These observations have been summarized in Table 20.

Table 20 Summary of children's vulnerability to environmental health hazards (Bearer, 1995; WHO & EEA, 2002)

Developmental stage	Developmental characteristics	Exposure	Vulnerability
Preconception	Lack of awareness of gonadal exposure	All environmental exposures	Potential for genotoxicity
Pregnancy	High calory intake Permeable placenta	All environmental exposures Ad-hoc diagnostic investigations	Potential for teratogenicity due to embryonic development of various organs and apparatuses

Developmental stage	Developmental characteristics	Exposure	Vulnerability
First three years	Oral exploration Beginning to walk Stereotyped diet	Food (milk and baby foods) Air (indoor) Water Mattress/carpets/floor	Potential for damage to brain (synapses) and lungs (developing alveoli) Allergic sensitization Injuries
Preschool and school-age child	Growing independence Playground activities	Food (milk, fruit, vegetables) Air (indoor and outdoor)	Potential for damage to brain (specific synapse formation, dendritic trimming) and lungs (volume expansion) Injuries
Adolescence	Puberty Growth spurt Risk-taking behavior Youth employment	Food (any) Air (indoor and outdoor) Water Occupational exposure	Potential for damage to brain (continued synapse formation), lungs (volume expansion) and pubertal development Injuries

Among the existing HBM studies, phthalates have shown to be a major concern for children as HBM studies and programmes from Denmark, Germany (GerES), and the USA (NHANES) all showed that children had higher body burden of several phthalate metabolites than adults (Becker et al., 2009; Calafat et al., 2011; Frederiksen et al., 2014). In addition, the GerES found that levels of organochlorine pesticides (such as HCB, HCH, and DDE) in children decreases with increasing age (Kolossa-Gehring et al., 2008), and data analysis from the NHANES survey showed that children aged 6-11 had the highest urinary level of the PAH metabolite 1-hydroxypyrene compared to adolescents and adults (Huang et al., 2006; Li et al., 2008). Other scientific HBM studies also indicated higher levels of PBDEs and fluorocarbons (PFOA/PFDA/PFNA) in children aged 1.5-9 than other subjects aged 9 or older (Lunder et al., 2010; Toms et al., 2009). These studies emphasises the need of HBM in children in order to generate the data appropriate for accurate risk assessment and management regarding children's exposure to chemicals.

4.2.2.3. Socioeconomic, regional and gender factors

Aside from age, study designs of many HBM programmes often include data collection of multiple factors from participants such as gender, living environment (urban vs. rural), SES, lifestyle habits (e.g. smoking, vegetarians), medical history (e.g. diabetes), etc. These factors have been proven useful for determining additional risk factors of higher body burden of chemicals. Table 21 shows a brief overview of the HBM findings associating different factors with chemical exposure.

Table 21 Factors that affect body burden of chemicals observed in HBM programmes

Factors	HBM findings
Gender	GerES IV: Boys had higher levels of As, Hg, and PCBs (except for PCB 138) than girls. ENNS/NHANES: Women had higher Cd levels than men. BIOAMBIENT.ES/PROBE/CHMS/KorEHS-C: Males had higher blood Pb level than females. PROBE: Men had higher blood Hg, Pd, and W levels than women while women had higher blood Co, Rh, V levels than men. CZ-HBM: Women had higher blood and urinary Hg levels than men. CHMS: Men had higher levels of PFOS than women, whereas women had higher levels of DDE than men. NHANES: Women had higher urinary parabens levels than men. KorSEP: Women had higher levels of urinary phthalate metabolites than men.
SES	GerES IV: Children with high SES had higher levels of PCBs, DDE, HCB, and β-HCH than children with low SES. CHMS: People with low household income had higher blood lead levels than people with high household income. NHANES: People with high household income had higher triclosan levels than people with low household income. KorSEP: Subjects with lower income had higher levels of urinary phthalate metabolites. KorEHS-C: Children with less educated parents had higher blood Pb level than children with higher educated parents.
Region	GerES: Children from large communities had higher As and DDE levels than children from small communities. FLEHS: People living in rural areas or near industrial hot-spots (i.e. waste incinerators, smelt plant) had higher exposure to persistent chlorinated compounds or metals such as Cd and Cu, respectively, compared to their respective control groups. CZ-HBM: Levels of indicator PCB congeners in breast milk samples in PCB hot-spots area of Uherské Hradiště were reported. Slovenia HBM: Children from rural areas had higher blood Cd and Pb levels than children from urban areas. Blood and urine Hg levels were higher in children from urban areas. Adults from urban areas showed the highest As level. KorEHS-C: Children from urban areas had higher levels of Pb.
Smoking	GerES/ENNS/PROBE/CZ-HBM: Increase Cd levels PROBE/CHMS: Increase Pb level NHANES: Increase urinary PAH and haemoglobin acrylamide adduct levels

In summary, most HBM programmes take age, gender, regional and socioeconomic strata, and lifestyle habits into account. However, specific populations such as vegetarians, people with illnesses such as diabetics, and ethnic groups (except for Canada's CHMS and USA's NHANES) are often excluded from HBM studies for reasons of representativity and thereby generalisability.

4.2.2.4. Older adults

As a part of the aging process, the body gradually deteriorates and physiologic and metabolic limitations arise. Changes that occur in organ anatomy and function present challenges for dealing with environmental stressors of all kinds, ranging from temperature regulation to drug metabolism and excretion. The elderly are not just older adults, but rather are individuals with unique challenges and different medical needs than younger adults. The ability of the body to respond to physiological challenge presented by environmental chemicals is dependent upon the health of the organ systems that eliminate those substances from the body. Any compromise in the function of those organ systems may result in a decrease in the body's ability to protect itself from the adverse effects of xenobiotics. With increasing life expectancy, more and more people will confront the problems associated with advancing years. Moreover, although proper diet and exercise may lessen the immediate severity of some aspects of aging, the process will continue to gradually degrade the ability to cope with a variety of injuries and diseases. Thus, the adverse effects of long-term, low-level exposure to environmental substances will have a longer time to be manifested in a physiologically weakened elderly population. When such exposures are coupled with concurrent exposure to prescription medications, the effects could be devastating (Risher et al., 2010).

Among the HBM programmes, it has been observed that several metals appear to accumulate in the elderly population. FLEHS findings showed that the highest levels of total Hg in blood were found in the elderly (aged 50-65) (Croes et al., 2014), and the PROBE study also showed that both blood lead and palladium concentrations increased with age (Alimonti et al., 2011). The Slovenian HBM study found that the blood cadmium, blood lead, and hair mercury levels were the highest among the older women (aged 50-60) compared to children or adults (Tratnik et al., 2013). Aside from metals, urinary levels of phthalates also appeared to be higher among subjects with older age in the South Korean KorSEP study (Lee et al., 2011), and a scientific HBM study from Australia observed the highest level of PFOS in the serum of subjects aged 60 or older (Toms et al., 2009). These findings suggest slower clearance of these chemicals out of the body. Therefore, it is likely that the elderly is at a higher risk of developing adverse effects from exposure to chemicals, making it important to monitor the chemical levels in the elderly within a HBM programme.

4.2.3. Reference values and health-based guidance values

4.2.3.1. Reference values

Reference values permit to assess the exposure of individuals or population groups compared to the ubiquitous background exposure. They indicate the upper margin of a measured pollutant concentration level in the general population to a given environmental toxin at a given time. Since environmental conditions are changing reference values have to be checked and updated continuously. Reference values are strictly statistically derived values, and do not represent health-related criteria for the evaluation of human biological monitoring data. According to the calculation from the International Union of Pure and Applied Chemistry (IUPAC), a reference value is defined as the 95th population percentile (P95) along with the 95% confidence interval (CI) of a substance's concentration (Poulson et al., 1997).

HBM programmes have been proven to be useful in establishing reference values, which can be used to determine individuals of possible high exposure to chemicals. Usually, stratification by age or by

gender has been performed among the programmes. Several HBM programmes such as FLEHS (Flanders) and ENNS (France) have released such values in their reports, and other programmes such as GerES (Germany) and PROBE (Italy) have specifically published RVs based on this definition (Bocca et al., 2013; Schulz et al., 2012b). Among the reviewed HBM programmes, there are a total of 165 substances with a reported reference values (Table 40 in Appendix C.). The overview of the reference values for most studied chemicals within these HBM studies are reported in Appendix Table 43

The purpose of using RVs is to identify and assess the potential high-risk exposure of individuals or population groups when compared to the background population exposure, but it should be emphasised that RVs do not represent toxicologically derived biological exposure limits and should not be used for health-related evaluation of HBM data (Bocca et al., 2013; Schulz et al., 2009). For consideration of potential health risks from chemical exposure, several health-based guidance values have been developed.

4.2.3.2. Health-based guidance values

In food risk assessment, a number of authorities at European and international level, particularly EFSA, the FAO/WHO, and US EPA, aim at setting an exposure level of chemicals that show no appreciable health risk. Such values in risk assessment are known as health-based guidance value (HBGV).

The establishment of a HBGV, is commonly based on a reference point (RP) derived from mathematical modelling of the dose-response relationship. The EFSA Scientific Committee recommended the use of a benchmark dose lower confidence limit (BMDL) as the RP (EFSA, 2009). If modelling is not considered appropriate, another RP may be used such as the no-observed-adverse-effect level (NOAEL). The HBGV is established by dividing the RP by uncertainty factors to account for extrapolation from animals to humans and for variability in human sensitivity (Alexander et al., 2012). Depending on the RP, EFSA and FAO/WHO establish HBGVs such as acceptable or tolerable daily/weekly intakes (ADIs/TDIs/TWIs), whereas the US EPA determines reference doses (RfD). If human exposure to the substance from food and other sources is below the HBGV, competent authorities usually conclude that such exposure does not pose an appreciable risk to human health.

The HBGV approach, however, is valid only for chemicals that have thresholds of toxicity (i.e. non-genotoxic chemicals) whilst another approach needs to be developed for genotoxic chemicals/substances.

For genotoxic substances, the EFSA Scientific Committee proposed the margin of exposure (MOE) approach as a harmonised approach for the risk assessment of substances that are both genotoxic and carcinogenic. The MOE is the ratio between a defined point on the dose-response curve for the adverse effect and the human intake, and therefore, it makes no implicit assumptions about a “safe” intake (EFSA, 2005). The MOE approach, similar to the setting of a HBGV, uses an RP on the dose-response relationship, corresponding to a dose that causes a low, but measurable cancer incidence in animals. This RP is then compared with various dietary exposure estimates in humans, taking into account differences in consumption patterns. The MOE approach is not confined to substances that are genotoxic and carcinogenic and it can also be applied to cases where the data are insufficient or otherwise considered inappropriate to establish a HBGV.

Collectively, EFSA, FAO/ WHO and US EPA have derived HBGVs for 187 of the reviewed substances in this report.

Apart from to a number of heavy metals, dioxins (TCDD) and polychlorinated Biphenyls (PCBs), polybrominated diphenyl ethers (PBDE), pentachlorophenol (PCP), bisphenol A (BPA), phthalate metabolites, arcylamide, and triclosan, the authorities have established a large number of HBGVs for perfluorinated compounds (PFCs), perchlorate, monochlorpropane, and a wide range of pesticides. Furthermore, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has derived and reported HBGVs for an extensive list of chemicals used in food additives, as flavouring agents, in food preservatives, veterinary drugs, etc.

An overview on HBGVs developed by European and US authorities as well as FAO/WHO is provided in Table 41 of Appendix C. while a list of pesticides with EU limit values from the EU Pesticides Database is provided in Table 42 of Appendix C.

4.2.3.3. HBM and BE values

From the point of view of human biomonitoring health based guidance values are considered as values that allow for interpretation of HBM survey data for risk management purposes. Such values called "Human Biomonitoring Values" (HBM-I and HBM-II) in Germany or Biomonitoring Equivalents (BE) in the USA translate established reference values (e.g. TDIs, RfDs) into a biomarker concentration (Angerer et al., 2011).

The German Commission has defined and derived health-related human biomonitoring values (HBM-I and HBM-II), based on reported human toxicological and epidemiological studies. HBM-I serves as a control value and represents the concentration of a substance in human biological matrix below which there is no risk for adverse health effects and consequently no need for action. Concentrations higher than HBM-I but lower than HBM-II should be reanalysed. HBM-II serves as an action value and represents the concentration of a substance in a human biological matrix above which there is an increased risk for adverse health effects and consequently a need for exposure reduction measures and the provision of biomedical advice or care.

BEs are defined as the concentrations of chemical (or metabolite) in a human biological matrix consistent with exposure guidance values such as TDI, RfD, or any risk specific (e.g. cancer) doses (Hays & Aylward, 2012). Similar to HBM values, BEs serve as a basis for risk assessment and management such that concentrations above BEs should prompt for follow-up analysis, evaluation of exposure sources, and a call for reduction in exposure. BE values are interpreted as follows: measured concentrations below the BEs derived from the RfD (BE_{RfD}) suggest a low priority for risk assessment follow-up; meanwhile, concentrations above the BEs derived from the point-of-departure (BE_{POD}) suggest high priority. Concentrations between BE_{RfD} and BE_{POD} would be considered as medium priority (Aylward & Hays, 2008).

HBM values have been established for 10 chemicals thus far (Cd, Hg, Tl, PCBs, PCP, BPA, glycol ether, phthalates DEHP and DPHP, and phthalate substitute DINCH) due to the lack of relevant human studies (UBA, 2014). However, the German Commission recently shifted towards an alternative approach using estimates such as ADIs and known uncertainties to derive HBM values for substances with no appropriate human studies. HBM values for the phthalate DEHP have already been established via this method (Schulz et al., 2012b), and HBM-I values for the another phthalate DPHP and phthalate substitute DINCH have recently been derived (Kolossa-Gehring et al., 2014).

In addition, BEs for 56 chemicals have been derived as of 2014, which 20 of these established values have been reviewed in this report. Such BEs comprise heavy metals (As, Cd, Se), PBDE99, BPA, triclosan, pthtalate metabolites, acrylamide, the herbicide 2,4-D, and two pyrethroids (Cyfluthrin and Deltamethrin). An overview of all HBM and BE values has been summarised in Table 43 of Appendix

C. Overall, as depicted in Figure 14, a comparison among HBM reference values, HBM values, BEs values and the HBGVs from EFSA, FAO/WHO and the US EPA shows that there is a significant lack of overlaps between HBM-established reference values and HBGVs. A total of 118 out of 187 reviewed substances with HBGVs that do not have an established HBM RV mostly due to the lack of HBM data for several classes of pesticides, mycotoxins, 3-MCPD, etc. (refer to Table 40-42 of Appendix C.). On the other hand, there are 92 out of 165 substances with established HBM RVs that do not have HBGVs. This comparison however, is somehow biased, as it is mainly due to the number of RVs for individual dioxin and PCB congeners and differentPFCs. This constitutes a major deficit for efficient use of HBM in food risk assessment, which needs to be overcome.

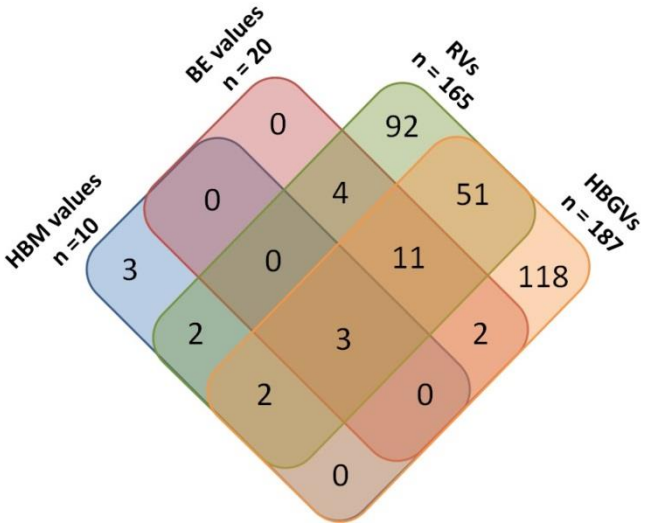

Figure 14 The number of overlaps and non-overlaps among the reviewed HBM-established reference values (RVs; green), health-based guidance values (HBGVs; orange), HBM values (blue) and biological equivalent values (BE; red)

The fact that use of HBM in conjunction with HBGVs would provide high added value shall be illustrated at this point with a recent example. In 2014, the EFSA CONTAM stated in its scientific opinion on the risks for human and animal health related to the presence of modified forms of certain mycotoxins in food and feed that the upper bound of the 95th percentile exposure to zearalenone was at least 2.2-fold the TDI and that the fumonisin exposure of toddlers and children exceeded the provisional maximum TDI (PMTDI), which could be of concern (EFSA CONTAM Panel, 2014). A verification of this estimate would be urgently needed to be able to take measures accordingly.

4.2.4. Inventory of validated biomarkers of exposure to chemicals

This chapter provides an overview on biomarkers of exposure to chemicals that have been identified in the investigated HBM surveys, and for which sufficient evidence for validity was considered available.

BMs of exposure are an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism. Ideally the biomarker is associated with the overall individual exposure providing a measure of the internal dose. Biomarkers also ideally are sensitive, specific, biologically relevant, feasible,

practical and inexpensive. However, existing BMs do not commonly meet all of these criteria. Most biomarkers represent a compromise. Some BMs are stable over time while others reflect exposures with very short half-life. Some markers are easy to measure with standard laboratory techniques, whilst others require highly sophisticated techniques (see chapter 3.4).

Most of the biomarkers used in population studies are covered by standard operating procedures (SOPs) as well as by internal and external quality assessment schemes. Therefore, HBM results from the leading laboratories worldwide are analytically reliable and comparable. A number of sensitive analytical methods have been developed to measure low concentrations including trace amounts of various chemicals in biological samples such as urine and blood. There are specialised laboratories that are able to elaborate the analytical prerequisites for chemicals that gain political or scientific interest in limited time. However, even these laboratories are challenged to keep up with the progress in instrumental analyses.

The choice of matrix and biomarker depends on factors such as physio- and toxicokinetics, the validity (specificity and sensitivity) and toxicological significance of the biomarkers available, their stability and reproducibility, the purpose of the HBM program, the size and characteristics of the study population, etc. Further important aspects are an estimate of the cost-benefit and/or risk-benefit analysis, and an evaluation of the ethical procedures and constrains (Manno et al., 2010b).

In general, urinary concentrations are not necessarily directly informative about concentrations at target tissues of interest in the body. However, as urine collection is a non-invasive procedure that is easily applicable for almost all population (sub-) groups, it remains an essential matrix in all population HBM surveys or for studies that require repeated sampling. Blood biomarker concentrations provide a measure of exposure that is more closely related to target tissue concentrations. However, relationship between the biomarker being measured and the toxicologically active compound has to be taken into account (Smolders et al., 2009; Aylward et al., 2014). Sometimes the ratio between the concentration of a metabolite product and that of the parent chemical in blood or urine is the biomarker and not the chemical or the metabolite per se. (Manno et al., 2010a). For further information, see chapter 3.4. The selection of the matrix and the biomarker is a matter of the pharmacokinetics of the substance in question, balanced with the invasiveness of sampling, analytical complexity and related costs. Finally comparisons with existing data from other programs and RVs may also guide your choices.One major limitation for use of HBM in risk assessment is the fact that the measurement of a BM alone cannot provide information how long a chemical has been in the body, and that many factors may affect the quality of the samples and the variability of measurement results in particular for substances with short half-lives and for low tissue levels. As biomarker concentrations vary both within and between individuals, the variation in biomarker concentrations observed in a population biomonitoring study is not always easy to interprete. For further details, please see chapter 3.4.1.

Against this background validity of BMs must be ascertained in order to consider biomarker analyses as useful for risk assessment. In general, a need to refine and validate biomarkers of exposure follows the introduction of new chemicals (e.g. perfluorinated compounds and brominated flame retardants) to be monitored and increased interest in detecting lower exposure levels. Schulte and Mazzuckelli (1991) describe in detail the internal and external validities BMs need to have. Briefly, validation of a biomarker requires the measurement to be an appropriate reflection of the "phenomenon under study." This means that a valid biomarker of exposure should reliably and accurately reflect the level of the internal dose (target tissue concentration and the temporal exposure pattern of the chemical of interest), and can be measured in a robust, consistent and reproducible way, without ethical, financial legal or regulatory issues that would prevent use. This requires a validation of the analytical test

methods (sample preparation, reagents, etc.) demonstrating besides other appropriate selectivity and specificity, accuracy, precision, reproducibility, and analyte stability. Furthermore, the validation process includes measurements among heterogeneous populations of appropriate sample sizes with reliable and reproducible findings that can be generalised to other populations. Validation is furthermore related to internal and external quality checks of the analytical methods with repeated analyses.

Following these criteria for the validation of a biomarker (i.e. reproducible findings from heterogeneous populations of large sample sizes with internal and external quality checks), biomarkers from HBM programmes with a large sample size of more than 1000 participants, completed chemical analyses, and internal and external quality checks specified in the respective literature sources have been considered as validated biomarkers in this report.

For metals, dioxins, furans, PCBs, PBDEs, parabens, and mycotoxins etc., direct measurement of the parent compounds in the matrices (blood, urine) are commonly used as validated BM of choice for exposure assessment.

In contrast, one or several metabolites or haemoglobin adducts are used as validated BM of exposure for substances (groups) such as phthalates, polyaromatic hydrocarbons, organophosphate pesticides, organochlorine pesticides, acrylamide, nitrosamine, and pyrethroid pesticides, etc.).

It is promising that 8-OHdG is envisaged to be analysed as first biomarker of oxidative DNA damage in two programmes that have recently been started to collect samples, so that results will be available in a few years. Unfortunately however, there are no validated BM in the investigated programmes for a large range of pesticides, veterinary pharmaceuticals, and food additives.

A detailed compilation of the validated BMs identified in the investigated surveys is given in Table 39 of Appendix B.

This summary analysis however, shows that there is a lack of validated BM for a considerable number of substances for which health based guidance values (HBGVs) are set by EFSA or other risk assessment authorities (see chapter 4.2.3). This leads to major deficits in the current possibility to monitor substances of interest.

4.2.4.1. Validated biomarkers and appropriate biological matrix

Depending on the properties and the toxicokinetics of the chemical, blood and urine are the main biological matrices for measuring biomarkers of exposure in most HBM programmes. Nevertheless, there are also other non-invasive matrices such as hair and breast milk that are used to determine temporal exposure pattern and to measure chemical exposure in newborns, respectively.

Blood is the predominant biological matrix for fluorocarbons, dioxins, furans, PCBs, BFRs, and organochlorine pesticides, as these chemicals are persistent in nature and can accumulate in the serum over a long period of time.

Urine is the predominant biological matrix for phenols and chlorophenols, herbicides such as 2,4-D and 2,4,5-T, and metabolites of PAHs, phthalates, organophosphates, and pyrethroids, as these compounds are short-lived in the body and are quickly excreted. Also Cotinine is measured in urine in all the HBM programmes except for NHANES, which measures cotinine in serum for quantitative risk assessment purpose (CDC, 2013).

Breast milk is the preferred biological matrix for measurement of perinatal exposure to persistent contaminants. The biomarkers covered comprise mainly POPs (i.e. fluorocarbons, PCDDs/Fs, PCBs, BFRs, and organochlorine pesticides) and some metals (e.g. As, Cd, Hg, and Pb). The WHO released a guideline protocol in collaboration with UNEP for promoting reliability and comparability in 2007 (WHO, 2007). Breast milk was used in ELFE (France), CZ-HBM (Czech Republic), national HBM programme in Slovenia, Uppsala Mothers programme in Sweden, the Hokkaido study (Japan), the Tohoku study (Japan), POPs in breast milk study (China).

Keratinic matrices such as hair and nails are attractive biological samples for chemical exposure measurements because of the non-invasive collection and the stability of the measured substance due to its incorporation into the keratinic matrix.

Hair has been analysed often for the exposure of heavy metals, especially methyl mercury (Esteban & Castano, 2009). Seafood consumption is known to be a major contributor of methyl mercury exposure, and several HBM programmes (Pirard et al., 2014; Puklova et al., 2010) and studies (Ip et al., 2004; Iwasaki et al., 2003) have found an association between total hair-Hg levels and fish consumption.

Nails can also be employed to measure exposure of heavy metals such as As, Hg, Cd, and Pb (Hussein Were et al., 2008; Kim & Kim, 2011). The Finnish selenium HBM programme measured selenium levels in toenail as an indicator of long-term selenium exposure (Alfthan et al., 2014), and one study reported the relationship between the As concentrations in drinking water and As levels in toenails (Orloff et al., 2009).

In contrary cadmium and lead levels measured in hair (Castano et al., 2012; Kim & Kim, 2011) may not reflect total body burden or may be highly variable (Esteban & Castano, 2009) and analysis of PFAS and nicotine/cotinine in nails (Liu et al., 2011; Stepanov et al., 2006) need further validation.

The biggest drawback of using hair and nails is the possibility of external contamination as these matrices are exposed in the environment and chemicals could be easily deposited within these matrices. (Esteban & Castano, 2009).

4.2.4.2. Emerging Biomarkers and biological matrices

Novel biomarkers of exposure are being developed in saliva. Recently a portable and sensitive biosensor for the direct detection of trichloropyridinol (TCP), a specific biomarker of chlorpyrifos exposure, has been developed and the use of salivary carboxylesterase as biomarker for environmental organophosphate exposure have been reported (Bulgaroni et al., 2012; Zhang et al., 2013). Saliva is easy and simple to collect and inexpensive to analyse. However, there are drawbacks to using saliva due to small sample volume, low concentrations of analytes of interest, and the restriction to recent exposure (Caporossi et al., 2010). Further research is warranted to validate the use of saliva in HBM.

Exposures are multifold and vary over time, which has raised the request of more integrated exposure assessment - exposome as described previously where biomarker data contribute as an element in the exposure characterisation. Similarly, adverse effects are multifold, and integrated biomarkers of effects predicting adverse health effects are requested by study persons, communities, medical doctors and others.

Biomarkers of effect and the "exposome" are a current research priority. Much is expected from the new -omics technologies, where adverse effects may be traced at protein, RNA or DNA level at an early stage of disease development. An example is exhaled air analysis, which shows clear distinctions in proteins and metabolites between asthma and non-asthma patients.

The "exposome" concept was developed "to draw attention to the critical need for more complete environmental exposure data in epidemiological studies." The exposome contains several overlapping domains of nongenetic factors contributing to disease risk, including a general external domain (social, societal, urban environment, climate factors), a specific external domain (specific contaminants, lifestyle factors, tobacco, occupation), gut microflora, inflammation, oxidative stress) (Wild, 2012).

The exposome calls for improvement of often uncertain exposure data, for integration of data on biological mechanisms, and for a more holistic exposure approach in epidemiological studies. Furthermore, it has been proposed that the exposome may serve an important purpose in characterising not only the complex mixtures of already-identified exposures but also, through its untargeted approach and the use of high-throughput "omics" techniques, relevant exposures that have thus far remained unidentified (Rappaport 2011; Rappaport and Smith 2010).

However, there are still large challenges in developing the exposome concept into a workable approach, including the consideration of multiple, longitudinal time periods of interest and of temporal variability, the acknowledgement of exposure uncertainty in an exposome study, the integration of omics data, and the development of powerful statistical techniques to analyse the associations between exposome data and adverse health end points (Vrijheid et al., 2014).

Currently a number of ongoing EU-wide research projects have focused on developing the use of omics technology in HBM and in risk assessment.

The EXPOsOMICS project (see chapter 3.7.19.8) is currently investigating the potential use of metabolomics, adductomics, transcriptomics, proteomics, and epigenomics in estimating the burden of environmental diseases (Vineis et al., 2013).

The HELIX project (see chapter 3.7.19.9) has its general aim to implement tools and methods (e.g. biomarkers, omics-based approaches, remote sensing and GIS-based spatial methods, personal exposure devices, statistical tools for combined exposures, and burden of disease methodologies) to characterise early-life exposure to a wide range of chemical and physical environmental factors and to associate these with data on major child health outcomes (e.g. growth and obesity, neurodevelopment, respiratory health), thus developing an "early-life exposome" approach. (Vrijheid et al., 2014).

The HEALS project (see chapter 3.7.19.10) introduces the integrated approach to health risk assessment. The external exposome will be derived by data and model fusion using algorithms for mining existing environmental monitoring datasets and ubiquitous sensing using geo-localised sensors and mobile phones and the coupling of these data with agent-based models.

4.3. Political challenges and obstacles in the European Union

In the light of the huge and constantly increasing number of chemicals on the European market, there is need for tools that may identify or verify exposure of human to substances of concern that can be used in risk assessment in several policy areas including risk assessment of food safety. In addition to regulatory processes, the development of processes and tools for the identification of "emerging" hazards (pollutants of concern) has been requested by European institutions and by EFSA in particular (see chapter 4.2.1). For this reason, there is a need for appropriate tools that can be used for identification of human exposure.

HBM is becoming more acknowledged as a tool for human exposure assessment. As an example, the European Committee for Risk Assessment (RAC) in 2012 expressed a specific request for additional HBM data to follow up uncertainties regarding future exposure to four classified phthalates (DEHP,

DBP, BBP, and DIBP) in articles proposed for restriction under REACH (ECHA, 2012). This highlights the importance of this tool for decision making on chemicals and product regulation. But there are particular requirements and challenges that hamper use of HBM in the European Union. Due to the subsidiary principle with major responsibilities and institutional capacities in all Member States, the European Union is facing particular challenges, which are not an issue in individual countries.

In countries like the USA and Canada one institution takes the overall responsibility for all the tasks related to HBM and its translation into policies. In the USA the Centers for Disease Control and Prevention (CDC) are the governmental body responsible for organisation of the national nutrition and health survey NHANES, and in this function, is also responsible to organise the selection of substances and nomination procedures including selection criteria to include or remove a certain substances from the list. In Canada, the federal public health authority is coordinating the surveys and performs science and research that support biomonitoring. This includes the development of new chemical measurements and analytical methodologies, the development of tools to better interpret biomonitoring results, and the investigation of possible adverse health effects that may result from exposure to environmental chemicals.

In the European Union in contrast the situation is different. From the European policy perspective it is essential to be able to perform evaluation and interpretation of information on average and range, or proportion of population above a guidance or limit value, time and spatial trends, or interregional variability on a European scale. On the other hand data collection and surveillance measures lay in the responsibility of Members States that have divergent interests, legislation and data protection standards, capacities and financial means. In addition responsibilities for HBM related issues are widespread in the European Union both on Community level as well as on national level unlike the situation in countries like the United States of America.

The major responsibilities for risk reduction policies and surveillance systems, is generally shared between the Ministries of Environment and Health and the related agencies. Accordingly existing surveillance structures and responsibilities depend on the allocation of responsibilities in national administration. In general, Member States rely on either health or environmental agencies or national institutes.

Against this background particular challenges in the European Union are for example the prioritisation of substances, the development of biomarkers and analytical methods, survey design data interpretation and communication issues, as well as the chemical analysis. In order to ensure comparable monitoring data on a European scale, there is a need for guidance and advice on protocol development, quality standards and quality assurance systems.

In addition sharing of research and development work, shared funding solutions, and effective use of existing resources and synergies are particular challenges and prerequisites for an efficient use of HBM. In this context it was considered important to coordinate to the extent possible the guidance and protocols developed by national, European and international monitoring programmes/initiatives. Read-across of monitoring and research results from one country to another was suggested as another option to increase efficiency and reduce costs.

5. Conclusion

Based on 252 references (235 full text publications), which were selected by the project team in an extensive literature search on human biomonitoring (HBM) for the period 2002-2014 in major relevant databases such as Medline and SCOPUS, in recent conference proceedings, in grey literature, and in publicly available information from scientific research studies and supplemental searches from an initial set of almost 18,000 hits, this study could show that human biomonitoring (HBM) would be a suitable tool for human risk assessment in relation to food safety, when the necessary developments and adjustments have been made.

HBM has a long tradition for human exposure assessment in occupational health care. HBM is requested by law in occupational health and is used in public health survey. Its use in environmental health policies started in the seventieths. Also within the European Union, significant resources have been spent on HBM in the filed of environment and health, however, the lack of a coherent approach and integration between countries and studies limits the use for European health impact assessments. To allow a better use of the data and to allow evaluations at European scale, harmonisation of activities was considered important and a process towards coherent HBM programmes in the European Union was started in 2003.

Even if there is no official definition of HBM it is commonly understood as a method for assessing human exposure to exogenous substances by measuring the substances or their metabolites, or the product of an interaction between a xenobiotic agent and some target molecule or cell in human tissues or specimens. HBM relies on the use of biomarkers in human tissues or specimens.

Some biomarkers are stable over time, others have very short half-life. Some markers are easy to measure with standard laboratory techniques whilst others require specialized techniques. Currently different types of liquid or gas chromatography in combination with different types of mass spectrometry are used as suitable and reliable analytical methods for analysis of biomarkers of exposure. The CALUX assay is tested for high throughput quantification of hormone activation from dioxins. As sensitivity and specificity of the analytical method, the reliability and replicability of the results and the inter-comparability with data from other surveys are important factors, chemical analysis of HBM samples should follow well-defined standard operation procedures and QS/QA systems to ensure validity of the result.

HBM can be performed for many chemical substances which are in the focus of the worldwide discussion of environmental health, but this number is still small in comparison with the number of chemicals and contaminants in the environment. Depending on biomarkers (BM) used, HBM does not only allow to monitor exposure but also to detect early health effects. BM of biological effect are more closely related to adverse health effects but are more difficult to validate. Protein adducts specifically and sensitively measure exposure as well as biochemical effect. High throughput technologies (Omics technologies) have recently revolutionised the monitoring of BM of effect.

HBM implies the development of a study protocol, recruitment of study persons, informed consent, sampling, and sample processing, sample analysis and interpretation, data reporting and communication. HBM programmes can be cross-sectional or vertical in design. Given the wide range of BMs, biological matrices, analytical methods and other influencing factors, the study design is a critical aspect in efficient use of HBM in risk assessment. This comprises the planning of which BM(s) should be measured, in which biological fluid or tissue, when and how many samples should be collected and from which study populations.

Recruitment of participants can be done via hospitals, census registries, local newspapers or organisations, or at workplaces. It shall ensure a study population which is representative with age groups, gender, exposure risks (habitation, occupation, and socio-economic status) being equally distributed. HBM can be done with cross-sectional or cohort design, the study design includes the power of the study and the number of samples to request from each study person. However, recruitment is costly. In addition it is often a challenging issue and participant rates tend to be low. Therefore it is recommended to use surveillance synergies where possible.

Sampling, and sample handling are decisive factors for the study results and need to be carefully designed. The samples must be handled in a uniform manner (e.g. cooling procedure) securing reproducible results. HBM can be accompanied by questionnaires, environmental monitoring and clinical investigations to collect additional information about exposure risks and vulnerability, or can be linked with registry data. Harmonisation of Data Treatment and Evaluation is necessary when comparing measurements and for publication purposes.

Interpretation and communication of study results are other crucial but difficult aspects of HBM. At this stage there remain many challenges for a valid interpretation in terms of risk assessment. HBM based guidance values, translate the measured dose to intake estimates, but the number of such values is limited. Good communication at all stages of a HBM can increase participation rate, supports the collection of reliable data and fosters dissemination of results, but is a challenge. Communication needs to be considered right from the start of the study and should be multidisciplinary, as it requires a thorough translation of scientific results a proper appraisal of uncertainties with a balanced consideration of benefit and risks. Ethical issues are a challenge in particular in the absence of clear health guidance. Existing survey compare with existing health based guidance values, reference values and information from other countries, and aim at monitoring time trends.

Based on the analysis of the investigated references HBM can be considered applicable to the **different steps of human risk assessment** (hazard identification, hazard characterisation, exposure assessment and risk characterisation) (as relevant for EFSA) where HBM can make a significant or unique contribution (e.g. assessment of human exposure to chemical contaminants, or regulated chemical substances such as food contact materials, pesticides, etc.).

The application of HBM in risk assessment of chemical contaminants in food is closely linked to its potential to provide knowledge about the human exposure to these substances via food and other routes, and their potential to cause adverse health effects. The core role of HBM in risk assessment is human exposure assessment whether for environmental contamination, contamination from air, water or consumer products or in food safety areas. Hazard identification and hazard characterisation is conventionally performed in toxicology studies in vivo or in vitro. But in certain cases HBM could contribute to the elucidation of the dose-response relationship or to hazard identification in highly exposed subgroups. In risk characterisation HBM can be used to validate exposure assessment.

A particular strength of HBM in exposure assessment of chemical substances from food source (chemical contaminants and regulated chemical substances) is the fact that HBM is the only available tool that integrates exposures from all sources and provides data to epidemiology enabling studies of strengths of associations, dose response relationships. Biomonitoring data reflect the internal dose at a point in time. HBM can provide results that are stratified by regions and subgroups, hence allowing to identify populations at particular risks as well as population of increased vulnerability due to age, gender, region, SES, lifestyle and dietary habits, and thus can reduce the number of assumptions that have to be made regarding consumption rates.

One major limitation for use of HBM in risk assessment is the fact that HBM alone cannot provide information how long a chemical has been in the body, and that many factors may affect the quality of the samples and the variability of measurement results in particular for substances with short half-lives and for low tissue levels.

The other major limitation is the fact that HBM alone cannot provide information about the source of exposure or the health risk. For interpretation in risk assessment HBM data need to be combined with other data and tools such as environmental and health registry data, modelling data from PBPK models or HBM based guidance values like Human Biomonitoring Values (HBM I and HBM II) and Biomonitoring Equivalents (BE) that translate established guidance values (HBGV) from risk assessment (e.g. ADI/TDI, RfD) into a biomarker concentration.

Finally HBM raises ethical and privacy issues because it involves human samples. But those challenges can be overcome.

HBM can absolutely be considered useful for the **implementation of a systematic Post Market Monitoring (PMM)** approach for regulated chemical substances, because it can verify risk assessment results. It could be used to monitor real exposure if estimated daily intake (EDI) is close to the acceptable daily intake (ADI) in different exposure groups, and can detect exposure in case of unexpected complaints. Strength and limitations apply like for exposure assessment.

The inventory of the different HBM surveillance programmes/initiatives at national, EU and international level and the relevant HBM studies published in the literature provides an excellent overview on the substances covered, analytical methods applied and existing reference and health based guidance values, and provides a good information source on major challenges. Overall the comparative analysis of the results from the investigated HBM studies shows that HBM can bring added value for chemical risk assessment in food safety areas, but that further work needs to be done to improve usability. Although a number of HBM programmes have extensive data and well-structured study design, there are some major deficits and challenges regarding its use in chemical risk assessment for food safety in the European Union, which need to be reduced.

As national HBM Programmes are generally funded, coordinated and managed by the respective governmental bodies important infrastructural prerequisites for a systematic longterm use are already established also in the European Union today. On the other hand HBM programmes except of NHANES do not occur yearly but in intervals and only in very few European Member States (Flanders, Slovenia, Germany, Sweden, Czech Republic) a long-term regular surveillance system has been established.

Whereas globally the majority of the national HBM programmes are cross-sectional surveys with repeated monitoring over time to assess reference values and trends, some countries, also choose longitudinal mother-child cohorts to better be able to determine particular risks for vulnerable groups (newborn) and potential health effects. Retrospective analysis of time trends based on bio-banked samples currently is only done in Germany. Whereas study populations still range from less than 1000 to more than 100,000 participants, it is good to see a tendency towards larger cohorts in recent years. From a risk assessment point of view it is a positive signal, that elderly, adolescents, children and new-borns are increasingly included, even if the majority of investigated HBM programmes is still focusing on adults.

The inventory shows clearly that blood and urine are by far the most approved biological matrices. In addition human milk has frequently been used for persistent organic pollutants, and hair and saliva have become important specimens in more recent years. This choice is determined by the analytical

needs to reliably determine the internal dose combined with the attempt to use easily available low invasive samples. Combinations of maternal blood, cord blood, placenta, and amniotic fluid are used in birth cohorts. The fact that most programmes are using similar analytical methods reflects the fact that established validated standards are used for the substances covered by the selected HBM studies.

The analysis of the national/regional HBM programmes reveals that they allow to establish HBM reference values (RV) for the general population as well as to identify highly exposed subgroups. RV tend to be stratified by region, age and gender or life-style and RVs s are compared with HBGV, if such values exist. On the other hand it is disappointing that population reference values (RV) exist only for roughly 70 chemical groups (165 isomers but 92 without HBGV) such as PFCs, dioxins/furans/PCBs, metals, PBDEs, PAHs, phthalates, phenols, cotinine as well as carbamate/organophosphate/organochlorine/pyrethroid pesticides., and that in addition, the calculation of reference values varies in the European Union with the geometric mean with P95 not being consistently used.

It is promising, that in the majority of the longer running programmes the number of analysed substance groups was increased considerable over time. The broadest range of chemicals is covered in NHANES, CHMS, FLEHS, ESTEBAN and JECS. But the range of analysed substances (substance groups) remains highly variable, and in the European Union the availability of data is still limited. Heavy metals (particularly cadmium, lead, and mercury), PCBs and cotinine are the most investigated classes of chemicals and have been analysed in more than 65% of the investigated HBM programmes. Organophosphates, pyrethroids, and chlorinated phenols were analysed in 20% of the programmes each, whereas acrylamide and carbamates were rarely measured. Mycotoxins, Fungus-specific IgE, selected fungicides, perchlorate, nitrosamine and alkaloids have only been measured in single programmes.

Hence the major deficit of the large scale HBM programmes and studies identified up to 2014, is a lack of data on a considerable number of key food contaminants, food additives or food contact materials, for which HBGVs have been developed by EFSA or FAO/WHO. To date 118 out of the 187 reviewed substances with HBGVs do not have an established RV. Deficits are particularly strong for several classes of pesticides (e.g. neonicotinoids or triazoles), mycotoxins, veterinary pharmaceuticals, food contact materials and food additives, flavouring agents, food preservatives. But there are also deficits for nitrosamine, perchlorate, 3-MCPD, mineral oil hydrocarbons, In addition there are deficits in knowledge about the exposure sources or environmental levels and about associations between measured body burdens and health effects.

It is disappointing that accompanying environmental monitoring or measurements in food are rare. Food-related questions have been used in roughly 60% of the investigated studies, but unfortunately, this is not very convincing from the point of view of risk assessment in food. In addition there is an important lack of standardisation and validation of food questionnaires and customised 24-hr food recall method according to EFSA recommendations was only used in France's ENNS, Czech Republic's CZ-HBM, and the USA's NHANES.

The review of the results from the investigated HBM studies shows that there are examples where HBM contributed to the identification of a new hazard in the sense of the EFSA definition of emerging risks with the term "new" being considered as new scientific evidence, or not regulated in the EU, or not yet addressed by EFSA. HBM programmes can inform policy about emerging threats and trigger exposure prevention and restriction strategies, e.g. by means of screening substances for which science has generated some evidence of potential risks. However, there are not too many striking results with a particular focus on the exposure to foods. When screening the analysed HBM programmes for changes over time, the project team detected that some pesticides (pyrethroids, herbicides), parabens,

acrylamide/glycidamide, nitrosamine and nitrate as smoke flavouring (NHANES), and perchlorate as well as perfluorinated compounds (PFCs) have been recently added to the monitoring because they have been considered as new risks with a potential correlation to food source. In the past other substances groups such as heavy metals, dioxins and PCBs, brominated flame retardants, carbamates, and mycotoxins have been investigated as "emerging" chemicals.

With respect to **identification of vulnerable groups** it can be stated that existing HBM programmes commonly stratify results by age and gender, and life-style or race with some aspects including dietary habits. In this context pregnant women and foetuses, children, and in some cases elderly have been identified in varying contexts as possibly higher exposed sub-groups or specific vulnerable groups for specific groups of chemicals, including some with food as major exposure source. Higher socio-economic class can either be a protective or a risk factor to contamination from food source. However, so far there is no systematic investigation for fundamental dietary life-style decisions such as conventional versus organic or vegetarian food.

National, regional and international HBM programmes that have been selected for this report use **validated biomarkers** with standard operating procedures (SOPs) as well as by internal and external quality assessment schemes. Validated BM of exposure to chemicals that can be found in the diet from the investigated HBM programmes are either the chemical itself (i.e., metals, dioxins, furans, PCBs, PBDEs, parabens, mycotoxins, etc.) directly measured as the parent compounds in the matrices, or a metabolite or haemoglobin adducts (e.g. phthalates, polyaromatic hydrocarbons, organophosphate pesticides, organochlorine pesticides, acrylamide, nitrosamine, and pyrethroid pesticides, etc.). The selection of the biomarker is a matter of the pharmacokinetic properties of the substance in question balanced with the invasiveness of sampling, analytical complexity and related costs. It is promising that 8-OHdG is envisaged to be analysed as first biomarker of oxidative DNA damage in two programmes that have recently been started to collect samples, so that results will be available in a few years. Unfortunately however, there are no validated BM in the investigated programmes for a large range of pesticides, veterinary pharmaceuticals, and food additives. Also the use of biobanks for HBM is currently still very limited in the European Union and across the world.

In addition to the above mentioned results, it can be concluded that there are three major other aspects that are relevant for use of HBM in risk assessment in food safety.

The first one relates to biomarkers of effect and the "exposome" as attempts to establish high throughput tools and to close the causality gaps. Both are current research priority, but there is a lot of further research needed to allow for application in surveillance for food risk assessment.

The second one relates to the possibility to link HBM data with external monitoring and food intake estimates. In this context it can be emphasised that the EU wide HBM pilot projects (COPHES/DEMOCOPHES) could show that it was possible to use good quality data to support interpretation of HBM data related to food source. The study however, showed at the same time, that quality of data about food quality and quantity still needs to be improved and needs to become more readily available across Member States.

Finally there are particular political challenges and obstacles in the European Union, which hamper the use of HBM, even if it is more and more acknowledged as a tool for human exposure assessment.

National HBM programmes are designed to support, lead and assess policy and preventive actions in the field of environmental health. However, there is no EU legal framework that mandatorily requests

the use of HBM in risk assessment, unlike the legal embedding that is established for HBM in occupational health since several decades.

In addition, due to the subsidiary principle, major responsibilities, legislation and institutional capacities related to HBM is with Member States, which have divergent interest and possibilities, whilst European Institutions would need comparable data at European scale in order to be able to perform evaluation and interpretation of information on a European scale.

Particular challenges in the European Union are for example the prioritisation of substances, the shared or joined development of biomarkers and analytical methods, chemical analysis, survey design, data interpretation and communication issues, as well as the data management and transfer.

Even if the EU wide HBM pilot projects (COPHES/DEMOCOPHES) could show the added value of comparable HBM results for policy recommendations including food source, there remains a lack of a coherent approach and integration between European Member States, which hampers the cross-border comparison and the applicability of study results for risk assessments. To foster a better use of the data obtained and to allow evaluations at European and international scale, further efforts are needed towards a coherent approachsuch as the ongoing European Human Biomonitoring Initiative (EHBMI).

6. Recommendations

In order to improve the added value of HBM to food safety risk assessment, the following recommendations could be made:

- Foster the development of HBM specific health based guidance values as core tools to translate HBM data to intake limits set, and by further improving availability of suitable monitoring data for environmental and food contamination and reverse modelling tools to enhance interpretation of HBM data in risk assessment;
- Fasten development of appropriate BM and analytical methods to promote monitoring of substances of interest for EFSA and food related emerging risks (namely several classes of pesticides and fungicides, mycotoxins, veterinary pharmaceuticals, food contact materials and food additives, flavouring agents, food preservatives) in order to increase the number of HBM reference values in the EU;
- Expand substance coverage and ensure long-term establishment of HBM programmes throughout European Member States in order to improve data availability and trend analysis;
- Expand monitoring in different age groups, and for different dietary regimes (eg. vegetarian etc) to get better information on vulnerable and particularly exposed subgroups, and combine longitudinal and cross-sectional approaches for an improved knowledge on potential health risks;
- Promote coherent use of customised 24-hr food recall method according to EFSA recommendations and reporting on food quality and quantity in order to improve knowledge on exposure source;
- Establish coherent documentation for HBM data including a uniform measure for the central tendency as well as information on high exposures, in ordert to ensure better comparability of reported RF;
- Promote wider use of biobanking and biobanked samples in order to be able to trace back time trends of contamination with newly identified threats;
- Promote use of surveillance synergies (dietary intake surveys, health examination surveys and HBM) where possible to limit field work costs and increase participation rates;
- Continue research in BM of effect and OMICs technologies and evaluate its added value for application in surveillance for food risk assessment;
- Continue efforts towards reducing the particular political challenges and obstacles in the European Union, which hamper the use of HBM namely regarding prioritisation of substances, shared or joined method developments, chemical analysis, survey design, data interpretation and communication issues, as well as data management and transfer, by supporting the development of a European wide decision structure and exchange platform (such as EHBMI);
- Promote the use of HBM in exposure assessment and PMM in risk assessment in the food safety area as relevant for EFSA.

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APPENDICES

A. SEARCH STRATEGY FOR HBM REVIEW

Table 22 Search terms for the HBM literature review

	Related review questions	Search terms (combination AND)
1.1.a	How is HBM defined?	Human Biomonitoring Definition
1.1.b	Which biological matrices are used for HBM?	Human Biomonitoring human tissues Human Biomonitoring, Sample Matrix
1.1.c	Which kinds of studies are conducted?	Human Biomonitoring, cross sectional Human Biomonitoring, longitudinal Human Biomonitoring, mother child cohort
1.1.d	Which recruitment strategies are available and used?	Human Biomonitoring recruitment Human Biomonitoring participation
1.1.e	Which sampling strategies are available and used?	Human Biomonitoring sampling (Abstract) Human Biomonitoring sample collection
1.1.f	Which parameters can be analysed in which matrix?	Human Biomonitoring in **= answers of 1.1.b (e.g. blood, serum, urine, saliva, hair, ...)
1.1.g	Which analytical methods are suitable and used (for parameters and matrices individually)?	Human biomonitoring, and **= individual substance groups as indicated in Table 23 (Appendix A) Biomonitoring, and **= individual substance groups as indicated in Table 23 (Appendix A)
1.1.h	How are analysis data reported?	Human Biomonitoring reporting (Abstract)
1.1.i	How are analysis data are communicated (consider different target audiences)?	Human Biomonitoring communication (Abstract)
1.2	How is HBM generally applied to food risk assessment	Human Biomonitoring, food, Human Biomonitoring, food safety Human Biomonitoring, risk assessment
1.2.a	How is HBM applied to the risk assessment step "exposure assessment" in food safety areas	Human Biomonitoring, exposure assessment, food
1.3.a	How useful (including strengths and limitations) is HBM for exposure assessment of chemical substances from food source (chemical contaminants and regulated chemical substances)?	
1.2.b	How is HBM generally applied to the risk assessment step "hazard identification" in food safety areas	Human Biomonitoring, hazard identification food
1.2.c	How is HBM generally applied to the risk assessment step "hazard characterisation" in food safety areas	Human Biomonitoring, hazard characterisation food
1.2.d	How is HBM generally applied to the risk	Human Biomonitoring, risk characterisation,

	Related review questions	Search terms (combination AND)
	assessment step "risk characterisation" in food safety areas	food
1.3.b	How useful (including strengths and limitations) is HBM for the implementation of a systematic Post Market Monitoring (PMM) approach for regulated chemical substances.	Human Biomonitoring, Post Market Monitoring
2.1	Which HBM programmes/ initiatives are conducted	Human Biomonitoring, Programme Human Biomonitoring, survey, chemicals, Human Biomonitoring, nutrition survey, Human Biomonitoring, chemicals, food Human Biomonitoring, chemicals, nutrition survey Human Biomonitoring food contaminants Human Biomonitoring, pollutants, food (Abstracts only) Human Biomonitoring, environmental chemicals, food
2.1.a	Which HBM programmes/ initiatives are conducted on EU level? (general information)	Human Biomonitoring European Union Human Biomonitoring Europe (Abstract) Human Biomonitoring EU
2.2.a	Which HBM programmes/ initiatives are conducted on national levels? (general information)	Human Biomonitoring, [country name] *
2.3.a	Which HBM programmes/ initiatives are conducted on international level? (general information)	Human Biomonitoring ** **= countries individually
3.1.a	Which emerging chemicals, chemical classes can be identified with a focus on food?	Human Biomonitoring, emerging chemicals, food Human Biomonitoring, emerging substances, food Human Biomonitoring, new substances, food Human Biomonitoring, new chemicals, food
3.1.b	Which high exposed sub groups or specific vulnerable groups can be identified from HBM investigation with a focus on food?	Human Biomonitoring, vulnerable groups, food
3.2.a	Which biomarkers of exposure that can be found in the diet are validated?	Biomarkers of exposure, food, validated Biomarkers of exposure, diet, validated

* European countries/regions include the following: Germany, France, Flanders, Spain, Italy, Austria, Czech Republic, Slovenia, Denmark, Sweden, Norway

** International countries/regions include the following: Canada, the USA, Arctic regions (for the AMAP programme), South Korea, Japan, China

Table 23 Substance groups (any individual substances) covered by the HBM literature search

Chemical substance group	List of individual substances
Brominated flame retardants (BFRs)	2,4,4'-Tribromodiphenyl ether (BDE 28) 2,2',4,4'-Tetrabromodiphenyl ether (BDE 47) 2,2',4,4',5-Pentabromodiphenyl ether (BDE 99) 2,2',4,4',6-Pentabromodiphenyl ether (BDE 100) 2,2',4,4',5,5'-Hexabromodiphenylether (BDE 153) 2,2',4,4',5,6'-Hexabromodiphenyl ether (BDE 154) 2,2',3,4,4',5',6-Heptabromodiphenyl ether (BDE 183) 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE 209) Hexabromocyclododecanes (HBCDDs) Tetrabromobisphenol A (TBBPA) 2,4,6-tribromophenol (2,4,6-TBP) **emerging BFRs**: tris(2,3-dibromopropyl) phosphate (TDBPP) and the novel BFR 2,2-Bis(bromomethyl)-1,3-propanediol (DBNPG) 1,2-bis(2,4,6-tribromophenoxy)ethane (BTBPE) and hexabromobenzene (HBB)
Fluorocarbons (PFCs)	Perfluorobutane sulfonic acid (PFBuS) Perfluorodecanoic acid (PFDeA) Perfluorododecanoic acid (PFDoA) Perfluoroheptanoic acid (PFHpA) Perfluorohexane sulfonic acid (PFHxS) Perfluorononanoic acid (PFNA) Perfluorooctanoic acid (PFOA) Perfluorooctane sulfonic acid (PFOS) Perfluorooctane sulfonamide (PFOSA) Perfluoroundecanoic acid (PFUA) Perfluorohexanoic acid (PFHxA) Perfluoropentadecanoic acid (PFTeDA)

Chemical substance group	List of individual substances
	N-ethyl perfluoroalkane sulphonamide (N-EtFOSA)
Phthalates metabolites	Mono-benzyl phthalate (MBzP) Mono-isobutyl phthalate (MiBP) Mono-n-butyl phthalate (MnBP) Mono-cyclohexyl phthalate (MCHP) Mono-ethyl phthalate (MEP) Mono-2-ethylhexyl phthalate (MEHP) Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) Mono-(carboxynonyl) phthalate (MCNP) Mono-isononyl phthalate (MiNP) Mono-(carboxyoctyl) phthalate (MCOP) Mono-methyl phthalate (MMP) Mono-(3-carboxypropyl) phthalate (MCPP) Mono-n-octyl phthalate (MOP)
Phenols	Bisphenol A 4-tert-Octylphenol Triclosan 8-Hydroxyquinoline
Metals	Antimony Arsenic Barium Beryllium Cadmium Chromium VI Cesium Cobalt Fluoride Iridium

Chemical substance group	List of individual substances
	Lead
	Manganese
	Mercury, Organic
	Mercury, Inorganic
	Molybdenum
	Nickel
	Palladium
	Platinum
	Rhodium
	Selenium
	Silver
	Thallium
	Tin
	Tungsten
	Zinc
PAHs metabolites	2-Hydroxyfluorene
	3-Hydroxyfluorene
	9-Hydroxyfluorene
	1-Hydroxyphenanthrene
	2-Hydroxyphenanthrene
	3-Hydroxyphenanthrene
	4-Hydroxyphenanthrene
	9-Hydroxyphenanthrene
	1-Hydroxypyrene
	1-Hydroxynaphthalene (1-Naphthol)
	2-Hydroxynaphthalene (2-Naphthol)
	3-hydroxy- and 9-hydroxybenzo[a]pyrene
	hydroxypyrene glucuronide (1-OHPG)
	3-hydroxybenz[a]anthracene
	1-OH- Benzo[c]phenanthrene

Chemical substance group	List of individual substances
	2-OH- Benzo[c]phenanthrene
	3-OH- Benzo[c]phenanthrene
	1-OH- Benz[a]anthracene
	3-OH- Benz[a]anthracene
	9-OH- Benz[a]anthracene
	1-OH- Chrysene
	2-OH- Chrysene
	3-OH- Chrysene
	4-OH- Chrysene
	6-OH- Chrysene
	benzo[a]pyrene-trans-4,5-dihydrodiol (±)
	benzo[a]pyrene-trans-7,8-dihydrodiol (±)
	benzo[a]pyrene-trans-9,10-dihydrodiol (±)
	benzo[a]pyrene-3,6-dione
polychlorinated biphenols ***polybrominated biphenols***	**Dioxin-like PCBs (DL-PCBs):** 3,3',4,4'-Tetrachlorobiphenyl (PCB 77) 3,4,4',5-Tetrachlorobiphenyl (PCB 81) 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) 3,3',4,4',5,5'-Hexachlorobiphenyl (PCB 169) 2,3,3',4,4'-Pentachlorobiphenyl (PCB 105) 2,3,3',4,4'-Pentachlorobiphenyl (PCB 114) 2,3',4,4',5-Pentachlorobiphenyl (PCB 118) 2',3,4,4',5-Pentachlorobiphenyl (PCB 123) 2,3,3',4,4',5-Hexachlorobiphenyl (PCB 156) 2,3,3',4,4',5'-Hexachlorobiphenyl (PCB 157) 2,3',4,4',5,5'-Hexachlorobiphenyl (PCB 167) 2,3,3',4,4',5,5'-Heptachlorobiphenyl (PCB 189) **Non-dioxin-like PCBs (NDL-PCBs):** 2,4,4'-Trichlorobiphenyl (PCB 28) 2,2'3,5'-Tetrachloro biphenyl (PCB 44)

Chemical substance group	List of individual substances
	2,2',4,5'-Tetrachloro biphenyl (PCB 49)
	2,2',5,5'-Tetrachlorobiphenyl (PCB 52)
	2,3',4,4'-Tetrachlorobiphenyl (PCB 66)
	2,4,4',5-Tetrachlorobiphenyl (PCB 74)
	2,2',3,4,5'-Pentachlorobiphenyl (PCB 87)
	2,2',4,4',5-Pentachlorobiphenyl (PCB 99)
	2,2',4,5,5'-Pentachlorobiphenyl (PCB 101)
	2,3,3',4',6-Pentachlorobiphenyl (PCB 110)
	2,2',3,3',4,4'-Hexachlorobiphenyl (PCB 128)
	2,2',3,4,4',5' and 2,3,3',4,4',6-Hexachlorobiphenyl (PCB 138 & 158)
	2,2',3,4',5,5'-Hexachlorobiphenyl (PCB 146)
	2,2',3,4',5',6-Hexachlorobiphenyl (PCB 149)
	2,2',3,5,5',6-Hexachlorobiphenyl (PCB 151)
	2,2',4,4',5,5'-Hexachlorobiphenyl (PCB 153)
	2,2',3,3',4,4',5-Heptachlorobiphenyl (PCB 170)
	2,2',3,3',4,5,5'-Heptachlorobiphenyl (PCB 172)
	2,2',3,3',4,5',6'-Heptachlorobiphenyl (PCB 177)
	2,2',3,3',5,5',6-Heptachlorobiphenyl (PCB 178)
	2,2',3,4,4',5,5'-Heptachlorobiphenyl (PCB 180)
	2,2',3,4,4',5',6-Heptachlorobiphenyl (PCB 183)
	2,2',3,4',5,5',6-Heptachlorobiphenyl (PCB 187)
	2,2',3,3',4,4',5,5'-Octachlorobiphenyl (PCB 194)
	2,2',3,3',4,4',5,6-Octachlorobiphenyl (PCB 195)
	2,2',3,3',4,4',5,6' and 2,2',3,4,4',5,5',6-Octachlorobiphenyl (PCB 196 & 203)
	2,2',3,3',4,5,5',6-Octachlorobiphenyl (PCB 199)
	2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl (PCB 206)
	2,2',3,3',4,4',5,5',6,6'-Decachlorobiphenyl (PCB 209)
Dioxins	1,2,3,4,6,7,8-Heptabromodibenzo-p-dioxin (HpBDD)
	1,2,3,4,7,8 and 1,2,3,6,7,8-Hexabromodibenzo-p-dioxin (HxBDD)
	1,2,3,7,8,9-Hexabromodibenzo-p-dioxin (HxBDD)

Chemical substance group	List of individual substances
	1,2,3,7,8-Pentabromodibenzo-p-dioxin (PeBDD)
	2,3,7,8-Tetrabromorodienzo-p-dioxin (TBDD)
	1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (HpCDD)
	1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin (HxCDD)
	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin (HxCDD)
	1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (HxCDD)
	1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin (OCDD)
	1,2,3,7,8-Pentachlorodibenzo-p-dioxin (PeCDD)
	2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)
Furans	1,2,3,4,6,7,8-Heptabromodibenzofuran (HpBDF)
	1,2,3,4,7,8-Hexabromodibenzofuran (HxBDF)
	1,2,3,7,8-Pentabromodibenzofuran (PeBDF)
	2,3,4,7,8-Pentabromodibenzofuran (PeBDF)
	2,3,7,8-Tetrabromodibenzofuran (TBDF)
	1,2,3,4,6,7,8-Heptachlorodibenzofuran (HpCDF)
	1,2,3,4,7,8,9-Heptachlorodibenzofuran (HpCDF)
	1,2,3,4,7,8-Hexachlorodibenzofuran (HxCDF)
	1,2,3,6,7,8-Hexachlorodibenzofuran (HxCDF)
	1,2,3,7,8,9-Hexachlorodibenzofuran (HxCDF)
	2,3,4,6,7,8-Hexachlorodibenzofuran (HxCDF)
	1,2,3,4,6,7,8,9-Octachlorodibenzofuran (OCDF)
	1,2,3,7,8-Pentachlorodibenzofuran (PeCDF)
	2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)
	2,3,7,8-Tetrachlorodibenzofuran (TCDF)
Perchlorate	
Acrylamide and glycidamide	
3-Monochloropropane-1,2 Diol Ester (3-MCPD)	
Mycotoxin	Aflatoxins
	aflatoxin B1

Chemical substance group	List of individual substances
	aflatoxin M1 ochratoxin A Deoxynivalenol Nivalenol citrinin Zearalenone Fumonisin B1 or B2 T-2 toxin HT-2 toxin Alternaria toxins Beauvericin and enniatins Sterigmatocystin Moniliformin Diacetoxyscirpenol
Alkaloids (Piperidine, Pyrrolidine, Pyridine, Catecholamine, Phenylalanine, Indole, Quinoline, Purine)	Piperine, Niacine, Dopamine, Capsicain Ephedrine Serotonine, Quinine, Caffein, theobromine
Mineral oil hydrocarbons (MOH)	paraffins (comprising linear and branched alkanes), naphthenes (comprising alkyl-substituted cyclo-alkanes), and aromatics (including polyaromatic hydrocarbons (PAHs). Components divided into two main types, mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH).
regulated chemical substances such as food contact materials	Smoke flavourings: Plastic contact materials:see BPA Sweeteners: Enzymes:

Chemical substance group	List of individual substances
Pesticides - Neonicotinoid	Acetamiprid
	Imidaclorpid
	Thiacloprid
	Thiamethoxam
	Clothianidin
	Thiacloprid
	Thiamethoxam
Pesticides -Pyrethroids	Acrinathrin
	Beta-Cyfluthrin
	Esfenvalerate
	Bifenthrin
	Cyfluthrin
	Cypermethrin
	Deltamethrin
	Etofenprox
	Fenpropathrin
	Fenvalerate
	Lambda-cyhalothrin
	Permethrin
	Pyrethrins
	Resmethrin
	Taufluvalinate
	Tefluthrin
Pesticides -Triazoles	Amitrole
	Bitertanol

Chemical substance group	List of individual substances
	Bromuconazole
	Cyproconazole
	Difenoconazole
	Epoxiconazole
	Fenbuconazole
	Flusilazole
	Flutriafol
	Metconazole
	Myclobutanil
	Paclobutrazole
	Prothioconazole
	Tetraconazole
	Triticonazole
	Fuberidazole
	Propiconazole
	Triadimenol
	Hexaconazole
	Penconazole
	Tebuconazole
	Fluquinconazole
	Thiabendazole
	Terbuthylazine
Pesticides -Organochlorines	Aldrin
	Heptachlor epoxide
	Oxychlordane
	trans-Nonachlor

Chemical substance group	List of individual substances
	Mirex
	Chlordan
	Chlorobenzilate
	Chlorothalonil
	DDT
	Dicofol
	Dieldrin
	Endosulfan
	Endrin
	Heptachlor
	Hexachlorbenzene
	Hexachlorocyclohexane (HCH)
	Lindane
	Linuron
	Mepiquat
	Methoxychlor
	Quinoxyfen
	Quintozene
	Tetradifon
	Tolylfluanid
	Haloxyfop
	Carbofuranphenol
	2-Isopropoxyphenol
	2,4-Dichlorophenol
	2,5-Dichlorophenol
Pesticides -Organophosphates	Acephate

Chemical substance group	List of individual substances
	Azinphos-methyl
	Cadusafos
	Chlorfenvinphos
	Chlorpyrifos
	Chlorpyrifos methyl
	Diazinon
	Dichlorvos
	Dimethoate
	Ethephon
	Ethion
	Ethoprophos
	Fenamiphos
	Fenitrothion
	Fenthion
	Fosthiazate
	Malathion
	Methamidophos
	Methidathion
	Monocrotophos
	Oxydemeton-methyl
	Parathion & parathion methyl
	Phentoate
	Phosalone
	Phosmet
	Phoxim

Chemical substance group	List of individual substances
	Pirimiphos-methyl
	Profenofos
	Pyrazophos
	Tolcolflos-methyl
	Triazophos
	Trichlorfon
	Diethylphosphate (DEP)
	Dimethylphosphate (DMP)
	Diethylthiophosphate (DETP)
	Dimethylthiophosphate (DMTP)
	Diethyldithiophosphate (DEDTP)
	Dimethyldithiophosphate (DMDTP)
	Methamidophos
	Omethoate
Pesticides -Carbamates	Aldicarb
	Benfuracarb
	Carbaryl
	Carbendazim
	Carbofuran
	Carbosulfan
	Chlorpropham
	Dinocap
	Dithiocarbamates
	Fenoxycarb
	Formetanate
	Iprovalicarb

Chemical substance group	List of individual substances
	Methiocarb
	Methomyl
	Oxamyl
	Pirimicarb
	Propamocarb
	Thiophanate methyl
	Metam potassium, Metam sodium
	Molinate
	Prosulfocarb
Pesticides - Amides/Anilides	Flumioxazin
	Amitraz
	Diphenylamine
	Hexythiazox
	Methoxyfenozide
	Boscalid
	Propyzamide
	Tebufenozide
	Fenhexamid
	oxadixyl
	Diflufenican
	Dimethachlor
	Dimethenamid-P
	Flufenacet
	Napropamide
	Dichlofluanid

Chemical substance group	List of individual substances
	Zoxamide
Pesticides - Aniline	Pendimethalin Trifluralin Benfluralin
Pesticides - Pyrazoles	chlorfenapyr Fipronil Tebufenpyrad Fluxapyroxad
Pesticides -Imidazoles	Imazalil Prochloraz (2,4,5-Trichlorophenol, 2,4,6-Trichlorophenol as metabolites) Imazamox Imazaquin Thiabendazole
Pesticdes - Dicarboximide	Iprodione Procymidone Vinclozolin
Pesticides -Diphenylether	Aclonifen Bifenox
Pesticides -Pyrimidine	Bupirimate Cyprodinil Fenarimol Mepanipyrim Pyrimethanil
Pesticides -Pyrrole	Fludioxonil
Pesticides -Strobilurins	Azoxystrobin

Chemical substance group	List of individual substances
	Kresoxim-methyl
	Pyraclostrobin
	Trifloxystrobin
	Dimoxystrobin
Pesticides -Thiadiazines	Buprofezin
	Indoxacarb (Oxadiazine)
Pesticides - Triazine & Triazonine	Metribuzine
	Triazoxide
	Carfentrazone-ethy
	Terbuthylazine (chlorotriazine)
Pesticides – Xylylalanine	Metalaxyl
	Metalaxyl-M
Pesticides- Pyridazione	Chloridazon
	Pyridaben
Pesticides -Phtalimides	Flumioxazin
	Captan
	Folpet
Pesticides -Morpholines	Dimethomorph
	Fenpropimorph
Pesticides - Urea derivates	Azimsulfron
	Chlortoluron
	Diuron
	Fluometuron
	Lufenuron
	Imazosulfuron
	Pencycuron

Chemical substance group	List of individual substances
	Metsulfuron-methyl
	Teflubenzuron
	Triflumuron
Pesticides -Others	Diclofop (Chlorophenoxy acid or ester)
	Famoxadone (Oxazolidinedione)
	Quizalofop-P-tefuryl (Aryloxyphenoxy propionic acid)
	Sulcotrione (Benzoylcyclohexanedione)
	Clofentezine (Tetrazine)
	Spirodiclofen (Keto-enol)
	Chlormequat (quaternary ammonium compound)
	Pyriproxyfen (Juvenile hormone mimic)
	Diquat (dibromid) (Bipyridylium)
	Propargite (Sulfite ester)
	Spinosad (Macrocyclic Lactone)
	Oxadiazon (Oxadiazole)
	2,4-D (2,4-Dichlorophenoxyacetic acid)
	Fenbutatin Oxide
	Dicloran (Chloronitrobenzene)
	Fenazaquin (Quinazoline)
	Methyl nonyl ketone (Ketone)
	Glyphosate (Phosphonoglycine)
	Difenacoum (Coumarin)
	Tralkoxydim (Cyclohexenone derivate)
	Bromopropylate (Organobromine)
	Fluazifop (Aryloxypheoxy propionic acid)
	Abamectin (Botanical, Macrocyclic Lactone)
	Ethofumesate (Benzofuran)
	Bromide Ion
Pesticides (candidates for substitution)	8-Hydroxyquinoline incl. oxyquinoleine (Phenole)

Chemical substance group	List of individual substances
	Benfluralin
	Beta-Cyfluthrin
	Bifenox
	Copper compounds, Bordeaux mixture, Copper hydroxide, Copper oxide, Copper oxychloride
	Dimethoate
	Ioxynil
	Oxyfluorfen
	Quinoclamine

B. RESULTS FROM INVESTIGATED HBM STUDIES

Table 24 Chemical levels of student volunteers from ESBHum (Germany)

Chemical group	Substance	Matrix	Geometric mean
Metals	Arsenic	urine	5.66 µg/L
	Cadmium	blood	0.29 µg/L
	Copper	plasma	1.07 mg/L
		urine	5.80 µg/L
	Lead	blood	12.86 µg/L
	Mercury	blood	0.68 µg/L
		urine	0.13 µg/L
	Selenium	plasma	78.27 µg/L
	Strontium	urine	98.24 µg/L
	Thallium	blood	29.68 ng/L
		urine	0.19 µg/L
	Zinc	plasma	0.69 mg/L
		urine	210.57 µg/L
Organochlorines	HCB	plasma	0.10 µg/L
	PCP	plasma	0.77 µg/L
		urine	0.09 µg/L
	PCB 138	plasma	0.39 µg/L
	PCB 153	plasma	0.25 µg/L
	PCB 180	plasma	0.13 µg/L
Fluorocarbons	PFOA	plasma	4.03 µg/L
	PFOS	plasma	6.05 µg/L
Phthalate metabolites	5OH-MEHP	urine	9.49 µg/L
	5oxo-MEHP	urine	6.27 µg/L
	5cx-MEPP	urine	9.31 µg/L
	MEHP	urine	3.02 µg/L
	MnBP	urine	18.75 µg/L
	MiBP	urine	26.76 µg/L
	MBzP	urine	3.57 µg/L
Phenol	Bisphenol A	urine	1.33 µg/L

Table 25 Chemical levels of participants (children) in GerES IV (Germany)

Chemical Group	Substance	Matrix	Geometric mean
Metals	Arsenic	urine	4.4 µg/L
	Lead	blood	16.3 µg/L
	Cadmium	blood	<0.12 µg/L [(a)]
		urine	0.068 µg/L
	Nickel	urine	1.26 µg/L
	Mercury	blood	0.23 µg/L
		urine	<0.1 µg/L [(a)]
Organochlorines	PCB 28	blood	<0.001 µg/L [(a)]
	PCB 52	blood	<0.001 µg/L [(a)]
	PCB 101	blood	<0.001 µg/L [(a)]
	PCB 138	blood	0.089 µg/L
	PCB 153	blood	0.129 µg/L
	PCB 180	blood	0.065 µg/L
	Total PCB (138, 153, 180)	blood	0.286 µg/L
	α-HCH	blood	<LOQ
	β-HCH	blood	0.011 µg/L
	γ-HCH	blood	<LOQ
	DDE	blood	0.206 µg/L
	HCB	blood	0.098 µg/L
Tobacco smoke	Nicotine	urine	1.3 µg/L
	Cotinine	urine	2.5 µg/L
Organophosphates	DMP	urine	15.8 µg/L
	DMTP	urine	16.8 µg/L
	DMDTP	urine	0.56 µg/L
	DEP	urine	5.92 µg/L
	DETP	urine	1.09 µg/L
	DEDTP	urine	0.023 µg/L
Chlorophenols	2-MCP	urine	1.72 µg/L
	3-MCP	urine	4.49 µg/L
	2,4-DCP	urine	0.332 µg/L
	2,5-DCP	urine	0.853 µg/L
	2,6-DCP	urine	<0.10 µg/L [(a)]
	2,3,4-TCP	urine	<0.10 µg/L [(a)]
	2,4,5-TCP	urine	0.141 µg/L
	2,4,6-TCP	urine	0.208 µg/L
	2,3,4,6-TeCP	urine	<0.30 µg/L [(a)]
	PCP	urine	<0.60 µg/L [(a)]

Chemical Group	Substance	Matrix	Geometric mean
PAHs metabolites	1-hydroxypyrene	urine	0.129 µg/L
	1-Hydroxyphenanthrene	urine	0.185 µg/L
	2/9-Hydroxyphenanthrene	urine	0.119 µg/L
	3-Hydroxyphenanthrene	urine	0.162 µg/L
	4-Hydroxyphenanthrene	urine	0.024 µg/L
	Total OH-phenanthrene (1, 2/9, 3, 4)	urine	0.524 µg/L
Pyrethroid metabolites	cis-Cl_2CA	urine	0.136 µg/L
	trans-Cl_2CA	urine	0.280 µg/L
	Br_2CA	urine	0.110 µg/L
	3-PBA	urine	0.486 µg/L
	F-PBA	urine	<0.10 µg/L [(a)]

(a): The geometric mean is lower than the limit of quantification stated here.

Table 26 Overview of analysed chemicals in the three age groups of FLEHS II (2007-2011; Flanders)

Newborns/mothers	Adolescents (14–15 yrs)	Adults (20–40 yrs)
Cord blood:	Blood:	Blood:
Metals (Pb, Cd, Mn, Cu, Tl, As)	Metals (Pb, Cd, Mn, Cu, Tl, As)	Perfluorocompounds (PFOS, PFOA)
Persistent chlorinated compounds (PCBs, p,p'-DDE, HCB, Calux)	Persistent chlorinated compounds (PCBs, p,p'-DDE, HCB, Calux)	UV-screens (BP-3, DHB, DHMB, THB, HMS, DABI, 4-MBC)
Persistent brominated pollutants (BDE28, 47, 99, 100, 153, 154, 183, 209, HBCD, TBBPA)	Persistent brominated pollutants (BDE28, 47, 99, 100, 153, 154, 183, 209, HBCD, TBBPA)	
Perfluorocompounds (PFOS, PFOA)	Personal hygiene products (musks, galaxolide, tonalide)	
Personal hygiene products (triclosan, parabens, UV-screens)	UV-screens (BP-3, DHB, DHMB, THB, HMS, DABI, 4-MBC)	
Maternal blood:	Urine:	Urine:
Metals (Pb, Cd, Mn, Cu, Tl, As)	Metals (As, TRA)	Metals (Cd, As, TRA)
	PAHs (1-hydroxypyrene, BaP-tetrol, 1- and 2-naphtol)	PAHs (1-hydroxypyrene, BaP-tetrol, 1- and 2-naphtol)
	Benzene (t,t'-muconic acid)	Benzene (t,t'-muconic acid)
	Phthalates (MEHP, MEHHP,MEOHP, MNBP, MBzP)	Phthalates (MEHP, MEHHP,MEOHP, MNBP, MBzP)
	Bisphenol A	Organophosphate pesticides (DMP, DMTP, DMDTP, DEP, DETP, DEDTP)
	Organophosphate pesticides (DMP, DMTP, DMDTP, DEP, DETP, DEDTP)	Para dichlorobenzene (2,5-DCP)
	Para dichlorobenzene (2,5-DCP)	Cotinine
	Triclosan	Paraben metabolite (HBA)
	Cotinine	Herbicide (2,4–D)
	Paraben metabolite (HBA)	Carbamate pest (ETU)
	Herbicide (2,4–D)	Fungicides (3,5-DCA, 3,4-DCA, DCPU, DCPMU)
	Carbamate pest (ETU)	Pyrethroids (3-BPA, FPBA)
	Fungicides (3,5-DCA, 3,4-DCA, DCPU, DCPMU)	
	Pyrethroids (3-BPA, FPBA)	

Newborns/mothers	Adolescents (14–15 yrs)	Adults (20–40 yrs)
Maternal hair:	Hair:	
Metals (Hg, MeHg)	Metals (Hg, MeHg)	

Pb: lead; Cd: cadmium; Mn: manganese; Cu: copper; Tl: thallium; PCBs: polychlorinated biphenyls; p,p'-DDE: p,p'-dichlorodiphenyldichloroethylene; HCB: hexachlorobenzene; BDEs: brominated diphenylethers; HBCD: hexabromocyclododecane; TBBPA: tetrabromo bisphenol A; PFOS: perfluoroctanesulphonic acid; PFOA: perfluoroctanoic acid; Hg: mercury; MeHg: methylmercury; As: arsenic; TRA: toxic relevant arsene; PAHs: polycyclic aromatic hydrocarbons; 2,5-DCP: 2,5-dichlorophenol; ETU: ethylenethiourea 2,4-D: 2,4-dichlorophenoxy-acetic acid; BaP-tetrol: benzo[a]pyrene tetrol; MEHP = mono-2-ethylhexyl phthalate (primary metabolite of di-2-ethylhexyl phthalate [DEHP]); MEHHP = mono-2-ethyl-5-hydroxyhexyl phthalate (secundary metabolite of DEHP); MEOHP = mono-2-ethyl-5-oxohexyl phthalate (secundary metabolite of DEHP); MnBP = mono-n-butyl phthalate (metabolite of di-n-butyl phthalate [DBP]); MBzP = mono-benzyl phthalate (metabolite of benzylbutyl phthalate [BzBP]); DMP = dimethylphosphate; DMTP = dimethylthiophosphate; DMDTP = dimethyldithiophosphate; DEP = diethylphosphate; DETP = diethylthiophosphate; DEDTP = diethyldithiophosphate; HBA = para-hydroxybenzoic acid; 3,5-DCA = 3,5-dichloroaniline; 3,4-DCA = 3,4-dichloroaniline; DCPU = 3,4-dichlorophenyl urea; DCPMU = 3,4-dichlorophenyl-3-methylurea; 3-PBA = 3-phenoxybenzoic acid; FPBA = 4-fluoro-3-phenoxybenzoic acid; BP-3 = benzophenone-3; DHB = 2,4-dihydroxybenzophenone; DHMB = 2,2'-dihydroxy-4-methoxybenzophenone; THB = 2,3,4-trihydroxybenzophenone; HMS = homosalate; DABI = octyl dimethyl PABA; 4-MBC = 4-methylbenzylidenecamphor.

Table 27 Results from FLEHS I (Flanders)

Chemical	Unit	Age group	Geometric mean	95% CI
Dioxin-like compounds (CALUX)	pg/g Lipid	Newborn	23	21 - 24
		Adults	19.2	18.2 - 20.2
PCBs	ng/g Lipid	Newborns	64.4	61.1 - 67.9
		Adolescents	68	66 -70
		Adults	333	325 - 341
DDE	ng/g Lipid	Newborns	110	104 - 116
		Adolescents	94	89 - 99
		Adults	423	398 - 449
HCB	ng/g Lipid	Newborns	18.9	17.9 - 20
		Adolescents	20.9	20.4 - 21.3
		Adults	56.9	55.2 - 58.6
Blood Pb	µg/L	Newborns	14.7	14 - 15.5
		Adolescents	21.7	20.8 - 22.6
		Adults	39.6	38.4 - 40.9
Blood Cd	µg/L	Newborns	0.21	0.19 - 0.23
		Adolescents	0.36	0.33 - 0.38
		Adults	0.42	0.4 - 0.44
Urinary Cd	µg/ g Creatinine	Adults	0.62	0.6 - 0.64
1 HO-pyrene	µg/ g Creatinine	Adolescents	88	81 - 95
		Adults	147	138 - 157
Tt'-muconic acid	µg/ g Creatinine	Adolescents	72	66 -79
		Adults	85	79 -92

Table 28 Results from ENNS study (France)

Chemical Group	Substance	Matrix	Geometric mean
Metals	Antimony	urine	0.083 µg/L
	Arsenic	urine	13.42 µg/L
	Cadmium	urine	0.32 µg/L
	Chromium	urine	0.19 µg/L
	Cobalt	urine	0.24 µg/L
	Lead	blood	25.7 µg/L
	Mercury	hair	0.59 µg/g hair (adults) 0.37 µg/g hair (children)
	Nickel	urine	1.36 µg/L
	Tin	urine	0.50 µg/L
	Uranium	urine	4.9 ng/L
	Vanadium	urine	0.95 µg/L
Organochlorines	PCB 28	serum	2.2 ng/g lipid
	PCB 52	serum	0.27 ng/g lipid
	PCB 101	serum	1.08 ng/g lipid
	PCB 138	serum	70.8 ng/g lipid
	PCB 153	serum	113.3 ng/g lipid
	PCB 180	serum	93.7 ng/g lipid
	α-HCH	serum	0.66 ng/g lipid
	β-HCH	serum	30 ng/g lipid
	γ-HCH	serum	<LOD
	DDE	serum	118 ng/g lipid
	DDT	serum	33.2 ng/g lipid
	HCB	serum	24 ng/g lipid
Organophosphates	DMP	urine	7.19 µg/L
	DMTP	urine	6.65 µg/L
	DMDTP	urine	0.76 µg/L
	DEP	urine	3.94 µg/L
	DETP	urine	1.07 µg/L
	DEDTP	urine	0.02 µg/L
Chlorophenols	4-MCP	urine	5.56 µg/L
	2,4-DCP	urine	1.10 µg/L
	2,5-DCP	urine	10.56 µg/L
	2,6-DCP	urine	<LOD
	2,3,4-TCP	urine	<LOD
	2,4,5-TCP	urine	0.15 µg/L
	2,4,6-TCP	urine	0.37 µg/L
	PCP	urine	0.90 µg/L
Pyrethroid metabolites	cis-Cl_2CA	urine	0.17 µg/L
	trans-Cl_2CA	urine	0.39 µg/L
	Br_2CA	urine	0.37 µg/L
	3-PBA	urine	0.74 µg/L
	F-PBA	urine	<LOD

Table 29 Findings of Pb, Hg, and PCBs in BIOAMBIENT.ES (Spain)

a.

Sample	Geometric mean (blood lead levels)	95% CI
Total (n=1880)	24.03 µg/L	22.98-25.12
Males (n=962)	28.33 µg/L	26.76-29.99
Females (n=918)	19.47 µg/L	18.55-20.45

b.

Sample	Geometric mean (hair Hg levels)	95% CI
Total (n=604)	1.86 ng/mg	1.76-1.97

c.

Sample	Geometric mean (Σ PCB 138,153,180)	95% CI
Total (n=1880)	135.4 ng/g lipid	121.3-151.4

PCBs 28 and 52 were only detected in 1% of the total samples, and PCB 101 was detected in 6% of the total samples.

Table 30 The levels of metal [µg/L unless specified otherwise] found in the Italian population from the PROBE study

Metal	Fluid	Geometric Mean	P95
As	Blood	1.14	5.32
Be	Blood	0.08	0.18
Cd	Blood	0.53	1.42
Co	Blood	0.15	0.44
Cr	Blood	0.24	1.09
Hg	Blood	1.19	5.16
Ir	Serum	2.46 ng/L	7.05
Mn	Blood	8.19	14.5
Mo	Blood	1.21	2.05
Ni	Serum	0.35	0.94
Pb	Blood	19.9	51.7
Pd	Serum	10.6 ng/L	29.4
Pt	Serum	5.23 ng/L	13.3
Rh	Serum	9.28 ng/L	23.1
Sb	Blood	0.31	0.72
Sn	Blood	0.54	2.25
Tl	Blood	0.037	0.098
U	Blood	0.006	0.014
V	Serum	0.044	0.11
W	Blood	0.028	0.075

Table 31 Results of phthalate metabolites of Austrian children and adults (from the Schadstoffe im Menschen HBM study)

Substance	Matrix	Arithmetic mean	P95
MBzP	urine	2.7 µg/L	6.2 µg/L
MiBP	urine	13 µg/L	25 µg/L
MnBP	urine	9.6 µg/L	22 µg/L
MCHP	urine	<LOQ	<LOQ
MEP	urine	59 µg/L	214 µg/L
MEHP	urine	1.9 µg/L	5.2 µg/L
MEHHP (5OH-MEHP)	urine	6.2 µg/L	14 µg/L
MEOHP (5oxo-MEHP)	urine	3.6 µg/L	8.7 µg/L
MECPP (5cx-MEPP)	urine	43 µg/L	121 µg/L
MiNP	urine	<LOQ	<LOQ
MOP/MnOP	urine	<LOQ	<LOQ

Table 32 Results of the levels found in the tested substances of CHMS (Canada)

Chemical Group	Substance	Matrix	Geometric mean
Metals	Antimony	urine	0.048 µg/L
	Arsenic	blood	0.89 µg/L
		urine	9.1 µg/L
	Cadmium	blood	0.29 µg/L
		urine	0.39 µg/L
	Cesium	urine	4.9 µg/L
	Cobalt	urine	0.23 µg/L
	Copper	blood	900 µg/L
		urine	11 µg/L
	Fluoride	urine	500 µg/L
	Lead	blood	1.2 µg/dL
		urine	0.52 µg/L
	Manganese	blood	9.8 µg/L
		urine	<LOD
	Mercury	hair	0.70 µg/L
	Molybdenum	blood	0.66 µg/L
		urine	45 µg/L
	Nickel	blood	0.48 µg/L
		urine	1.3 µg/L
	Selenium	blood	190 µg/L
		urine	51 µg/L
	Silver	blood	<LOD
	Thallium	blood	0.23 µg/L
	Tungsten	urine	<LOD
	Uranium	blood	<LOD
	Vanadium	urine	<LOD
	Zinc	blood	5.9 µg/L
		urine	320 µg/L
PCBs	PCB 105	plasma	<LOD
	PCB 118	plasma	0.03 µg/L
	PCB 156	plasma	0.02 µg/L
	PCB 167	plasma	<LOD
	PCB 28	plasma	<LOD
	PCB 52	plasma	<LOD
	PCB 66	plasma	<LOD
	PCB 74	plasma	<LOD
	PCB 99	plasma	<LOD
	PCB 101	plasma	<LOD

Chemical Group	Substance	Matrix	Geometric mean
	PCB 128	plasma	<LOD
	PCB 138	plasma	0.06 µg/L
	PCB 146	plasma	0.01 µg/L
	PCB 153	plasma	0.11 µg/L
	PCB 170	plasma	0.03 µg/L
	PCB 178	plasma	<LOD
	PCB 180	plasma	0.09 µg/L
	PCB 183	plasma	<LOD
	PCB 187	plasma	0.02 µg/L
	PCB 194	plasma	0.02 µg/L
	PCB 196	plasma	0.01 µg/L
	PCB 206	plasma	<LOD
Fluorocarbons	PFBuS	plasma	<LOD
	PFDeA	plasma	0.20 µg/L
	PFHxS	plasma	1.8 µg/L
	PFNA	plasma	0.82 µg/L
	PFOA	plasma	2.3 µg/L
	PFOS	plasma	6.5 µg/L
	PFUA	plasma	0.12 µg/L
PBDEs	PBDE 17	plasma	<LOD
	PBDE 28	plasma	<LOD
	PBDE 47	plasma	0.06 µg/L
	PBDE 99	plasma	<LOD
	PBDE 100	plasma	<LOD
	PBDE 153	plasma	<LOD
	PBB 153	plasma	<LOD
Phthalates	MBzP	urine	7.5 µg/L
	MiBP	urine	14 µg/L
	MnBP	urine	20 µg/L
	MCHP	urine	<LOD
	MEP	urine	45 µg/L
	MEHP	urine	1.9 µg/L
	MEHHP	urine	13 µg/L
	MEOHP	urine	7.4 µg/L
	MiNP	urine	<LOD
	MMP	urine	<LOD
	MCPP	urine	1.9 µg/L
	MOP	urine	<LOD
Phenols	Bisphenol A	urine	1.2 µg/L

Chemical Group	Substance	Matrix	Geometric mean
	Triclosan	urine	16 µg/L
Carbamate pesticides	Carbofuranphenol	urine	<LOD
	2-isopropoxyphenol	urine	<LOD
Herbicide	2,4-D	urine	<LOD
Organophosphates	DMP	urine	3.3 µg/L
	DMTP	urine	2.7 µg/L
	DMDTP	urine	<LOD
	DEP	urine	2.8 µg/L
	DETP	urine	0.66 µg/L
	DEDTP	urine	<LOD
Pesticides	Aldrin	plasma	<LOD
	p,p'-DDE	plasma	0.91 µg/L
	p,p'-DDT	plasma	<LOD
	β-HCH	plasma	0.04 µg/L
	γ-HCH	plasma	<LOD
	HCB	plasma	0.05 µg/L
	Mirex	plasma	<LOD
	Oxychlordane	plasma	0.03 µg/L
	trans-Nonachlor	plasma	0.04 µg/L
Chlorophenols	2,4-DCP	urine	1.2 µg/L
	2,5-DCP	urine	5.5 µg/L
	2,4,5-TCP	urine	<LOD
	2,4,6-TCP	urine	<LOD
	PCP	urine	<LOD
PAHs metabolites	3-hydroxybenzo[a]pyrene	urine	<LOD
	2-hydroxyfluorene	urine	0.27 µg/L
	3-hydroxyfluorene	urine	0.096 µg/L
	9-hydroxyfluorene	urine	0.16 µg/L
	1-hydroxypyrene	urine	0.11 µg/L
	1-hydroxyphenanthrene	urine	0.15 µg/L
	2-hydroxyphenanthrene	urine	0.067 µg/L
	3-hydroxyphenanthrene	urine	0.087 µg/L
	4-hydroxyphenanthrene	urine	0.025 µg/L
	9-hydroxyphenanthrene	urine	0.039 µg/L
	1-hydroxynaphthalene	urine	1.5 µg/L
	2-hydroxynaphthalene	urine	3.8 µg/L
Pyrethroid metabolites	cis-Cl_2CA	urine	0.12 µg/L
	trans-Cl_2CA	urine	0.29 µg/L

Chemical Group	Substance	Matrix	Geometric mean
	Br_2CA	urine	0.012 µg/L
	3-PBA	urine	0.43 µg/L
	F-PBA	urine	<LOD
Tobacco smoke	Cotinine	urine	<LOD (non-smokers) 2600 µg/L (smokers)

Table 33 Results of the levels found in the tested substances of NHANES (USA)

Chemical Group	Substance	Matrix	Geometric mean
Metals	Antimony	urine	<LOD
	Arsenic	urine	6.84 µg/L
	Barium	urine	1.20 µg/L
	Beryllium	urine	<LOD
	Cadmium	blood	0.279 µg/L
		urine	0.154 µg/L
	Caesium	urine	3.82 µg/L
	Cobalt	urine	0.327 µg/L
	Copper	serum	114 µg/dL
	Lead	blood	0.973 µg/dL
		urine	0.358 µg/L
	Manganese	blood	9.35 µg/L
		urine	0.124 µg/L
	Mercury	blood	0.703 µg/L
		urine	0.323 µg/L
	Molybdenum	urine	36.9 µg/L
	Platinum	urine	<LOD
	Selenium	blood	190 µg/L
		serum	127 µg/L
	Strontium	urine	85.4 µg/L
	Thallium	urine	0.150 µg/L
	Tin	urine	0.617 µg/L
	Tungsten	urine	0.073 µg/L
	Uranium	urine	0.006 µg/L
	Zinc	serum	81.8 µg/dL
PCBs	PCB 77	serum	36.7 ng/g lipid [(a)]
	PCB 81	serum	<LOD
	PCB 126	serum	16.3 pg/g lipid
	PCB 169	serum	<LOD
	PCB 105	serum	1.20 pg/g lipid
	PCB 114	serum	2.83 ng/g lipid [(a)]
	PCB 118	serum	6.00 ng/g lipid
	PCB 123	serum	<LOD
	PCB 156	serum	2.54 pg/g lipid
	PCB 157	serum	0.605 pg/g lipid
	PCB 167	serum	0.494 pg/g lipid

Chemical Group	Substance	Matrix	Geometric mean
	PCB 189	serum	<LOD
	PCB 28	serum	4.90 ng/g lipid
	PCB 44	serum	2.06 ng/g lipid
	PCB 49	serum	1.29 ng/g lipid
	PCB 52	serum	2.66 ng/g lipid
	PCB 66	serum	1.39 ng/g lipid
	PCB 74	serum	4.81 ng/g lipid
	PCB 87	serum	0.656 ng/g lipid
	PCB 99	serum	4.16 ng/g lipid
	PCB 101	serum	1.65 ng/g lipid
	PCB 110	serum	1.22 ng/g lipid
	PCB 128	serum	<LOD
	PCB 138	serum	15.1 ng/g lipid
	PCB 146	serum	2.17 ng/g lipid
	PCB 149	serum	0.598 ng/g lipid
	PCB 151	serum	<LOD
	PCB 153	serum	19.8 ng/g lipid
	PCB 170	serum	5.46 ng/g lipid
	PCB 172	serum	0.647 ng/g lipid
	PCB 177	serum	1.13 ng/g lipid
	PCB 178	serum	0.933 ng/g lipid
	PCB 180	serum	15.1 ng/g lipid
	PCB 183	serum	1.45 ng/g lipid
	PCB 187	serum	4.23 ng/g lipid
	PCB 194	serum	2.69 ng/g lipid
	PCB 195	serum	<LOD
	PCB 196	serum	2.61 ng/g lipid
	PCB 199	serum	2.81 ng/g lipid
	PCB 206	serum	2.13 ng/g lipid
	PCB 209	serum	1.40 ng/g lipid
Perchlorate	Perchlorate	urine	2.97 µg/L
Fluorocarbons	PFBuS	serum	<LOD
	PFDeA	serum	0.279 µg/L
	PFDoA	serum	<LOD
	PFHpA	serum	<LOD
	PFHxS	serum	1.66 µg/L
	PFNA	serum	1.26 µg/L
	PFOA	serum	3.07 µg/L
	PFOS	serum	9.32 µg/L

Chemical Group	Substance	Matrix	Geometric mean
	PFOSA	serum	<LOD
	Et-PFOSA-AcOH	serum	<LOD
	Me-PFOSA-AcOH	serum	<LOD
	PFUA	serum	<LOD
Dioxins	1,2,3,4,6,7,8-HpBDD	serum	29.1 ng/g lipid [(a)]
	1,2,3,4,7,8-HxBDD and 1,2,3,6,7,8-HxBDD	serum	<LOD
	1,2,3,7,8,9-HxBDD	serum	<LOD
	1,2,3,7,8-PeBDD	serum	<LOD
	2,3,7,8-TBDD	serum	<LOD
	1,2,3,4,6,7,8-HpCDD	serum	25.3 pg/g lipid
	1,2,3,4,7,8-HxCDD	serum	<LOD
	1,2,3,6,7,8-HxCDD	serum	17.2 pg/g lipid
	1,2,3,7,8,9-HxCDD	serum	<LOD
	1,2,3,4,6,7,8,9-OCDD	serum	<LOD
	1,2,3,7,8-PeCDD	serum	<LOD
	2,3,7,8-TCDD	serum	<LOD
Furans	1,2,3,4,6,7,8-HpBDF	serum	19.6 ng/g lipid [(a)]
	1,2,3,4,7,8-HxBDF	serum	<LOD
	1,2,3,7,8-PeBDF	serum	<LOD
	2,3,4,7,8-PeBDF	serum	<LOD
	2,3,7,8-TBDF	serum	<LOD
	1,2,3,4,6,7,8-HpCDF	serum	<LOD
	1,2,3,4,7,8,9-HpCDF	serum	<LOD
	1,2,3,4,7,8-HxCDF	serum	<LOD
	1,2,3,6,7,8-HxCDF	serum	<LOD
	1,2,3,7,8,9-HxCDF	serum	<LOD
	2,3,4,6,7,8-HxCDF	serum	<LOD
	1,2,3,4,6,7,8,9-OCDF	serum	<LOD
	1,2,3,7,8-PeCDF	serum	<LOD
	2,3,4,7,8-PeCDF	serum	<LOD
	2,3,7,8-TCDF	serum	<LOD
PBDEs	PBDE 17	serum	<LOD
	PBDE 28	serum	1.19 ng/g lipid
	PBDE 47	serum	20.5 ng/g lipid
	PBDE 66	serum	<LOD
	PBDE 85	serum	<LOD
	PBDE 99	serum	<LOD
	PBDE 100	serum	3.93 ng/g lipid
	PBDE 153	serum	5.69 ng/g lipid

Chemical Group	Substance	Matrix	Geometric mean
	PBDE 154	serum	<LOD
	PBDE 183	serum	<LOD
	BDE 209	serum	<LOD
	PBB 153	serum	2.29 ng/g lipid
Phthalates	MBzP	urine	4.48 µg/L
	MiBP	urine	5.99 µg/L
	MnBP	urine	7.60 µg/L
	MCHP	urine	<LOD
	MEP	urine	37.6 µg/L
	MEHP	urine	1.37 µg/L
	MEHHP	urine	7.90 µg/L
	MEOHP	urine	5.08 µg/L
	MECPP	urine	12.9 µg/L
	MCNP	urine	2.48 µg/L
	MiNP	urine	<LOD
	MMP	urine	<LOD
	MCOP	urine	19.7 µg/L
	MCPP	urine	3.01 µg/L
	MOP	urine	<LOD
	MHNCH	urine	<LOD
Phenols	Benzophenone-3	urine	23.3 µg/L
	Bisphenol A	urine	1.51 µg/L
	Butyl paraben	urine	<LOD
	Ethyl paraben	urine	<LOD
	Methyl paraben	urine	40.6 µg/L
	Propyl paraben	urine	5.44 µg/L
	4-tert-octylphenol	urine	<LOD
	Triclosan	urine	12.0 µg/L
Nitrosamine	NNAL	urine	<LOD
Smoke flavouring	Nitrate	urine	42.0 mg/L
Carbamate pesticides	Carbofuranphenol	urine	<LOD
	2-isopropoxyphenol	urine	<LOD
Herbicides	2,4-D	urine	0.245 µg/L
	2,4,5-T	urine	<LOD
Organophosphates	Acephate	urine	<LOD
	Dimethoate	urine	<LOD
	Methamidophos	urine	<LOD
	Omethoate	urine	<LOD

Chemical Group	Substance	Matrix	Geometric mean
	Malathion diacid	urine	<LOD
	Paranitrophenol	urine	0.673 µg/L
	3,5,6-trichloropyridinol	urine	1.29 µg/L
	DMP	urine	<LOD
	DMTP	urine	2.28 µg/L
	DMDTP	urine	<LOD
	DEP	urine	<LOD
	DETP	urine	<LOD
	DEDTP	urine	<LOD
Pesticides	Aldrin	serum	<LOD
	Dieldrin	serum	<LOD
	Endrin	serum	<LOD
	Heptachlor epoxide	serum	<LOD
	p,p'-DDE	serum	238 ng/g lipid
	o,p'-DDT	serum	<LOD
	p,p'-DDT	serum	<LOD
	β-HCH	serum	<LOD
	γ-HCH	serum	<LOD
	HCB	serum	15.2 ng/g lipid
	Mirex	serum	<LOD
	Oxychlordane	serum	9.37 ng/g lipid
	trans-Nonachlor	serum	14.7 ng/g lipid
Chlorophenols	2,4-DCP	urine	0.696 µg/L
	2,5-DCP	urine	4.15 µg/L
	2,4,5-TCP	urine	<LOD
	2,4,6-TCP	urine	<LOD
	PCP	urine	<LOD
PAHs metabolites	2-hydroxyfluorene	urine	237 ng/L
	3-hydroxyfluorene	urine	92.4 ng/L
	9-hydroxyfluorene	urine	241 ng/L
	1-hydroxypyrene	urine	110 ng/L
	1-hydroxyphenanthrene	urine	125 ng/L
	2-hydroxyphenanthrene	urine	60.3 ng/L
	3-hydroxyphenanthrene	urine	61.3 ng/L
	4-hydroxyphenanthrene	urine	20.3 ng/L
	1-hydroxynaphthalene	urine	2.58 µg/L
	2-hydroxynaphthalene	urine	3.83 µg/L
Pyrethroid metabolites	Br_2CA	urine	<LOD
	3-PBA	urine	0.401 µg/L

Chemical Group	Substance	Matrix	Geometric mean
	F-PBA	urine	<LOD
Tobacco smoke	Cotinine	serum	0.041 ng/mL

(a): The arithmetic mean is reported here.

Table 34 Levels of metals and cotinine found in KNHANES (South Korea)

Chemical Group	Substance	Matrix	Geometric mean
Metals	Arsenic	urine	101.0 µg/g creatinine (low shellfish intake)
	Cadmium	blood	1.07 µg/L
	Lead	blood	2.49 µg/dL
	Manganese	blood	1.35 µg/dL
	Mercury	blood	5.19 µg/L
Tobacco smoke	Cotinine	urine	5.31 ng/mL (male non-smokers) 4.49 ng/mL (female non-smokers) 1221.93 ng/mL (male smokers) 822.93 ng/mL (female smokers)

Table 35 Levels of metals found in KorSEP III

Substances	Geometric mean	95% CI
Lead (blood)	19.1 µg/L	18.2-20.1
Mercury (blood)	3.23 µg/L	3.06-3.39
Manganese (blood)	10.8 µg/L	10.4-11.1
Arsenic (urine)	43.5 µg/L	41.6-45.4
Cadmium (urine)	0.65 µg/L	0.56-0.74

Table 36 Levels of PAH metabolites found in KorSEP III

Substances	Geometric mean	95% CI
1-hydroxypyrene (urine)	0.15 µg/L	0.13-0.17
2-naphthol (urine)	3.84 µg/L	3.57-4.11
Cotinine (urine)	47.42 µg/L	40.52-54.32

Table 37 Levels of phthalate metabolites found in KorSEP III

Substances	Geometric mean	Geometric standard error
MnBP	41.7 µg/L	1.9
MeHHP	38.1 µg/L	1.9
MeOHP	17.5 µg/L	1.9
MiBP	17.0 µg/L	2.2
MBzP	15.8 µg/L	2.8
MCHP	<LOD	N/A
MnOP	<LOD	N/A
MINP	<LOD	N/A
MiDP	Too low for quantification	N/A
MEHP	not reported	N/A

Table 38 A summary overview of the analytical methods used in the reviewed HBM programmes

Class of substances	HBM Programme	Method	Matrix
Acrylamide	MoBa (Norway), NHANES (USA)	LC-MS [(a)]	Blood [(d)]
	MoBa (Norway)	LC-MS	Urine
BFRs	FLEHS (Flanders), BIOAMBIENT.ES (Spain), Pollutants in humans (Austria), NHANES (USA)	GC-MS [(b)]	Blood
	CHMS (Canada)	GC-ECD [(c)]	
	AMAP	LC-MS	
	Mothers in Uppsala (Sweden), POPs in milk (China)	GC-MS	Breast milk
Bisphenol A	ESBHum (Germany), Pollutants in humans (Austria), Danish HBM (Denmark), NHANES (USA), MOCEH (South Korea), KorEHS-C (South Korea)	LC-MS	Urine
	ELFE (France), FLEHS (Flanders), MoBa (Norway), CHMS (Canada)	GC-MS	
Carbamate	CHMS (Canada), NHANES (USA)	GC-MS	Urine
Chlorophenols	ESBHum (Germany), GerES (Germany), ENNS (France), FLEHS (Flanders), CHMS (Canada)	GC-MS	Urine
	NHANES (USA)	LC-MS	
Cotinine	NHANES (USA)	LC-MS	Blood
	Hokkaido (Japan)	ELISA	
	GerES (Germany)	LC-UV detection	Urine
	FLEHS (Flanders)	Chemiluminescence	
	MoBa (Norway), CHMS (Canada)	LC-MS	
	KHNANES (South Korea), KorSEP (South Korea)	GC-MS	
	MOCEH (South Korea), KorEHS-C (South Korea)	ELISA	

Class of substances	HBM Programme	Method	Matrix
Fluorocarbons	ESBHum (Germany), FLEHS (Flanders), Tromsø cohort (Norway), MoBa (Norway), AMAP, CHMS (Canada), NHANES (USA), Hokkaido (Japan)	LC-MS	Blood
	ELFE (France), Hokkaido (Japan), POPs in milk (China)	LC-MS	Breast milk
Dioxins & furans	FLEHS (Flanders), Tohoku (Japan)	CALUX [(e)]	Blood
	NHANES (USA), Hokkaido (Japan)	GC-MS	
	ELFE (France), Mothers in Uppsala (Sweden), POPs in milk (China)	GC-MS	Breast milk
Herbicides (i.e. 2,4-D & 2,4,5-T)	FLEHS (Flanders), NHANES (USA) CHMS (Canada)	LC-MS GC-MS	Urine
Mercury	ESBHum (Germany), GerES (Germany), Tohoku (Japan), MOCEH (South Korea), KorEHS-C (South Korea)	CV-AAS	Blood
	BIOAMBIENT.ES (Spain), PROBE (Italy), CHMS (Canada), NHANES (USA)	ICP-MS	
	CZ-HBM (Czech Republic), Slovenia HBM, KNHANES (South Korea), KorSEP (South Korea)	DMA	
	AMAP	HPLC-MS	
	ESBHum (Germany), Slovenia HBM,	CV-AAS	Urine
	BIOAMBIENT.ES (Spain), NHANES (USA)	ICP-MS	
	ENNS (France), Pollutants in humans (Austria) FLEHS (Flanders)	ICP-MS AFS	Hair (for MeHg)
	BIOAMBIENT.ES (Spain), CZ-HBM (Czech Republic), Slovenia HBM	DMA	
	Hokkaido (Japan)	Atomic absorption detection	
	Tohoku (Japan)	CV-AAS	
	Slovenia HBM	CV-AAS	Milk
Metals (excluding	ESBHum (Germany), FLEHS (Flanders), BIOAMBIENT.ES (Spain), PROBE (Italy), Slovenia	ICP-MS	Blood

Class of substances	HBM Programme	Method	Matrix
mercury)	HBM, CHMS (Canada), NHANES (USA), Tohoku (Japan)		
	ESBHum (Germany), GerES (Germany), ENNS (France), CZ-HBM (Czech Republic), Selenium supplement (Finland)	ET-AAS	
	Tohoku (Japan), KorSEP (South Korea)	GF-AAS	
	ESBHum (Germany), ENNS (France), FLEHS (Flanders), BIOAMBIENT.ES (Spain), Slovenia HBM, CHMS (Canada), NHANES (USA)	ICP-MS	Urine
	GerES (Germany), CZ-HBM (Czech Republic)	ET-AAS	
	Slovenia HBM, Mothers in Uppsala (Sweden)	ICP-MS	Milk
Mycotoxin	NHANES (USA)	LC-MS	Blood
Nicotine	GerES (Germany)	LC-UV detection	Urine
Nitrosamine	NHANES (USA)	LC-MS	Urine
Organochlorines	ESBHum (Germany), FLEHS (Flanders), CZ-HBM (Czech Republic), Tromsø cohort (Norway), NHANES (USA), Tohoku (Japan)	GC-MS	Blood
	GerES (Germany), ENNS (France), CHMS (Canada)	GC-ECD	
	Tohoku (Japan), POPs in milk (China)	GC-MS	Breast milk
Organophosphate pesticides	NHANES (USA)	LC-MS	Urine
Organophosphate metabolites	GerES (Germany), ENNS (France), FLEHS (Flanders), MoBa (Norway), CHMS (Canada), NHANES (USA)	GC-MS	Urine
PAH metabolites	GerES (Germany), FLEHS (Flanders), BIOAMBIENT.ES (Spain), KorSEP (South Korea), MOCEH (South Korea), KorEHS-C (South Korea)	LC-MS	Urine
	CHMS (Canada), NHANES (USA)	GC-MS	
PCBs	ESBHum (Germany), BIOAMBIENT.ES (Spain), CZ-HBM (Czech Republic), Tromsø cohort (Norway), NHANES (USA), Hokkaido (Japan), Tohoku (Japan)	GC-MS	Blood

Class of substances	HBM Programme	Method	Matrix
	GerES (Germany), ENNS (France), CHMS (Canada)	GC-ECD	
	AMAP	LC-MS	
	ELFE (France), CZ-HBM (Czech Republic), Mothers in Uppsala (Sweden), Tohoku (Japan), POPs in milk (China)	GC-MS	Breast milk
Perchlorate	NHANES (USA)	IC-MS	Urine
Phenols	FLEHS (Flanders), Pollutants in humans (Austria), Danish HBM (Denmark), NHANES (USA)	LC-MS	Urine
Phthalates	ESBHum (Germany), ELFE (France), FLEHS (Flanders), Pollutants in humans (Austria), Danish HBM (Denmark), MoBa (Norway), CHMS (Canada), NHANES (USA), KorSEP (South Korea), MOCEH (South Korea), KorEHS-C (South Korea)	LC-MS	Urine
Pyrethroid metabolites	GerES (Germany), FLEHS (Flanders), ENNS (France), CHMS (Canada)	GC-MS	Urine
	NHANES (USA)	LC-MS	
Triclosan	FLEHS (Flanders), CHMS (Canada)	GC-MS	Urine

(a): Including LC-MS, HPLC-MS and UPLC-MS.

(b): Including GC-MSD.

(c): Including GC-ECD-MS.

(d): Including whole blood, serum, plasma samples.

(e): Total dioxins or furans were measured with this assay.

Table 39 Inventory of the validated biomarkers of exposure in various biological matrices measured in the national/European HBM programmes

Biological matrix	Validated biomarkers of exposure	HBM programme (region; age range)
Blood [(a)]	**Acrylamide/Glycidamide**	NHANES (USA; age ≥6)
	Aflatoxin B1	NHANES (USA; age ≥6)
	BFRs (PBDE 17, 28, 47, 66, 85, 99, 100, 153, 154, 183, BDE 209, HBCDDs, TBBPA, PBB 153)	BIOAMBIENT.ES (Spain; age ≥16); CHMS I (Canada; age 6-79); NHANES (USA; age ≥6)
	Cotinine	NHANES (USA; age ≥6)
	Dioxins (1,2,3,4,6,7,8-HpBDD, 1,2,3,4,7,8-HxBDD, 1,2,3,6,7,8-HxBDD, 1,2,3,7,8,9-HxBDD, 1,2,3,7,8-PeBDD, 2,3,7,8-TBDD, 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD)	NHANES (USA; age ≥6)
	Fluorocarbons (PFBuS, PFDeA/PFDA, PFDoA, PFHpA, PFHxS, PFNA, PFOA, PFOS, PFOSA, Et-PFOSA-AcOH, Me-PFOSA-AcOH, PFUA/PFUdA)	CHMS I-II (Canada; age 3-79)
	Furans (1,2,3,4,6,7,8-HpBDF, 1,2,3,4,7,8-HxBDF, 1,2,3,7,8-PeBDF, 2,3,4,7,8-PeBDF, 2,3,7,8-TBDF, 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF)	NHANES (USA; age ≥6)
	Metals (Sb, As, Be, Cd, Cr, Co, Cu, Ir, Pb, Mn, Hg, Mo, Ni, Pd, Pt, Rh, Se, Ag, Tl, Sn, W, U, V, Zn)	GerES IV (Germany; age 3-14); FLEHS I (Flanders; age 0-65); ENNS (France; age 3-74); BIOAMBIENT.ES (Spain; age ≥16); PROBE (Italy; age 18-65); CHMS I-II (Canada; age 3-79); NHANES (USA; age ≥6); KNHANES (South Korea; age ≥1)
	Organochlorine pesticides (Aldrin, Dieldrin, Endrin, Heptachlor, Heptachlor epoxide, DDT, DDE, Oxychlordane, trans-Nonachlor, HCB, α-HCH, β-HCH, γ-HCH, Mirex)	GerES IV (Germany; age 3-14); FLEHS I (Flanders; age 0-65); CHMS I (Canada; age 6-79); NHANES (USA; age ≥6)
	PCBs (PCB 28, 44, 49, 52, 66, 74, 77, 81, 87, 99, 101, 105, 110, 114, 118, 123, 126, 128, 138, 146, 149, 151, 153, 156, 157, 158, 167, 169, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 199, 203, 206, 209)	GerES IV (Germany; age 3-14); FLEHS I (Flanders; age 0-65); BIOAMBIENT.ES (Spain; age ≥16); CHMS I (Canada; age 6-79); NHANES (USA; age ≥6)

Biological matrix	Validated biomarkers of exposure	HBM programme (region; age range)
Urine	**4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonol** (NNAL)	NHANES (USA; age ≥6)
	Bisphenol A	CHMS I-II (Canada; age 3-79); NHANES (USA; age ≥6); COPHES/DEMOCOPHES (Europe; age 6-45)
	Carbamate pesticides (Carbofuranphenol, 2-isopropoxyphenol)	CHMS II (Canada; age 3-79); NHANES (USA; age ≥6)
	Chlorophenols (2-MCP, 4-MCP, 2,4-DCP, 2,5-DCP, 2,6-DCP, 2,3,4-TCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,6-TeCP, PCP)	GerES IV (Germany; age 3-14); CHMS I-II (Canada; age 3-79); NHANES (USA; age ≥6)
	Cotinine	GerES IV-V (Germany; age 3-17); CHMS I-II (Canada; age 3-79); KNHANES (South Korea; age ≥1); COPHES/DEMOCOPHES (Europe; age 6-45)
	Herbicides (2,4-D, 2,4,5-T)	CHMS I-II (Canada; age 3-79); NHANES (USA; age ≥6)
	Metals (Sb, As, Ba, Be, Cd, Cs, Cr, Co, Cu, Fl, Pb, Mn, Hg, Mo, Ni, Pt, Se, Ag, Sr, Tl, Sn, W, U, V, Zn)	GerES IV-V (Germany; age 3-17); ENNS (France; age 3-74); BIOAMBIENT.ES (Spain; age ≥16); CHMS I-II (Canada; age 3-79); NHANES (USA; age ≥6); KNHANES (South Korea; age ≥1); COPHES/DEMOCOPHES (Europe; age 6-45)
	Organophosphate pesticides & metabolites [3,5,6-trichloropyridinol, Acephate, Dimethoate, Malathion diacid, Methamidophos, Omethoate, Oxypyrimidine, Paranitrophenol, DEP, DMP, DETP, DMTP, DEDTP, DMDTP]	GerES IV-V (Germany; age 3-17); CHMS I-II (Canada; age 3-79); NHANES (USA; age ≥6)
	PAH metabolites (3-Hydroxybenzo(a)pyrene, 2-Hydroxyfluorene, 3-Hydroxyfluorene, 9-Hydroxyfluorene, 1-Hydroxyphenanthrene, 2-Hydroxyphenanthrene, 3-Hydroxyphenanthrene, 4-Hydroxyphenanthrene, 9-Hydroxyphenanthrene, 1-Hydroxypyrene, 1-Hydroxynaphthalene, 2-Hydroxynaphthalene)	GerES IV-V (Germany; age 3-17); FLEHS I (Flanders; age 0-65); BIOAMBIENT.ES (Spain; age ≥16); CHMS II (Canada; age 3-79); NHANES (USA; age ≥6)
	Perchlorate	NHANES (USA; age ≥6)
	Phenols (Benzophenone-3, Butyl paraben, Ethyl paraben, Methyl paraben, Propyl paraben, 4-tert-octylphenol, Triclosan)	GerES V (Germany; age 3-17); CHMS II (Canada; age 3-79); NHANES (USA; age ≥6)
	Phthalate metabolites (MBzP, MiBP, MnBP, MEP, MiNP, MCOP, MEHP, MEHHP/5OH-MEHP, MEOHP/5oxo-MEHP, MECPP/5cx-MEPP, MMP, MOP/MnOP, MCPP, MCHP, MCNP)	GerES V (Germany; age 3-17); CHMS II (Canada; age 3-79); NHANES (USA; age ≥6); COPHES/DEMOCOPHES (Europe; age 6-45)

Biological matrix	Validated biomarkers of exposure	HBM programme (region; age range)
	Pyrethroid pesticides & metabolites (cypermethrin, permethrin, cis-Cl_2CA, trans-Cl_2CA, F-PBA, Br_2CA, 3-PBA)	GerES IV-V (Germany; age 3-17); CHMS I-II (Canada; age 3-79); NHANES (USA; age ≥6)
Hair	**Metals** (total/methyl Hg)	ENNS (France; age 3-74); BIOAMBIENT.ES (Spain; age ≥16); COPHES/DEMOCOPHES (Europe; age 6-45)
Breast milk	**BFRs** (PBDE 47, 99, 100, 153, 154, 183, HBCDDs, TBBPA)	POPs in breast milk (China; mothers aged 18-35)
	Dioxins (1,2,3,4,6,7,8-HpCDD, 1,2,3,4,7,8-HxCDD, 1,2,3,6,7,8-HxCDD, 1,2,3,7,8,9-HxCDD, 1,2,3,4,6,7,8,9-OCDD, 1,2,3,7,8-PeCDD, 2,3,7,8-TCDD)	POPs in breast milk (China; mothers aged 18-35)
	Fluorocarbons (PFDeA/PFDA, PFHxS, PFNA, PFOS, PFOA, PFUA/PFUdA)	POPs in breast milk (China; mothers aged 18-35)
	Furans (1,2,3,4,6,7,8-HpCDF, 1,2,3,4,7,8,9-HpCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF, 1,2,3,7,8,9-HxCDF, 2,3,4,6,7,8-HxCDF, 1,2,3,4,6,7,8,9-OCDF, 1,2,3,7,8-PeCDF, 2,3,4,7,8-PeCDF, 2,3,7,8-TCDF)	POPs in breast milk (China; mothers aged 18-35)
	Organochlorine pesticides [Aldrin, Dieldrin, Endrin, Heptachlor, Heptachlor epoxide, DDT, DDE, Oxychlordane, trans-Nonachlor, HCB, α-HCH, β-HCH, γ-HCH, Mirex]	POPs in breast milk (China; mothers aged 18-35)
	PCBs (PCB 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, 189)	POPs in breast milk (China; mothers aged 18-35)

(a): including serum, plasma, and whole blood

C. SUBSTANCES WITH HEALTH-BASED GUIDANCE VALUES (HBGV) AND COVERAGE BY HBM GUIDANCE AND REFERENCE VALUES

Table 40 Substances with reference values (RVs) established by HBM programmes

Substance / family	Substance/ Biomarker	HBM Programmes with reference values
PFCs	PFDA	NHANES, CHMS, Tromsø
	PFDoA	NHANES
	PFHpA	NHANES, Tromsø
	PFHxS	NHANES, CHMS, Uppsala, Tromsø
	PFNA	NHANES, CHMS, Uppsala, Tromsø
	PFOA	GerES, FLEHS, NHANES, CHMS, Uppsala, Tromsø
	PFOS	GerES, FLEHS, NHANES, CHMS, Uppsala, Tromsø
	PFOSA	Uppsala, Tromsø
	Et-PFOSA-AcOH	NHANES
	Me-PFOSA-AcOH	NHANES
	PFUA	NHANES, CHMS, Uppsala, Tromsø
Dioxins	2,3,7,8-TCDD	NHANES, Uppsala
	1,2,3,7,8-PeCDD	NHANES, Uppsala
	1,2,3,6,7,8-HxCDD	NHANES, Uppsala
	1,2,3,4,6,7,8-HpCDD	NHANES
	1,2,3,4,6,7,8,9-OCDD	NHANES
Furans	2,3,4,7,8-PeCDF	NHANES, Uppsala
	1,2,3,4,7,8-HxCDF	NHANES
	1,2,3,6,7,8-HxCDF	NHANES
	1,2,3,4,6,7,8-HpCDF	NHANES

Substance / family	Substance/ Biomarker	HBM Programmes with reference values
PCBs	PCB28	ENNS, NHANES, CZ-HBM, Uppsala, Tromsø
	PCB44	NHANES
	PCB49	NHANES, Tromsø
	PCB52	ENNS, NHANES, CZ-HBM
	PCB66	NHANES
	PCB74	NHANES, CHMS
	PCB77	FLEHS
	PCB81	NHANES
	PCB87	NHANES
	PCB99	NHANES, CHMS, Tromsø
	PCB101	ENNS, NHANES, CZ-HBM, Tromsø
	PCB105	NHANES, CHMS, Uppsala, Tromsø
	PCB110	NHANES
	PCB118	NHANES, CHMS, CZ-HBM, Uppsala, Tromsø
	PCB123	Tromsø
	PCB126	NHANES, Uppsala
	PCB128	NHANES
	PCB138 & 158	GerES, FLEHS, ENNS, NHANES, CHMS, BIOAMBIENT.ES, CZ-HBM, Uppsala, Tromsø
	PCB146	NHANES, CHMS
	PCB149	NHANES
	PCB151	NHANES
	PCB153	GerES, FLEHS, ENNS, NHANES, CHMS, CZ-HBM, Uppsala, Tromsø
	PCB156	NHANES, CHMS, Uppsala, Tromsø

Substance / family	Substance/ Biomarker	HBM Programmes with reference values
	PCB157	NHANES, Tromsø
	PCB167	NHANES, CHMS, Uppsala, Tromsø
	PCB169	NHANES, Uppsala
	PCB170	NHANES, CHMS, CZ-HBM, Tromsø
	PCB172	NHANES
	PCB177	NHANES
	PCB178	NHANES, CHMS
	PCB180	GerES, FLEHS, ENNS, NHANES, CHMS, BIOAMBIENT.ES, CZ-HBM, Uppsala, Tromsø
	PCB183	NHANES, CHMS, Tromsø
	PCB187	NHANES, CHMS, Tromsø
	PCB189	NHANES, Tromsø
	PCB194	NHANES, CHMS, Tromsø
	PCB195	NHANES
	PCB196 & 203	NHANES, CHMS
	PCB199	NHANES
	PCB206	NHANES, CHMS
	PCB209	NHANES
Perchlorate	Perchlorate	NHANES
Metals and trace elements	Antimony (Sb)	GerES, ENNS, NHANES, CHMS, PROBE, Uppsala
	Arsenic (As)	GerES, ENNS, NHANES, CHMS, PROBE, Uppsala, KorSEP
	Barium (Ba)	NHANES, Uppsala
	Beryllium (Be)	NHANES, PROBE, Uppsala
	Cadmium (Cd)	GerES, FLEHS, ENNS, NHANES, CHMS, PROBE, CZ-HBM, Uppsala, KHNANES,

Substance / family	Substance/ Biomarker	HBM Programmes with reference values
		KorSEP
	Cesium (Cs)	NHANES, CHMS, Uppsala
	Chromium VI (Cr)	GerES, ENNS, PROBE, Uppsala
	Cobalt (Co)	ENNS, NHANES, CHMS, PROBE, Uppsala
	Copper (Cu)	FLEHS, NHANES, CHMS, Uppsala
	Fluoride (Fl)	CHMS
	Iridium (Ir)	PROBE
	Lead (Pb)	GerES, FLEHS, ENNS, NHANES, CHMS, PROBE, BIOAMBIENT.ES, CZ-HBM, Uppsala, KNHANES, KorSEP
	Manganese (Mn)	FLEHS, NHANES, CHMS, PROBE, Uppsala, KorSEP
	Mercury (Hg)	GerES, FLEHS, ENNS, NHANES, CHMS, PROBE, BIOAMBIENT.ES, CZ-HBM, Uppsala, KNHANES, KorSEP
	Molybdenum (Mo)	NHANES, CHMS, PROBE, Uppsala
	Nickel (Ni)	GerES, ENNS, CHMS, PROBE, Uppsala
	Palladium (Pd)	PROBE
	Platinum (Pt)	GerES, NHANES, PROBE
	Rhodium (Rh)	PROBE
	Selenium (Se)	GerES, NHANES, CHMS, Uppsala, Selenium (Finland)
	Silver (Ag)	CHMS, Uppsala
	Strontium (Sr)	NHANES, Uppsala
	Thallium (Tl)	GerES, FLEHS, NHANES, CHMS, PROBE
	Tin (Sn)	ENNS, NHANES, PROBE
	Tungsten (W)	NHANES, CHMS, PROBE
	Uranium (U)	GerES, ENNS, NHANES, CHMS, PROBE, Uppsala

Substance / family	Substance/ Biomarker	HBM Programmes with reference values
	Vanadium (V)	ENNS, CHMS, PROBE, Uppsala
	Zinc (Zn)	NHANES, CHMS, Uppsala
PAH metabolites	3-Hydroxyphenanthrene	GerES, NHANES, CHMS
	4-Hydroxyphenanthrene	GerES, NHANES, CHMS
	9-Hydroxyphenanthrene	GerES, CHMS
	1-Hydroxypyrene	GerES, FLEHS, NHANES, CHMS, KorSEP
	1-Hydroxynaphthalene	FLEHS, NHANES, CHMS
	2-Hydroxynaphthalene	FLEHS, NHANES, CHMS, KorSEP
PBDEs	PBDE 28	NHANES,
	PBDE 47	FLEHS, NHANES, CHMS, Uppsala
	PBDE 66	NHANES,
	PBDE 85	NHANES
	PBDE 99	NHANES, CHMS, Uppsala
	PBDE 100	NHANES, CHMS, Uppsala
	PBDE 153	FLEHS, NHANES, CHMS, Uppsala
	PBDE 154	NHANES
	BDE 209	NHANES
	PBB 153	NHANES
Phthalates metabolites	MBzP	GerES, FLEHS, NHANES, CHMS, KorSEP
	MiBP	GerES, NHANES, CHMS, KorSEP
	MnBP	GerES, FLEHS, NHANES, CHMS, KorSEP
	MCHP	CHMS
	MEP	NHANES, CHMS,

Substance / family	Substance/ Biomarker	HBM Programmes with reference values
	MEHP	FLEHS, NHANES, CHMS
	MEHHP; 5OH-MEHP	GerES, FLEHS, NHANES, CHMS, KorSEP
	MEOHP; 5oxo-MEHP	GerES, FLEHS, NHANES, CHMS, KorSEP
	MECPP; 5cx-MEPP	GerES, NHANES
	MCNP	NHANES
	MNP/MiNP	NHANES
	MCOP	NHANES
	MMP	NHANES, CHMS
	MCPP	NHANES, CHMS
	MHNCH	NHANES
Phenols	Benzophenone-3	NHANES
	Bisphenol A	FLEHS, NHANES, CHMS, Uppsala
	Butyl paraben	FLEHS, NHANES
	Ethyl paraben	FLEHS, NHANES
	Methyl paraben	FLEHS, NHANES
	Propyl paraben	FLEHS, NHANES
	4-tert-octylphenol	NHANES
	Triclosan	FLEHS, NHANES, CHMS
Herbicides	2,4-D	NHANES, CHMS
	2,4,5-T	NHANES
Organophosphate pesticides	Malathion diacid	NHANES
	Paranitrophenol	NHANES
	3,5,6-trichloropyridinol	NHANES

Substance / family	Substance/ Biomarker	HBM Programmes with reference values
	DEP	GerES, FLEHS, ENNS, NHANES, CHMS
	DMP	GerES, FLEHS, ENNS, NHANES, CHMS
	DETP	GerES, ENNS, NHANES, CHMS
	DMTP	GerES, FLEHS, ENNS, CHMS
	DEDTP	GerES, ENNS
	DMDTP	GerES, ENNS, NHANES, CHMS
Organochlorine pesticides	Dieldrin	NHANES
	Heptachlor epoxide	NHANES
	p,p'-DDT (4,4'-DDT)	ENNS, NHANES, CHMS, CZ-HBM, Tromsø
	o,p'-DDT (2,4′-DDT)	CZ-HBM
	p,p'-DDE (4,4'-DDE)	GerES, FLEHS, ENNS, NHANES, CHMS, CZ-HBM, Tromsø
	Oxychlordane	NHANES, CHMS, Tromsø
	trans-Nonachlor	NHANES, CHMS, Tromsø
	HCB	GerES, FLEHS, ENNS, NHANES, CHMS, CZ-HBM, Tromsø
	α-HCH	GerES, ENNS, CZ-HBM
	β-HCH	GerES, ENNS, NHANES, CHMS, CZ-HBM, Tromsø
	γ-HCH	CZ-HBM
	Mirex	NHANES, CHMS, Tromsø
Chlorophenols	2-MCP	GerES
	4-MCP	GerES, ENNS
	2,4-DCP	GerES, ENNS, NHANES, CHMS
	2,5-DCP	GerES, FLEHS, CHMS
	2,6-DCP	GerES, ENNS

Substance / family	Substance/ Biomarker	HBM Programmes with reference values
	2,3,4-TCP	GerES
	2,4,5-TCP	GerES, ENNS, NHANES
	2,4,6-TCP	GerES, ENNS
	2,3,4,6-TeCP	GerES
	PCP	GerES, ENNS, NHANES, CHMS
Pyrethroids	F-PBA	FLEHS, ENNS, NHANES, CHMS
	Br_2CA	ENNS, NHANES, CHMS
	cis-Cl_2CA	GerES, ENNS, CHMS
	trans-Cl_2CA	GerES, ENNS, CHMS
	3-PBA	GerES, FLEHS, ENNS, NHANES, CHMS

Table 41 Reported HBGVs (e.g. TDIs, RfDs) by EFSA, the WHO, and US EPA for the substances covered in this report

Substance class	Substance/ Biomarker	EFSA		WHO		US EPA
		Value	Unit	Value	Unit	RfD
3-Monochloropropane-1,2 Diol Ester (3-MCPD)	3-MCPD	2 µg/kg bw	TDI	2 µg/kg bw per day	PMTDI	
Acrylamide + metabolite	Acrylamide					0.002 mg/kg bw per day
	Glycidamide					$4x10^{-4}$ mg/kg bw per day
Alkaloids	Ergot	1. 0.6 µg/kg bw per day 2. 1 µg/kg bw	1. Group TDI 2. Acute RfD			
Chlorophenols	2,3,4,6-TeCP					0.03 mg/kg bw per day
	PCP					0.005 mg/kg bw per day
	2,4,5-TCP					0.1 mg/kg bw per day
	2,4-DCP					0.003 mg/kg bw per day
Dioxins	1,2,3,4,6,7,8-HpCDD			70 pg/kg bw per month	PTMI (applied to intake of PCDDs, PCDFs and coplanar PCBs)	
	1,2,3,4,7,8-HxCDD					
	1,2,3,6,7,8-HxCDD					
	1,2,3,7,8,9-HxCDD					
	1,2,3,4,6,7,8,9-OCDD					
	1,2,3,7,8-PeCDD					
	2,3,7,8-TCDD					$7x10^{-10}$ mg/kg bw per day
Fluorocarbons (PFCs)	PFOA	1.5 µg/kg bw	TDI			
	PFOS	150 ng/kg bw	TDI			
Furans	1,2,3,4,6,7,8-HpCDF			70 pg/kg bw per month	PTMI (applied to intake of PCDDs,	
	1,2,3,4,7,8,9-HpCDF					
	1,2,3,4,7,8-HxCDF					

Substance class	Substance/ Biomarker	EFSA Value	EFSA Unit	WHO Value	WHO Unit	US EPA RfD
	1,2,3,6,7,8-HxCDF				PCDFs and coplanar PCBs)	
	1,2,3,7,8,9-HxCDF					
	2,3,4,6,7,8-HxCDF					
	1,2,3,4,6,7,8,9-OCDF					
	1,2,3,7,8-PeCDF					
	2,3,4,7,8-PeCDF					
	2,3,7,8-TCDF					
Herbicides	2,4-D					0.01 mg/kg bw per day
	2,4,5-T					0.01 mg/kg bw per day
Metals	Antimony (Sb)					$4x10^{-4}$ mg/kg bw per day
	Arsenic (As)	0.3-8 µg/kg bw-day	$BMDL_{01}$ for inorganic As			$3x10^{-4}$ mg/kg bw per day (inorganic As)
	Barium (Ba)					0.2 mg/kg bw per day
	Beryllium (Be)					0.002 mg/kg bw per day
	Cadmium (Cd)	2.5 µg/kg bw	TWI	25 µg/kg bw per month	PTMI	$5x10^{-4}$ mg/kg bw per day (water) 0.001 mg/kg bw per day (food)
	Chromium VI (Cr)					$3x10^{-3}$ mg/kg bw per day
	Copper (Cu)			0.5 mg/kg bw per day	PMTDI	
	Fluoride (Fl)					0.06 mg/kg bw per day
	Manganese (Mn)					0.14 mg/kg bw per day

Substance class	Substance/ Biomarker	EFSA Value	EFSA Unit	WHO Value	WHO Unit	US EPA RfD
	Mercury (Hg)	1.3 µg/kg bw	TWI for MeHg	1. 4 µg/kg bw 2. 1.6 µg/kg bw	1. PTWI for total Hg 2. PTWI for MeHg	$1x10^{-4}$ mg/kg bw per day (for MeHg)
	Mercury, Inorganic	4 µg/kg bw	TWI			
	Molybdenum (Mo)					0.005 mg/kg bw per day
	Nickel (Ni)					0.02 mg/kg bw per day
	Selenium (Se)					0.005 mg/kg bw per day
	Strontium (Sr)					0.6 mg/kg bw per day
	Tin (Sn)			14 mg/kg bw per day	PTWI	
	Uranium (U)			0.6 µg/kg bw	TDI	
	Zinc (Zn)			0.3-1 mg/kg bw per day	PMTDI	0.3 mg/kg bw per day
Mineral oil hydrocarbons (MOH)	MOHs	1. 12 mg/kg bw 2. 10 mg/kg bw 3. 0.01 mg/kg bw	1. ADI for MOHs (high viscosity) 2. ADI for MOHs (med-low viscosity - Class I) 3. ADI for MOHs (med-low viscosity - Class II+III)	0-20 mg/kg bw	ADI for MOHs (high viscosity)	
Mycotoxins	ochratoxin A	120 ng/kg bw	TWI	112 ng/kg bw per week	PTWI	
	patulin			0.4 µg/kg bw	PMTDI	
	Deoxynivalenol			1. 1 µg/kg bw-day 2. 8 µg/kg bw	1. PMTDI 2. ARfD	

Substance class	Substance/ Biomarker	EFSA Value	EFSA Unit	WHO Value	WHO Unit	US EPA RfD
	Zearalenone	0.25 µg/kg bw-day	TDI	0.5 µg/kg bw per day	PMTDI	
	Fumonisin B1 or B2			2 µg/kg bw-day	PMTDI	
	T-2 toxin	100 ng/kg bw	TDI for the sum of T-2 and HT-2	60 ng/kg bw per day	PMTDI for the sum of T-2 and HT-2	
	HT-2 toxin					
Organophosphate pesticides	Acephate					0.004 mg/kg bw per day
	Malathion diacid					0.02 mg/kg bw per day
Organochlorine pesticides	Aldrin					$3x10^{-5}$ mg/kg bw per day
	Dieldrin					$5x10^{-5}$ mg/kg bw per day
	Endrin					$3x10^{-4}$ mg/kg bw per day
	Heptachlor					$5x10^{-4}$ mg/kg bw per day
	Heptachlor epoxide					$1.3x10^{-5}$ mg/kg bw per day
	DDT			0.01 mg/kg bw per day	PTDI for DDT	$5x10^{-4}$ mg/kg bw per day
	HCB					$8x10^{-4}$ mg/kg bw per day
	Mirex					$2x10^{-4}$ mg/kg bw per day
PBDEs	PBDE 47					$1x10^{-4}$ mg/kg bw per day
	PBDE 85					0.002 mg/kg bw per day
	PBDE 99					$1x10^{-4}$ mg/kg bw per day
	PBDE 100					0.002 mg/kg bw per day
	PBDE 119					0.002 mg/kg bw per day
	PBDE 126					0.002 mg/kg bw per day
	PBDE 153					$2x10^{-4}$ mg/kg bw per day
	BDE 209					$7x10^{-3}$ mg/kg bw per day
	HBB					0.002 mg/kg bw per day

Substance class	Substance/ Biomarker	EFSA Value	EFSA Unit	WHO Value	WHO Unit	US EPA RfD
PCBs	PCB 77	14 pg WHO-TEQ/kg bw	TWI	70 pg/kg bw per month	PTMI (applied to intake of PCDDs, PCDFs and coplanar PCBs)	
	PCB 81					
	PCB 126					
	PCB 169					
	PCB 105					
	PCB 114					
	PCB 118					
	PCB 123					
	PCB 156					
	PCB 157					
	PCB 167					
	PCB 189					
Perchlorate	Perchlorate	0.3 µg/kg bw	TDI	0.01 mg/kg bw	PMTDI	$7x10^{-4}$ mg/kg bw per day
Phenols	Bisphenol A	5 µg/kg bw/day	TDI			0.05 mg/kg bw per day
Phthalates metabolites	Mono-benzyl phthalate (MBzP)	0.5 mg/kg bw	TDI for benzylbutyl phthalate (BBzP)			0.2 mg/kg bw per day
	Mono-isobutyl phthalate (MiBP)	0.01 mg/kg bw	TDI for dibutyl phthalate (DBP)			0.1 mg/kg bw per day
	Mono-n-butyl phthalate (MnBP)					
	Mono-ethyl phthalate (MEP)					0.8 mg/kg bw per day
	Mono-2-ethylhexyl phthalate (MEHP)	0.05 mg/kg bw	TDI for bis(2-ethylhexyl)phthalate			0.02 mg/kg bw per day

Substance class	Substance/ Biomarker	EFSA Value	EFSA Unit	WHO Value	WHO Unit	US EPA RfD
	Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP; 5OH-MEHP)		(DEHP)			
	Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP; 5oxo-MEHP)					
	Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP; 5cx-MEPP)					
	Mono-(carboxynonyl) phthalate (MCNP)	0.15 mg/kg bw	TDI for di-isodecyl phthalate (DIDP)			
	Mono-isononyl phthalate (MNP/MiNP)	0.15 mg/kg bw	TDI for di-isononyl phthalate (DiNP)			
Pyrethroids	Bifenthrin					0.015 mg/kg bw per day
	Cyfluthrin			0-0.02 mg/kg bw	ADI for cyfluthrin	
	Cyhalothrin			0-0.005 mg/kg bw	ADI for cyhalothrin	0.005 mg/kg bw per day
	Cypermethrin			0-0.02 mg/kg bw	ADI for cypermethrin	0.01 mg/kg bw per day
	Deltamethrin			0-0.01 mg/kg bw	ADI	
	Permethrin					0.05 mg/kg bw per day
regulated chemical substances such as food contact materials	Smoke flavourings	0.5 mg/kg bw	TDI for phenol			
	BADGE	0.15 mg/kg bw	TDI			
	Sweeteners			Covered[(a)]		
	Enzymes			Covered[(a)]		

Table 42 Pesticides with EU limit values (Pesticides Database) not covered by HBM reference values

Substance/ Biomarker	ADI [mg/kg bw]	Substance/Biomarker	ADI [mg/kg bw]
(Hydr)oxyquinoline	0.05	Fluxapyroxad	0.02
Abamectin (aka avermectin)	0-0.002	Formetanate	0.004
Aclonifen	0.07	Fuberidazole	0.0072
Amitrole (aminotriazole)	0.001	Haloxyfop-P (Haloxyfop-R)	0.00065
Azimsulfuron	0.1	Imazamox	9
Benfluralin	0.005	Imazaquin	0.25
Bifenox	0.3	Imazosulfuron	0.75
Bitertanol	0.003	Ioxynil	0.005
Carbendazim	0.02	Linuron	0.003
Carfentrazone-ethyl	0.03	Lufenuron	0.015
Chloridazon (aka pyrazone)	0.1	Metam	0.001
Chlorothalonil	0.015	Methiocarb (aka mercaptodimethur)	0.013
Chlorotoluron	0.04	Methomyl	0.0025
Cyprodinil	0.03	Methoxyfenozide	0.1
Diclofop	0,001	Metribuzin	0.013
Difenacoum	N/A	Metsulfuron-methyl	0.22
Diflufenican	0.2	Molinate	0.008
Dimethachlor	0.1	Napropamide	0.3
Dimethenamid-P	0.02	Oxadiazon	0.0036
Dimethoate	0.001	Oxyfluorfen	0.003
Dimoxystrobin	0.004	Paclobutrazol	0.022
Diquat (dibromide)	0.002	Pencycuron	0.2
Diuron	0.007	Pendimethalin	0.125
Ethofumesate	0.07	Pirimicarb	0.035
Ethoprophos	0.0004	Prochloraz	0.01
Famoxadone	0.012	Prosulfocarb	0.005
Fenamiphos (aka phenamiphos)	0.0008	Pyraclostrobin	0.03
Fenbutatin oxide	0.05	Quinoclamine	0.002
Fenpropimorph	0.003	Quinoxyfen	0.2
Fipronil	0.0002	Quizalofop-P-tefuryl	0.013
Flufenacet	0.005	Spirodiclofen	0.015
Flumioxazine	0.009	Sulcotrione	0.0004
Fluometuron	0.0005	Tebufenpyrad	0.01

Substance/ Biomarker	ADI [mg/kg bw]
Terbuthylazine	0.004
Tralkoxydim	0.005
Triazoxide	0.0002
Trifloxystrobin	0.1
Bromuconazole	0,01
Cyproconazole	0.02
Epoxiconazole	0.008
Fenbuconazole	0.006
Fluquinconazole	0.002
Flusilazole	0.002
Metconazole	0.01
Myclobutanil	0.025
Propiconazole	0.04
Acrinathrin	0,01
Bifenthrin	0,015
Cyfluthrin	0.003
Cyhalothrin	0-0.02
Cypermethrin	0.05
Esfenvalerate	0.02
Permethrin	0-0.05
Tefluthrin	0.005
Imidacloprid	0.06

Table 43 Summary of the published human biomonitoring (HBM) and biological equivalent (BE) values

	HBM values			Biological equivalents		
Chemical name	**Reference population**	**HBM-I**	**HBM-II**	**BE_{RfD}**	**BE_{POD}**	**Basis for BEs**
2,3,7,8- TCDD				15 ng TEQ/kg lipid (serum)	45 ng/kg lipid	MRL (ATSDR)
PCBs 138+153+180	Infants and women of childbearing age	3.5 µg/L (serum)	7 µg/L			
Acrylamide				8 fmol/mg globin (blood; AAVal) 13 µg/L (urine; AAMA)	25.3 fmol/mg globin (blood) 130 µg/L (urine)	
Glycidamide				13 fmol/mg globin (blood; GAVal)	39.8 fmol/mg globin	
Arsenic (total)				6.4 µg/L (urine)	19.3 µg/L	RfD (US EPA) & chronic MRL (ATSDR)
Cadmium	1. Children and adolescents 2. Adults	1. 0.5 µg/L 2. 1 µg/L (urine)	1. 2 µg/L 2. 4 µg/L	1.5 µg/L (urine) 1.7 µg/L (blood)	4.6 µg/L (urine) 5.3 µg/L (blood)	RfD (US EPA)
Mercury	Children and adults	7 µg/L (urine) 5 µg/L (blood)	25 µg/L (urine) 15 µg/L (blood)			
Selenium				400 µg/L (blood) 180 µg/L (plasma) 90 µg/L (urine)	1200 µg/L (blood) 540 µg/L	RfD (US EPA) & chronic MRL

	HBM values			Biological equivalents		
Chemical name	**Reference population**	**HBM-I**	**HBM-II**	**BE_{RfD}**	**BE_{POD}**	**Basis for BEs**
					(plasma) 280 µg/L (urine)	(ATSDR)
Thallium	General population	5 µg/L (urine)	N/A			
PBDE 99				520 ng/g lipid (blood)	51.6 mg/kg lipid	RfD (US EPA)
Mono-benzyl phthalate (MBzP)				3.8 mg/L (urine)	38 mg/L	RfD (US EPA)
Mono-n-butyl phthalate (MnBP)				2.7 mg/L (urine)	27 mg/L	RfD (US EPA)
Mono-ethyl phthalate (MEP)				18 mg/L (urine)	180 mg/L	RfD (US EPA)
Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP; 5cx-MEPP)				400 µg/L (urine; sum of MEHP + MEHHP + MEOHP + 5cx-MEPP)	4000 µg/L	RfD (US EPA)
Mono-isononyl phthalate (MNP/MiNP)				72 µg/L (urine)	720 µg/L	ADI (US CPSC)
Metabolites of di(2-ethylhexyl)phthalate (DEHP)	1. Children (age 6-13) 2. Women of childbearing age 3. Men (age >14) and rest of the general population	1. 500 µg/L 2. 300 µg/L 3. 750 µg/L (urine)	N/A	260 µg/L (urine; sum of MEHP + MEHHP + MEOHP)	2600 µg/L	RfD (US EPA)

	HBM values			Biological equivalents		
Chemical name	**Reference population**	**HBM-I**	**HBM-II**	**BE_{RfD}**	**BE_{POD}**	**Basis for BEs**
	(sum of MEHHP + MEOHP)					
Metabolites of di(2-propylheptyl)phthalate (DPHP)	1. Children 2. Adults	1. 1163 µg/L 2. 1744 µg/L (urine)				
Diisononylcyclohex-anoate (DINCH)	1. Children 2. Adults	1. 3200 µg/L 2. 4800 µg/L (urine)				
Bisphenol A	1. Children 2. Adults	1. 1.5 mg/L 2. 2.5 mg/L (urine)	N/A	2 mg/L (urine)	20 mg/L	RfD (US EPA)
Triclosan				6.4 mg/L (urine)	64 mg/L	RfD (US EPA)
2,4-dichlorophenoxyacetic acid (2,4-D)				5 µg/L (plasma) 200 µg/L (urine)	170 µg/L (plasma) 20,000 µg/L (urine)	
DDT				4 mg/kg lipid (total DDT)	14 mg/kg lipid	RfD (US EPA)
DDT+DDE+DDD				5 mg/kg lipid	16 mg/kg lipid	RfD (US EPA)
Hexachlorobenzene (HCB)				340 ng/g lipid	3384 ng/g lipid	RfD (US EPA)
Pentachlorophenol (PCP)	General population	40 µg/L (serum) 25 µg/L (urine)	70 µg/L (serum) 40 µg/L (urine)			

	HBM values			Biological equivalents		
Chemical name	**Reference population**	**HBM-I**	**HBM-II**	**BE_{RfD}**	**BE_{POD}**	**Basis for BEs**
4-Fluoro-3-phenoxybenzoic acid (F-PBA)				240 µg/L (urine)	2400 µg/L	chronic RfD (US EPA)
cis-3-(2,2-dibromo-vinyl)-2,2-dimethylcyclo-propane carboxylic acid (Br_2CA)				50 µg/L (adults) 7 µg/L (infants & children) (urine)	540 µg/L (adults) 720 µg/L (infants & children)	RfD (US EPA)

D. REFERENCE VALUES

This appendix provides an overview of the substances with 3 or more reported reference values (RV). RV in this report is defined as the 95th percentile (P95; unless stated otherwise).

Table 44 Perfluorooctanoic acid (PFOA)

Country	Reference values (matrix)	95% CI	Study population	Study period	Reference
Germany	**10 µg/L (plasma)**	N/A	Women, men, and children aged <10 years	2003-2007	(Schulz et al., 2012b)
Flanders	**1.2.56 µg/L (plasma)** **2. 5.70 µg/L (serum)**	1. 2.35-2.76 2. 5.10-6.20	1. Newborns 2. Adults	2007-2009	FLEHS II [(a)]
USA	**7.50 µg/L (serum)**	6.20-9.70	Males and females (age 12 or older)	2009-2010	NHANES (Fourth report) [(b)]
Canada	**5.30 µg/L (plasma)**	3.90-6.70	Canadian population (age 12-79)	2009-2011	CHMS II (Second Report) [(c)]
Sweden	**3.8 ng/mL (serum)** [(d)]	2.4-5.3 [(e)]	Primiparous Swedish women	2004	(Karrman et al., 2007)
Norway	**3.2 ng/mL (serum)** [(d)]	1.3-6.8 [(e)]	Norwegian adult males	2007	(Nøst et al., 2014)

(a): All FLEHS II results were retrieved from http://www.milieu-en-gezondheid.be/resultaten/referentiebiomonitoring/Eindrapport_referentiewaarden_finaal_met_voorblad.pdf
(b): All NHANES results were retrieved from http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Jul2014.pdf
(c): All CHMS II results were retrieved from http://www.occupationalcancer.ca/wp-content/uploads/2013/05/2ndHumanBiomonitoringReport.pdf
(d): The mean value is reported here as the P95 value is not reported in this study.
(e): The range value (min-max) is reported here.

Table 45 Perfluorooctane sulfonic acid (PFOS)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1. 20 µg/L (plasma)** **2. 25 µg/L (plasma)** **3. 10 µg/L (plasma)**	N/A	1. Women 2. Men 3. Children <10 years	2003-2007	(Schulz et al., 2012b)
Flanders	**1. 5.10 µg/L (plasma)** **2. 24.80 µg/L (serum)**	1. 4.59-5.61 2. 20.70-28.90	1. Newborns 2. Adults	2007-2009	FLEHS II
USA	**32.0 µg/L (serum)**	22.6-48.5	Males and females (age 12 or older)	2009-2010	NHANES (Fourth report)
Canada	**18 µg/L (plasma)**	13-23	Canadian population (age 12-79)	2009-2011	CHMS II (Second Report)
Sweden	**20.7 ng/mL (serum)** [(a)] **0.201 ng/mL (milk)** [(a)]	8.2-48 (serum) [(b)] 0.060-0.47 (milk) [(b)]	Primiparous Swedish women	2004	(Karrman et al., 2007)
Norway	**33 ng/mL (serum)** [(a)]	11-65 [(b)]	Norwegian adult males	2007	(Nøst et al., 2014)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

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Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**<0.1 µg/L (whole blood)**	N/A	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
France	**5.70 ng/g lipid (serum)**	5.10-7.40	French adults (age 18-74)	2006-2007	ENNS report (pollutants) [(a)]
Spain	**Could not be calculated (serum)**	N/A	Adults (age 16 or older)	March 2009 – July 2010	(Huetos Hidalgo et al., 2013)
USA	**11.30 ng/g lipid (serum)**	10.7-11.8	Males and females (age 12 or older)	2003-2004	NHANES (Fourth report)
Canada	**Could not be calculated (plasma)**	<LOD	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report) [(b)]
Czech Rep	**35 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Sweden	**2.8 ng/g lipid (serum)** [(c)]	<0.50-31 [(d)]	Swedish mothers	1996-2006	(Lignell et al., 2009)
Norway	**2.7 ng/g lipid (serum)** [(c)]	1.3-6.1 [(d)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): All results from ENNS analyses of pollutants were retrieved from http://www.invs.sante.fr/content/download/63890/250887/version/2/file/rapport_enns_tome_2.pdf
(b): All CHMS I results were retrieved from http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/chms-ecms/report-rapport-eng.pdf
(c): The mean value is reported here as the P95 value is not reported in this study.
(d): The range value (min-max) is reported here.

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Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**<0.1 µg/L (whole blood)**	N/A	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
France	**1.76 ng/g lipid (serum)**	1.40-1.88	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
Spain	**Could not be calculated (serum)**	N/A	Adults (age 16 or older)	March 2009 – July 2010	(Huetos Hidalgo et al., 2013)
USA	**7.60 ng/g lipid (serum)**	7.01-8.00	Males and females (age 12 or older)	2003-2004	NHANES (Fourth report)
Canada	**Could not be calculated (plasma)**	<LOD	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Rep	**138.7 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Norway	**Could not be calculated (serum)**	N/A	Norwegian adult males	2007	(Nøst et al., 2013)

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Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**<0.1 µg/L (whole blood)**	N/A	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
France	**3.66 ng/g lipid (serum)**	3.23-4.16	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
Spain	**Could not be calculated (serum)**	N/A	Adults (age 16 or older)	March 2009 – July 2010	(Huetos Hidalgo et al., 2013)
USA	**5.83 ng/g lipid (serum)**	5.29-6.66	Males and females (age 12 or older)	2003-2004	NHANES (Fourth report)
Canada	**Could not be calculated (plasma)**	<LOD	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Rep	**15 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Norway	**2.7 ng/g lipid (serum)** [(a)]	1.2-7.7 [(b)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 49 PCB 138

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.3 µg/L (whole blood)**	0.28-0.32	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	0.4-2.2 µg/L (whole blood)	N/A	Adults (age 18-69)	1997-1999	(Schulz et al., 2012b)
Flanders	**1. 112 ng/g fat (plasma)** [(a)] **2. 98 ng/g fat (plasma)** [(a)]	1. 98-126 2. 83-115	1. Newborns 2. Adolescents (age 14-15)	2002-2006	FLEHS I [(b)]
France	**139.9 ng/g lipid (serum)**	163.0-225.0	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
Spain	**135.4 ng/g lipid (serum)** [(a, c)]	121.3-151.4 [(d)]	Adults (age 16 or older)	March 2009 – July 2010	(Huetos Hidalgo et al., 2013)
USA	**75.3 ng/g lipid (serum)**	69.0-81.8	Males and females (age 12 or older)	2003-2004	NHANES (Fourth report)
Canada	**0.28 µg/L (plasma)**	0.23-32	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Rep	**347 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Sweden	**29 ng/g lipid (serum)** [(e)]	7.8-94 [(f)]	Swedish mothers	1996-2006	(Lignell et al., 2009)
Norway	**140 ng/g lipid (serum)** [(e)]	45-310 [(f)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): This value is the sum of the marker PCBs (PCB 138, 153, and 180).
(b): All FLEHS I results were retrieved from http://www.milieu-en-gezondheid.be/English/results.html
(c): The geometric mean is reported here as the P95 value is not reported in this study.
(d): The 95% CI for the geometric mean is reported here.
(e): The mean value is reported here as the P95 value is not reported in this study.
(f): The range value (min-max) is reported here.

Table 50 PCB 153

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.40 µg/L (whole blood)**	0.40-0.45	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	0.60-3.30 µg/L (whole blood)	N/A	Adults (age 18-69)	1997-1999	(Schulz et al., 2012b)
Flanders	**1. 112 ng/g fat (plasma)** [(a)] **2. 98 ng/g fat (plasma)** [(a)]	1. 98-126 2. 83-115	1. Newborns 2. Adolescents (age 14-15)	2002-2006	FLEHS I
France	**286.9 ng/g lipid (serum)**	263.9-369.3	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
Spain	**135.4 ng/g lipid (serum)** [(a, b)]	121.3-151.4 [(c)]	Adults (age 16 or older)	March 2009 – July 2010	(Huetos Hidalgo et al., 2013)
USA	**97.1 ng/g lipid (serum)**	88.8-111	Males and females (age 12 or older)	2003-2004	NHANES (Fourth report)
Canada	**0.54 µg/L (plasma)**	0.42-0.66	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Rep	**498 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Sweden	**58 ng/g lipid (serum)** [(d)]	12-186 [(e)]	Swedish mothers	1996-2006	(Lignell et al., 2009)
Norway	**200 ng/g lipid (serum)** [(d)]	67-470 [(e)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): This value is the sum of the marker PCBs (PCB 138, 153, and 180).
(b): The geometric mean is reported here as the P95 value is not reported in this study.
(c): The 95% CI for the geometric mean is reported here.
(d): The mean value is reported here as the P95 value is not reported in this study.
(e): The range value (min-max) is reported here.

Table 51 PCB 180

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.3 µg/L (whole blood)**	0.27-0.32	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	0.3-2.4 µg/L (whole blood)	N/A	Adults (age 18-69)	1997-1999	(Schulz et al., 2012b)
Flanders	**1. 112 ng/g fat (plasma)** [(a)] **2. 98 ng/g fat (plasma)** [(a)]	1. 98-126 2. 83-115	1. Newborns 2. Adolescents (age 14-15)	2002-2006	FLEHS I
France	**274.4 ng/g lipid (serum)**	225.0-296.4	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
Spain	**135.4 ng/g lipid (serum)** [(a, b)]	121.3-151.4 [(c)]	Adults (age 16 or older)	March 2009 – July 2010	(Huetos Hidalgo et al., 2013)
USA	**81.5 ng/g lipid (serum)**	75.8-89.9	Males and females (age 12 or older)	2003-2004	NHANES (Fourth report)
Canada	**0.49 µg/L (plasma)**	0.38-0.60	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Rep	**388.5 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Sweden	**28 ng/g lipid (serum)** [(d)]	5.0-84 [(e)]	Swedish mothers	1996-2006	(Lignell et al., 2009)
Norway	**150 ng/g lipid (serum)** [(d)]	66-370 [(e)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): This value is the sum of the marker PCBs (PCB 138, 153, and 180).
(b): The geometric mean is reported here as the P95 value is not reported in this study.
(c): The 95% CI for the geometric mean is reported here.
(d): The mean value is reported here as the P95 value is not reported in this study.
(e): The range value (min-max) is reported here.

Table 52 Antimony (Sb)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.300 µg/L (urine)**	0.305-0.335	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
France	**0.320 µg/L (urine)**	0.290-0.340	French adults (age 18-74)	2006-2007	ENNS report (metals) [(a)]
Italy	**0.720 µg/L (blood)** **0.265 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report [(b)]
USA	**0.184 µg/L (urine)**	0.169-0.222	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.19 µg/L (urine)**	0.16-0.22	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
Sweden	**0.042 µg/L (breast milk)** [(c)]	0.018-0.15 [(d)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): All results from ENNS analyses of metals were retrieved from http://www.invs.sante.fr/publications/2011/exposition_polluants_enns/rapport_exposition_polluants_enns.pdf
(b): All PROBE results were retrieved from http://www.iss.it/binary/publ/cont/11_9_web.pdf
(c): The mean value is reported here as the P95 value is not reported in this study.
(d): The range value (min-max) is reported here.

Table 53 Arsenic (As)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**15 µg/L (urine)**	12.8-14.3	Children without fish consumption 48h prior to sample collection (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	15 µg/L (urine)	14.9-16.3	Adults without fish consumption 48h prior to sample collection (age 18-69)	GerES III (1997-1999)	(Wilhelm et al., 2004)
Flanders	**1. 2.18 µg/L (cord blood)** **2. 2.04 µg/L (maternal blood)** **3. 2.12 µg/L (whole blood)** **90.0 µg/L (urine)** **4. 85.3 ng/L (urine)**	1. 1.53-2.83 2. 1.38-2.69 3. 1.52-2.71 (blood) 60.7-119.4 (urine) 4. 61.7-108.8	1. Newborns 2. Mothers of newborns 3. Adolescents (age 14-15) 4. Adults	2007-2009	FLEHS II
France	**72.75 µg/L (urine)**	63.74-76.49	French adults (age 18-74)	2006-2007	ENNS report (metals)
Italy	**5.32 µg/L (blood)** **3.12 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**52.4 µg/L (urine)**	42.5-66.3	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**1. 4.08 µg/L (blood)** **2. 76 µg/L (urine)**	1. 2.94-5.23 (blood) 2. 58-94 (urine)	1. Canadian population (age 6-79) 2. Canadian population (age 3-79)	1. 2007-2009 2. 2009-2011	1. CHMS I (First Report) 2. CHMS II (Second Report)
South Korea	**119.7 µg/L (urine)**	112.7-126.8	Adults (age 20 or older)	2008	(Lee et al., 2012)
Sweden	**0.55 µg/L (breast milk)** [(a)]	0.041-4.6 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 54 Cadmium (Cd)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.2 µg/L (urine)** **<0.3 µg/L (blood)**	0.20-0.22 (urine) 0.25-0.29 (blood)	Non-smoking children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	0.8 µg/L (urine) **1 µg/L (blood)**	0.74-0.80 (urine) 0.83-0.90 (blood)	Non-smoking adults (age 18-69)	GerES III (1997-1999)	(Wilhelm et al., 2004)
Flanders	**1. 0.160 µg/L (cord blood)** **2. 0.728 µg/L (maternal blood)** **3. 0.471 µg/L (whole blood)** **4. 444 ng/L (urine)**	1. 0.095-0.226 2. 0.592-0.864 3. 0.333-0.609 4. 363-525	1. Newborns 2. Mothers of newborns 3. Adolescents (age 14-15) 4. Adults	2007-2009	FLEHS II
France	**0.95 µg/L (urine)**	0.91-0.99	French adults (age 18-74)	2006-2007	ENNS report (metals)
Italy	**1.42 µg/L (blood)** **0.269 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**1. 1.50 µg/L (blood)** **2. 0.873 µg/L (urine)**	1. 1.30-1.70 2. 0.807-1.02	1. Males and females (age 1 or older) 2. Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**2.6 µg/L (blood)** **1.8 µg/L (urine)**	2.1-3.0 (blood) 1.6-2.0 (urine)	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**2.62 µg/L (blood)**	N/A	Adults (age 18 or older)	August 2007 - April 2008	(Son et al., 2009)
	3.11 µg/L (urine)	2.58-3.43	Adults (age 20 or older)	2008	(Lee et al., 2012)
Czech Republic	**1.0 µg/L (blood)** [(a)] **1.3 µg/L (urine)** [(a)]	N/A	Non-smoking adults	2005-2009	(Cerna et al., 2012)
Sweden	**0.086 µg/L (breast milk)** [(b)]	0.028-0.27 [(c)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The reference value (which is not defined as the P95) is directly provided in the literature source.
(b): The mean value is reported here as the P95 value is not reported in this study.
(c): The range value (min-max) is reported here.

Table 55 Chromium (Cr)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.62 µg/L (urine)**	N/A	Adults (age 25-69)	1990-1992	(Seifert et al., 2000)
France	**0.65 µg/L (urine)**	0.61-0.68	French adults (age 18-74)	2006-2007	ENNS report (metals)
Italy	**1.09 µg/L (blood)** **0.294 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
Sweden	**0.30 µg/L (breast milk)** [(a)]	0.026-1.6 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 56 Cobalt (Co)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
France	**1.40 µg/L (urine)**	1.25-1.66	French adults (age 18-74)	2006-2007	ENNS report (metals)
Italy	**0.443 µg/L (blood)** **0.607 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**1.30 µg/L (urine)**	1.10-1.49	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.40 µg/L (urine)**	0.36-0.43	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
Sweden	**0.059 µg/L (breast milk)** [(a)]	0.022-0.38 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 57 Copper (Cu)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**1. 754 µg/L (cord blood)** **2. 1715 µg/L (maternal blood)** **3. 938 µg/L (whole blood)**	1. 711-797 2. 1631-1799 3. 908-967	1. Newborns 2. Mother of newborns 3. Adolescents (age 14-15)	2007-2009	FLEHS II
USA	**169 µg/dL (serum)**	162-180	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**1200 µg/L (blood)** **28 µg/L (urine)**	1200-1300 (blood) 27-29 (urine)	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
Sweden	**471 µg/L (breast milk)** [(a)]	327-670 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 58 Lead (Pb)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**35 µg/L (whole blood)**	35.0-37.7	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	70 µg/L (blood; female) **90 µg/L (blood; male)**	63-67 (female) 78-83 (male)	Adults (age 18-69)	GerES III (1997-1999)	(Wilhelm et al., 2004)
Flanders	**1. 15.9 µg/L (cord blood)** **2. 18.9 µg/L (maternal blood)** **3. 27.6 µg/L (whole blood)**	1: 13.9-17.9 2. 17.1-20.7 3. 23.1-32.1	1. Newborns 2. Mothers of newborns 3. Adolescents (age 14-15)	2007-2009	FLEHS II
France	**73 µg/L (blood)**	68-77	French adults (age 18-74)	2006-2007	ENNS report (metals)
Spain	**56.80 µg/L (blood)**	N/A	Adults (age 16 or older)	March 2009 – July 2010	(Cañas et al., 2014)
Italy	**51.7 µg/L (blood)** **0.60 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**1. 3.16 µg/dL (blood)** **2. 1.45 µg/L (urine)**	1. 2.77-3.68 2. 1.24-1.75	1. Males and females (age 1 or older) 2. Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**3.2 µg/dL (blood)** **1.9 µg/L (urine)**	2.9-3.4 (blood) 1.7-2.0 (urine)	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**4.01 µg/dL (blood)**	N/A	Adults (age 18 or older)	August 2007 - April 2008	(Son et al., 2009)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
	42.3 µg/L (blood)	40.4-44.7	Adults (age 20 or older)	2008	(Lee et al., 2012)
Czech Republic	**1. 80 µg/L (blood)** [(a)] **2. 50 µg/L (blood)** [(a)] **3. 45 µg/L (blood)** [(a)]	N/A	1. Men 2. Women 3. Children	2005-2009	(Cerna et al., 2012)
Sweden	**1.5 µg/L (breast milk)** [(b)]	0.74-6.4 [(c)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The reference value (which is not defined as the P95) is directly provided in the literature source.
(b): The mean value is reported here as the P95 value is not reported in this study.
(c): The range value (min-max) is reported here.

Table 59 Manganese (Mn)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**1. 52.2 µg/L (cord blood)** **2. 18.6 µg/L (maternal blood)** **3. 13.6 µg/L (whole blood)**	1. 47.6-56.8 2. 16.8-20.5 3. 12.8-14.4	1. Newborns 2. Mothers of newborns 3. Adolescents (age 14-15)	2007-2009	FLEHS II
Italy	**14.5 µg/L (blood)** **1.41 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**1. 16.7 µg/L (blood)** **2. 0.38 µg/L (urine)**	1. 16.2-17.3 2. 0.32-0.45	1. Males and females (age 1 or older) 2. Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**15 µg/L (blood)** **0.36 µg/L (urine)**	14-16 (blood) 0.32-0.40 (urine)	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**19.8 µg/L (blood)**	18.7-21.7	Adults (age 20 or older)	2008	(Lee et al., 2012)
Sweden	**3.0 µg/L (breast milk)** [(a)]	0.79-8.4 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 60 Mercury (Hg)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.8 µg/L (whole blood)** **0.4 µg/L (urine)**	0.67-0.82 (blood) 0.39-0.48 (urine)	Whole blood: children with fish consumption ≤3 times/month Urine: children without amalgam fillings for teeth (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	2.0 µg/L (blood) **1.0 µg/L (urine)**	2.01-2.25 (blood) 0.86-0.99 (urine)	Blood: adults with fish consumption ≤3 times/month Urine: adults without amalgam fillings for teeth (age 18-69)	GerES III (1997-1999)	(Wilhelm et al., 2004)
Flanders	**1. 0.821 µg/g hair (hair)** **2. 0.468 µg/g hair (hair)**	1. 0.676-0.965 2. 0.363-0.573	1. Mothers of newborns 2. Adolescents (age 14-15)	2007-2009	FLEHS II
France	**1. 1.20 µg/g hair (hair)** **2. 1.80 µg/g hair (hair)**	1. 1.00-1.40 2. 1.72-1.90	1. Children (age 3-17) 2. Adults (age 18-74)	2006-2007	ENNS report (metals)
Italy	**5.16 µg/L (blood)** **1.89 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
Spain	**6.4 ng/mg hair (hair)**	5.5-8.4	Adults (average age 43±11)	2008	Esteban M. (2010) [(a)]
USA	**1. 4.40 µg/L (blood)** **2. 1.83 µg/L (urine)**	1. 3.50-5.71 2. 1.61-2.14	1. Males and females (age 1 or older) 2. Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Canada	**5.5 µg/L (blood)**	3.3-7.6	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**14.94 µg/L (blood)**	N/A	Adults (age 18 or older)	August 2007 – April 2008	(Son et al., 2009)
	11.00 µg/L (blood)	10.22-11.89	Adults (age 20 or older)	2008	(Lee et al., 2012)
Czech Republic	**1. 2.6 µg/L (blood)** [(b)] **2. 9 µg/L (urine)** [(b)]	N/A	1. Adults with little to no fish consumption 2. Adults	2005-2009	(Cerna et al., 2012)
Sweden	**0.94 µg/L (blood)** [(c)]	0.19-2.5 [(d)]	Swedish mothers	1994-1995	(Vahter et al., 2000)

(a): Esteban, M. (2010, December). *Non-invasive biomonitoring of metals using hair*. Workshop presentation on non-invasive human biomonitoring, Brussels, Belgium. Retrieved from http://www.eu-hbm.info/cophes/project-work-packages/hbm-research/documents/EstebanHairDec2010.pdf
(b): The reference value (which is not defined as the P95) is directly provided in the literature source.
(c): The median value is reported here as the P95 value is not reported in this study.
(d): The range value (min-max) is reported here.

Table 61 Molybdenum (Mo)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Italy	**2.05 µg/L (blood)** **1.83 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**145 µg/L (urine)**	140-158	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**1.5 µg/L (blood)** **170 µg/L (urine)**	1.4-1.5 (blood) 150-190 (urine)	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
Sweden	**3.5 µg/L (breast milk)** [(a)]	0.80-12 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 62 Nickel (Ni)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**4.5 µg/L (urine)**	4.20-4.72	Children (ages 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
France	**4.54 µg/L (urine)**	4.30-4.97	French adults (age 18-74)	2006-2007	ENNS report (metals)
Italy	**2.62 µg/L (blood)** **0.94 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
Canada	**1.1 µg/L (blood)** **4.8 µg/L (urine)**	1.1-1.2 (blood) 4.2-5.3 (urine)	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
Sweden	**0.96 µg/L (breast milk)** [(a)]	<LOD-47 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 63 Platinum (Pt)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.01 µg/L (urine)**	0.008-0.011	Adults without any dental inlays, crowns, bridge elements (age 18-69)	GerES III (1997-1999)	(Wilhelm et al., 2004)
Italy	**31.6 ng/L (blood)** **13.3 ng/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**0.016 µg/L (urine)**	0.009-0.049	Males and females (age 6 or older)	2009-2010	NHANES (Fourth Report)

Table 64 Selenium (Se)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1. 50-120 µg/L (serum)** [(a)] **2. 33-84 µg/L (serum)** [(a)]	N/A	1. Females & males 2. Children (age 0-16)	2002	(Wilhelm et al., 2004)
USA	**1. 236 µg/L (blood)** **2. 161 µg/L (serum)**	1. 231-241 2. 155-164	1. Males and females (age 1 or older) 2. Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**240 µg/L (blood)** **130 µg/L (urine)**	230-250 (blood) 130-140 (urine)	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
Sweden	**13 µg/L (breast milk)** [(b)]	8.8-18 [(c)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)
Finland	**1.4 µmol/L (serum)** [(d)]	N/A	Healthy Finnish population	2010	(Alfthan et al., 2014)

(a): The range of reference values from lowest to highest is reported here.
(b): The mean value is reported here as the P95 value is not reported in this study.
(c): The range value (min-max) is reported here.
(d): The reference value (which is not defined as the P95) is directly provided in the literature source.

Table 65 Thallium (Tl)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.6 µg/L (urine)**	0.56-0.61	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
Flanders	**1. 0.025 µg/L (cord blood)** **2. 0.038 µg/L (maternal blood)** **3. 0.036 µg/L (whole blood)**	1. 0.023-0.028 2. 0.036-0.040 3. 0.034-0.038	1. Newborns 2. Mothers of newborns 3. Adolescents (age 14-15)	2007-2009	FLEHS II
Italy	**0.098 µg/L (blood)** **0.071 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**0.438 µg/L (urine)**	0.385-0.522	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.62 µg/L (blood)**	0.55-0.70	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 66 Tungsten (W)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Italy	**0.075 µg/L (blood)** **0.235 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**0.434 µg/L (urine)**	0.341-0.522	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.63 µg/L (urine)**	0.50-0.76	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 67 Uranium (U)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**40 ng/L (urine)**	36.7-41.4	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
France	**21.2 ng/L (urine)**	18.4-26.4	French adults (age 18-74)	2006-2007	ENNS report (metals)
Italy	**0.0140 µg/L (blood)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
USA	**0.029 µg/L (urine)**	0.022-0.041	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.0051 µg/L (urine)**	<LOD-0.0070	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
Sweden	**0.42 µg/L (breast milk)** [(a)]	0.0097-2.0 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 68 Vanadium (V)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
France	**2.79 µg/L (urine)**	2.63-2.99	French adults (age 18-74)	2006-2007	ENNS report (metals)
Italy	**0.146 µg/L (blood)** **0.115 µg/L (serum)**	N/A	Adults (age 18-65)	2008-2010	PROBE report
Canada	**<LOD (urine)**	<LOD-0.12 µg/L	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
Sweden	**0.050 µg/L (breast milk)** [(a)]	0.015-0.56 [(b)]	Swedish mothers	2002-2009	(Bjorklund et al., 2012)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 69 PBDE 28

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**Could not be calculated (serum)**	N/A	Newborns & adolescents (age 14-15)	2007-2011	FLEHS II
USA	**8.00 ng/g lipid (serum)**	5.40-11.3	Males and females (age 12 or older)	2003-2004	NHANES (Fourth Report)
Canada	**Could not be calculated (plasma)**	<LOD	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)

Table 70 PBDE 47

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**1.70 ng/g fat (serum)**	1.92-2.12	Adolescents (age 14-15)	2007-2009	FLEHS II
USA	**163 ng/g lipid (serum)**	108-240	Males and females (age 12 or older)	2003-2004	NHANES (Fourth Report)
Canada	**0.41 µg/L (plasma)**	0.33-0.49	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Sweden	**1.9 ng/g lipid (breast milk)** [(a)]	<0.40-16 [(b)]	Swedish mothers	1996-2006	(Lignell et al., 2009)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 71 PBDE 99

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**Could not be calculated (serum)**	N/A	Adolescents (age 14-15)	2007-2009	FLEHS II
USA	**42.2 ng/g lipid (serum)**	33.3-54.8	Males and females (age 12 or older)	2003-2004	NHANES (Fourth Report)
Canada	**0.08 µg/L (plasma)**	0.07-0.09	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Sweden	**0.45 ng/g lipid (breast milk)** [(a)]	<0.12-5.2 [(b)]	Swedish mothers	1996-2006	(Lignell et al., 2009)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 72 PBDE 100

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**Could not be calculated (serum)**	N/A	Adolescents (age 14-15)	2007-2009	FLEHS II
USA	**36.5 ng/g lipid (serum)**	24.6-54.0	Males and females (age 12 or older)	2003-2004	NHANES (Fourth Report)
Canada	**0.09 µg/L (plasma)**	0.06-0.12	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Sweden	**0.36 ng/g lipid (breast milk)** [(a)]	<0.1-5.1 [(b)]	Swedish mothers	1996-2006	(Lignell et al., 2009)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 73 PBDE 153

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**1.43 ng/g fat (serum)**	1.20-1.65	Adolescents (age 14-15)	2007-2009	FLEHS II
USA	**65.7 ng/g lipid (serum)**	54.9-88.4	Males and females (age 12 or older)	2003-2004	NHANES (Fourth Report)
Canada	**0.22 µg/L (plasma)**	0.14-0.29	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Sweden	**0.64 ng/g lipid (breast milk)** [(a)]	<0.20-4.6 [(b)]	Swedish mothers	1996-2006	(Lignell et al., 2009)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 74 1-Hydroxyphenanthrene (PAH metabolite for phenanthrene)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.6 µg/L (urine)**	0.54-0.64	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
USA	**565 ng/L (urine)**	476-699	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.69 µg/L (urine)**	0.53-0.84	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 75 2-Hydroxyphenanthrene (PAH metabolite for phenanthrene)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.4 µg/L (urine)**	0.32-0.37	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
USA	**285 ng/L (urine)**	259-317	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.23 µg/L (urine)**	0.18-0.29	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 76 3-Hydroxyphenanthrene (PAH metabolite for phenanthrene)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.5 µg/L (urine)**	0.44-0.52	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
USA	**371 ng/L (urine)**	270-491	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.39 µg/L (urine)**	0.31-0.46	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 77 4-Hydroxyphenanthrene (PAH metabolite for phenanthrene)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.2 µg/L (urine)**	0.16-0.23	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
USA	**98.0 ng/L (urine)**	88.0-113	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.13 µg/L (urine)**	0.11-0.15	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 78 1-Hydroxypyrene (PAH metabolite for pyrene)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.5 µg/L (urine)**	0.42-0.57	Adults (age 18-69)	GerES III (1997-1999)	(Wilhelm et al., 2008)
	0.5 µg/L (urine)	0.40-0.48	Non-smoking children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
Flanders	**1. 281 ng/L (urine)** **2. 281 ng/L (urine)**	1. 216-347 2. 223-338	1. Adolescents (age 14-15) 2. Adults	2007-2009	FLEHS II
USA	**629 ng/L (urine)**	513-833	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.57 µg/L (urine)**	0.47-0.68	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**0.15 µg/L (urine)** [(a)]	0.13-0.17 [(b)]	Adults (age 20 or older)	2008-2009	(Sul et al., 2012)

(a): The geometric mean is reported here as the P95 value is not reported in this study.
(b): The 95% CI for the geometric mean is reported here.

Table 79 1-Hydroxynaphthalene (1-Naphthol; PAH metabolite for naphthalene)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**1. 3.26 µg/L (urine)** [(a)] **2. 9.58 µg/L (urine)** [(a)]	N/A	1. Adolescents (age 14-15) 2. Adults	2007-2011	FLEHS II
USA	**29.2 µg/L (urine)**	22.2-41.1	Males and females (age 6 or older)	2007-2008	NHANES (Fourth Report)
Canada	**15 µg/L (urine)**	12-19	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

(a): The geometric mean is reported here as the P95 value is not reported in this study.

Table 80 2-Hydroxynaphthalene (2-Naphthol; PAH metabolite for naphthalene)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**1. 7.49 µg/L (urine)** [(a)] **2. 12.27 µg/L (urine)** [(a)]	N/A	1. Adolescents (age 14-15) 2. Adults	2007-2011	FLEHS II
USA	**26.7 µg/L (urine)**	23.1-30.8	Males and females (age 6 or older)	2007-2008	NHANES (Fourth Report)
Canada	**24 µg/L (urine)**	18-30	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**3.84 µg/L (urine)** [(a)]	3.57-4.11 [(b)]	Adults (age 20 or older)	2008-2009	(Sul et al., 2012)

(a): The geometric mean is reported here as the P95 value is not reported in this study.
(b): The 95% CI for the geometric mean is reported here.

Table 81 Mono-benzyl phthalate [MBzP; phthalate metabolite for benzylbutyl phthalate (BzbP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1. 75 µg/L (urine)** **2. 15 µg/L (urine)**	N/A	1. Children (age 3-14) 2. Adults (age 20-29)	1. 2003-2006 2. 2006 & 2008	(Schulz et al., 2012b)
Flanders	**1. 109.4 µg/L (urine)** **2. 71.6 µg/L (urine)**	1. 83.4-135.5 2. 52.6-90.5	1. Adolescents (age 14-15) 2. Adults	2007-2009	FLEHS II
USA	**33.6 µg/L (urine)**	28.6-39.4	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**57 µg/L (urine)**	48-65	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**15.8 µg/L (urine)** [(a)]	2.8 [(b)]	Adults (age 18-70)	2009	(Lee et al., 2011)

(a): The geometric mean is reported here as the P95 value is not reported in this study.
(b): The standard error of the geometric mean is reported here.

Table 82 Mono-isobutyl phthalate [MiBP; phthalate metabolite for dibutyl phthalates (DBP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1. 300 µg/L (urine)** **2. 140 µg/L (urine)**	N/A	1. Children (age 3-14) 2. Adults (age 20-29)	1. 2003-2006 2. 2006 & 2008	(Schulz et al., 2012b)
USA	**36.0 µg/L (urine)**	32.4-41.0	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**64 µg/L (urine)**	50-79	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**17.0 µg/L (urine)** [(a)]	2.2 [(b)]	Adults (age 18-70)	2009	(Lee et al., 2011)

(a): The geometric mean is reported here as the P95 value is not reported in this study.
(b): The standard error of the geometric mean is reported here.

Table 83 Mono-n-butyl phthalate [MnBP; phthalate metabolite for dibutyl phthalates (DBP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1. 300 µg/L (urine)** **2. 70 µg/L (urine)**	N/A	1. Children (age 3-14) 2. Adults (age 20-29)	1. 2003-2006 2. 2006 & 2008	(Schulz et al., 2012b)
Flanders	**1. 87.6 µg/L (urine)** **2. 84.5 µg/L (urine)**	1. 72.7-102.4 2. 61.9-107.0	1. Adolescents (age 14-15) 2. Adults	2007-2009	FLEHS II
USA	**53.1 µg/L (urine)**	43.3-70.4	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**87 µg/L (urine)**	74-100	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**41.7 µg/L (urine)** [(a)]	1.9 [(b)]	Adults (age 18-70)	2009	(Lee et al., 2011)

(a): The geometric mean is reported here as the P95 value is not reported in this study.
(b): The standard error of the geometric mean is reported here.

Table 84 Mono-cyclohexyl phthalate [MCHP; phthalate metabolite for dicyclohexyl phthalate (DCHP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
USA	**Could not be calculated (urine)**	N/A	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**0.47 µg/L (urine)**	0.28-0.67	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**Could not be calculated (urine)**	N/A	Adults (age 18-70)	2009	(Lee et al., 2011)

Table 85 Mono-2-ethylhexyl phthalate [MEHP; phthalate metabolite for di-2-ethylhexyl phthalate (DEHP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**1. 12.4 µg/L (urine)** **2. 9.9 µg/L (urine)**	1. 8.7-16.2 2. 7.5-12.4	1. Adolescents (age 14-15) 2. Adults	2007-2009	FLEHS II
USA	**8.8 µg/L (urine)**	7.6-10	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**9.0 µg/L (urine)**	7.8-10	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 86 Mono-(2-ethyl-5-hydroxyhexyl) phthalate [MEHHP/5OH-MEHP; phthalate metabolite for di-2-ethylhexyl phthalate (DEHP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1. 160 µg/L (urine)** **2. 30 µg/L (urine)**	N/A	1. Children (age 3-14) 2. Adults (age 20-29)	1. 2003-2006 2. 2006 & 2008	(Schulz et al., 2012b)
Flanders	**1. 75.1 µg/L (urine)** **2. 35.7 µg/L (urine)**	1. 57.8-92.3 2. 24.3-47.0	1. Adolescents (age 14-15) 2. Adults	2007-2009	FLEHS II
USA	**43.8 µg/L (urine)**	40.3-47.2	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**59 µg/L (urine)**	48-70	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**38.1 µg/L (urine)** [(a)]	1.9 [(b)]	Adults (age 18-70)	2009	(Lee et al., 2011)

(a): The geometric mean is reported here as the P95 value is not reported in this study.
(b): The standard error of the geometric mean is reported here.

Table 87 Mono-(2-ethyl-5-oxohexyl) phthalate [MEOHP/5oxo-MEHP; phthalate metabolite for di-2-ethylhexyl phthalate (DEHP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1. 120 µg/L (urine)** **2. 20 µg/L (urine)**	N/A	1. Children (age 3-14) 2. Adults (age 20-29)	1. 2003-2006 2. 2006 & 2008	(Schulz et al., 2012b)
Flanders	**1. 116.5 µg/L (urine)** **2. 71.9 µg/L (urine)**	1. 85.7-147.2 2. 45.0-98.9	1. Adolescents (age 14-15) 2. Adults	2007-2009	FLEHS II
USA	**26.6 µg/L (urine)**	23.5-30.5	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**34 µg/L (urine)**	30-39	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**17.5 µg/L (urine)** [(a)]	1.9 [(b)]	Adults (age 18-70)	2009	(Lee et al., 2011)

(a): The geometric mean is reported here as the P95 value is not reported in this study.
(b): The standard error of the geometric mean is reported here.

Table 88 Mono-isononyl phthalate [MNP/MiNP; phthalate metabolite for di-isononyl phthalate (DiNP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
USA	**19.5 µg/L (urine)**	13.7-28.3	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**Could not be calculated (urine)**	<LOD	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**Could not be calculated (urine)**	N/A	Adults (age 18-70)	2009	(Lee et al., 2011)

Table 89 Mono-n-octyl phthalate [MOP/MnOP; phthalate metabolite for di-*n*-octyl phthalate (DOP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
USA	**Could not be calculated (urine)**	N/A	Males and females (age 6 or older)	2009-2010	NHANES (Fourth Report)
Canada	**Could not be calculated (urine)**	N/A	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)
South Korea	**Could not be calculated (urine)**	N/A	Adults (age 18-70)	2009	(Lee et al., 2011)

Table 90 Bisphenol A

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**6.60 µg/L (urine)**	4.61-8.59	Adolescents (age 14-15)	2007-2009	FLEHS II
USA	**8.9 µg/L (urine)**	7.6-11	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**6.7 µg/L (urine)**	4.8-8.6	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 91 Triclosan

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**91.5 µg/L (urine)**	41.5-141.4	Adolescents (age 14-15)	2007-2009	FLEHS II
USA	**565 µg/L (urine)**	427-747	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**710 µg/L (urine)**	540-880	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 92 p,p'-DDT (4,4'-DDT)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
France	**33.2 ng/g lipid (serum)**	10.7-47.8	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**19.5 ng/g lipid (serum)**	15.1-27.5	Males and females (age 12 or older)	2003-2004	NHANES (Fourth Report)
Canada	**0.09 µg/L (plasma)**	<LOD-0.15	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Republic	**98 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Norway	**5.3 ng/g lipid (serum)** [(a)]	0.20-25 [(b)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): The mean value is reported here as the P95 value is not reported in this study.
(b): The range value (min-max) is reported here.

Table 93 2,4,5-trichlorophenol (2,4,5-TCP)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1: 0.5 µg/L (urine)** **2: 1 µg/L (urine)**	N/A	1: Children (age 3-14) 2: Adults (age 18-69)	1: 2003-2006 2: 1997-1999	(Schulz et al., 2012b)
France	**0.67 µg/L (urine)**	0.43-0.76	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**0.30 µg/L (urine)**	0.20-0.30	Males and females (age 6 or older)	2009-2010	NHANES (Fourth Report)
Canada	**Could not be calculated (urine)**	<LOD	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 94 2,4,6-trichlorophenol (2,4,6-TCP)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1: 0.7 µg/L (urine)** **2: 1.5 µg/L (urine)**	N/A	1: Children (age 3-14) 2: Adults (age 18-69)	1: 2003-2006 2: 1997-1999	(Schulz et al., 2012b)
France	**1.00 µg/L (urine)**	0.80-1.06	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**1.10 µg/L (urine)**	1.00-1.40	Males and females (age 6 or older)	2009-2010	NHANES (Fourth Report)
Canada	**Could not be calculated (urine)**	<LOD	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 95 2,4-dichlorophenol (2,4-DCP)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1: 2 µg/L (urine)** **2: 3 µg/L (urine)**	N/A	1: Children (age 3-14) 2: Adults (age 18-69)	1: 2003-2006 2: 1997-1999	(Schulz et al., 2012b)
France	**7.62 µg/L (urine)**	4.92-17.45	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**9.10 µg/L (urine)**	5.70-12.6	Males and females (age 6 or older)	2011-2012	NHANES (Fourth Report)
Canada	**12 µg/L (urine)**	7.1-18	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 96 2,5-dichlorophenol (2,5-DCP)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1: 6 µg/L (urine)** **2: 20 µg/L (urine)**	N/A	1: Children (age 3-14) 2: Adults (age 18-69)	1: 2003-2006 2: 1997-1999	(Schulz et al., 2012b)
Flanders	**1. 8.88 µg/L (urine)** **2. 14.2 µg/L (urine)**	1. 4.90-12.86 2. 8.2-20.2	1. Adolescents (age 14-15) 2. Adults	2007-2011	FLEHS II
France	**216.23 µg/L (urine)**	107.41-933.79	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**227 µg/L (urine)**	126-404	Males and females (age 6 or older)	2009-2010	NHANES (Fourth Report)
Canada	**77 µg/L (urine)**	35-120	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 97 Diethylphosphate [DEP; organophosphate metabolite for dialkyl phosphate (DAP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**30 µg/L (urine)**	27.6-35.4	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	16 µg/L (urine)	N/A	General population	1998	(Schulz et al., 2012b)
Flanders	**1. 11.8 µg/L (urine)** **2. 8.2 µg/L (urine)**	1. 7.7-15.8 2. 5.8-10.6	1. Adolescents (age 14-15) 2. Adults	2007-2011	FLEHS II
France	**22.44 µg/L (urine)**	17.88-46.72	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**15.3 µg/L (urine)**	13.1-17.8	Males and females (age 6 or older)	2007-2008	NHANES (Fourth Report)
Canada	**19 µg/L (urine)**	16-21	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 98 Dimethylphosphate [DMP; organophosphate metabolite for dialkyl phosphate (DAP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**75 µg/L (urine)**	69.3-88.0	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	135 µg/L (urine)	N/A	General population	1998	(Schulz et al., 2012b)
Flanders	**1. 20.6 µg/L (urine)** **2. 14.7 µg/L (urine)**	1. 15.4-25.9 2. 10.6-18.9	1. Adolescents (age 14-15) 2. Adults	2007-2011	FLEHS II
France	**64.95 µg/L (urine)**	43.98-108.18	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**35.6 µg/L (urine)**	30.3-39.4	Males and females (age 6 or older)	2007-2008	NHANES (Fourth Report)
Canada	**26 µg/L (urine)**	22-29	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 99 Diethylthiophosphate [DETP; organophosphate metabolite for dialkyl phosphate (DAP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**10 µg/L (urine)**	7.79-10.7	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
Flanders	**Could not be calculated (urine)**	N/A	Newborns & adolescents (age 14-15)	2007-2011	FLEHS II
France	**8.18 µg/L (urine)**	5.28-9.91	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**4.35 µg/L (urine)**	2.95-6.01	Males and females (age 12 or older)	2007-2008	NHANES (Fourth Report)
Canada	**5.3 µg/L (urine)**	3.2-7.4	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 100 Dimethylthiophosphate [DMTP; organophosphate metabolite for dialkyl phosphate (DAP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**100 µg/L (urine)**	93.1-123	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	160 µg/L (urine)	N/A	General population	1998	(Schulz et al., 2012b)
Flanders	**1. 16.6 µg/L (urine)** **2. 19.0 µg/L (urine)**	1. 11.3-21.4 2. 13.2-24.8	1. Adolescents (age 14-15) 2. Adults	2007-2009	FLEHS II
France	**62.95 µg/L (urine)**	49.24-75.80	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**36.8 µg/L (urine)**	27.8-45.7	Males and females (age 6 or older)	2007-2008	NHANES (Fourth Report)
Canada	**37 µg/L (urine)**	27-47	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 101 Diethyldithiophosphate [DEDTP; organophosphate metabolite for dialkyl phosphate (DAP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**<0.3 µg/L (urine)**	0.20-0.36	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
Flanders	**Could not be calculated (urine)**	N/A	Newborns & adolescents (age 14-15)	2007-2011	FLEHS II
France	**0.358 µg/L (urine)**	0.134-0.762	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**Could not be calculated (urine)**	<LOD	Males and females (age 6 or older)	2007-2008	NHANES (Fourth Report)
Canada	**Could not be calculated (urine)**	<LOD	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 102 Dimethyldithiophosphate [DMDTP; organophosphate metabolite for dialkyl phosphate (DAP)]

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**10 µg/L (urine)**	6.10-12.9	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
Flanders	**Could not be calculated (urine)**	N/A	Newborns & adolescents (age 14-15)	2007-2011	FLEHS II
France	**6.94 µg/L (urine)**	4.88-9.43	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**5.60 µg/L (urine)**	4.62-6.79	Males and females (age 6 or older)	2007-2008	NHANES (Fourth Report)
Canada	**6.5 µg/L (urine)**	5.2-7.8	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 103 p,p'-DDE (4,4'-DDE)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1.4 µg/L (whole blood)**	1.31-2.00	Children living in eastern Germany (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	1.5-31 µg/L (whole blood) [(a)]	N/A	Adults (age 18-69)	1997-1999	(Schulz et al., 2012b)
Flanders	**1. 192 ng/g fat (serum)** **2. 207 ng/g fat (serum)**	1. 162-221 2. 151-263	1. Newborns 2. Adolescents (age 14-15)	2007-2011	FLEHS II
France	**729 ng/g lipid (serum)**	604-934	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**1860 ng/g lipid (serum)**	1400-2380	Males and females (age 12 or older)	2003-2004	NHANES (Fourth Report)
Canada	**6.51 µg/L (plasma)**	4.37-8.66	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Republic	**880 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Norway	**210 ng/g lipid (serum)** [(b)]	29-770 [(c)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): The range of reference values from lowest to highest is reported here.
(b): The mean value is reported here as the P95 value is not reported in this study.
(c): The range value (min-max) is reported here.

Table 104 Hexachlorobenzene (HCB)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.2 µg/L (whole blood)**	0.21-0.23	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	0.4-5.8 µg/L (whole blood) [(a)]	N/A	Adults (age 18-69)	1997-1999	(Schulz et al., 2012b)
Flanders	**1. 22.5 ng/g fat (serum)** **2. 14.0 ng/g fat (serum)**	1. 19.9-25.1 2. 12.4-15.7	1. Newborns 2. Adolescents (age 14-15)	2007-2011	FLEHS II
France	**73 ng/g lipid (serum)**	60-117	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**28.9 ng/g lipid (serum)**	25.6-32.8	Males and females (age 12 or older)	2003-2004	NHANES (Fourth Report)
Canada	**0.17 µg/L (plasma)**	0.14-0.20	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Republic	**642.3 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Norway	**43 ng/g lipid (serum)** [(b)]	15-85 [(c)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): The range of reference values from lowest to highest is reported here.
(b): The mean value is reported here as the P95 value is not reported in this study.
(c): The range value (min-max) is reported here.

Table 105 beta-Hexachlorocyclohexane (β-HCH)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**0.1 µg/L (whole blood)**	0.077-0.097	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	0.1-0.9 µg/L (whole blood) [(a)]	N/A	Adults (age 18-69)	1997-1999	(Schulz et al., 2012b)
France	**190 ng/g lipid (serum)**	160-260	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**56.5 ng/g lipid (serum)**	43.7-69.4	Males and females (age 12 or older)	1999-2000	NHANES (Fourth Report)
Canada	**0.54 µg/L (plasma)**	0.07-1.01	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Republic	**75.2 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Norway	**8.8 ng/g lipid (serum)** [(b)]	1.4-25 [(c)]	Norwegian adult males	2007	(Nøst et al., 2013)

(a): The range of reference values from lowest to highest is reported here.
(b): The mean value is reported here as the P95 value is not reported in this study.
(c): The range value (min-max) is reported here.

Table 106 gamma-Hexachlorocyclohexane (γ-HCH)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**Could not be calculated (whole blood)**	<LOD	Children (age 7-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
France	**Could not be calculated (serum)**	<LOD	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**Could not be calculated (serum)**	<LOD	Males and females (age 12 or older)	2007-2008	NHANES (Fourth Report)
Canada	**Could not be calculated (plasma)**	<LOD	Canadian adults (age 20-79)	2007-2009	CHMS I (First Report)
Czech Republic	**19.8 ng/g lipid (breast milk)**	N/A	Mothers (Median age: 26)	1993-2003	(Mikeš et al., 2012)
Norway	**Could not be calculated (serum)**	<LOD	Norwegian adult males	2007	(Nøst et al., 2013)

Table 107 cis-2,2-dichlorovinyl-2,2-dimethylcyclopropane-1-carboxylic acid (cis-Cl_2CA; pyrethroid metabolite)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**1 µg/L (urine)**	0.64-1.65	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	1 µg/L (urine)	N/A	General population	1998	(Schulz et al., 2012b)
France	**1.42 µg/L (urine)**	0.67-2.17	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
Canada	**2.2 µg/L (urine)**	0.78-3.6	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 108 trans-2,2-dichlorovinyl-2,2-dimethylcyclopropane-1-carboxylic acid (trans-Cl_2CA; pyrethroid metabolite)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**2 µg/L (urine)**	1.66-2.22	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	2 µg/L (urine)	N/A	General population	1998	(Schulz et al., 2012b)
France	**3.85 µg/L (urine)**	2.44-5.27	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
Canada	**6.8 µg/L (urine)**	2.1-11	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

Table 109 3-phenoxybenzoic acid (3-PBA)

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Germany	**2 µg/L (urine)**	2.24-2.87	Children (age 3-14)	GerES IV (2003-2006)	(Schulz et al., 2009)
	2 µg/L (urine)	N/A	General population	1998	(Schulz et al., 2012b)
Flanders	**1. 0.41 µg/L (urine)** [(a)] **2. 0.58 µg/L (urine)** [(a)]	N/A	1. Adolescents (age 14-15) 2. Adults	2007-2011	FLEHS II
France	**4.36 µg/L (urine)**	3.41-6.15	French adults (age 18-74)	2006-2007	ENNS report (pollutants)
USA	**6.63 µg/L (urine)**	4.99-8.24	Males and females (age 6 or older)	2007-2008	NHANES (Fourth Report)
Canada	**5.9 µg/L (urine)**	2.2-9.5	Canadian population (age 3-79)	2009-2011	CHMS II (Second Report)

(a): The geometric mean is reported here as the P95 value is not reported in this study.

Table 110 Cotinine

Country	Reference values (matrix)	95% CI	Reference population	Study period	Reference
Flanders	**1. 2329 µg/g creatinine (urine)** [(a)] **2. 4572 µg/g creatinine (urine)** [(a)]	N/A	1. Adolescent smokers (age 14-15) 2. Adult smokers	2007-2011	FLEHS II
USA	**1.29 ng/mL (serum)**	1.04-1.61	Non-smokers (age 3 or older)	2009-2010	NHANES (Fourth Report)
Canada	**1. Could not be calculated (urine)** **2. 2600 µg/L (urine)**	1. N/A 2. 2100-3100	1. Non-smokers (age 3-79) 2. Smokers (age 12-79)	2009-2011	CHMS II (Second Report)
South Korea	**1. 769.88 µg/L (urine)** [(a)] **2. 21.52 µg/L (urine)** [(a)]	1. 610.55-929.21 [(b)] 2. 19.11-23.93 [(b)]	1. Non-smokers (age 20 or older) 2. Smokers (age 20 or older)	2008-2009	(Sul et al., 2012)

(a): The geometric mean is reported here as the P95 value is not reported in this study.
(b): The 95% CI for the geometric mean is reported here.

ABBREVIATIONS

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
3-MCPD	3-monochloropropane-1,2 diol ester
3-PBA	3-phenoxybenzoic acid
5cx-MEPP/MECPP	Mono(2-ethyl-5-carboxypentyl) phthalate
5OH-MEHP/MEHHP	Mono(2-ethyl-5-hydroxyhexyl) phthalate
5oxo-MEHP/MEOHP	Mono(2-ethyl-5-oxohexyl) phthalate
6-CINA	6-chloronicotinic acid
8-OHdG	8-hydroxydeoxyguanosine
AAS	Atomic absorption spectrometry
ADI	Acceptable Daily Intake
AFC	The Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (EFSA)
AFS	Atomic Fluorescence Spectroscopy
Ag	Silver
Al	Aluminium
ALARA	As Low As Reasonably Achievable
AMAP	Arctic Monitoring and Assessment Programme
AMI	Danish National Institute of Occupational Health
ANMI	Associazione Nazionale Per La Lotta Contro Le Microcitemie [National Italian Association against Microcythemia (Italy)]
ANS	The Panel on Food Additives and Nutrient Sources Added to Food (EFSA)
APCI	Atmospheric Pressure Chemical Ionisation
As	Arsenic
Au	Gold
AVIS	Associazione Volontari Italiani Sungue (Italian Blood Volunteer Association)
B	Boron
Ba	Barium
BAL	Biomonitoring Action Level
BBzP	Butyl-benzyl phthalate
Be	Beryllium
BE	Biological Equivalent
BE_{POD}	Biological Equivalent derived from the Point-of-Departure

BE_{RfD}	Biological Equivalent derived from the Reference Dose
BEI	Biological Exposure Indices
BFR	Brominated Flame Retardant
BM	Biomarker
BMBF	Bundesministerium für Bildung und Forschung [Federal Ministry of Education and Research (Germany)]
BMDL	Benchmark Dose Lower Confidence Limit
BMI	Body Mass Index
BMUB	Bundesministerium für Umwelt, Naturschutz, Bau und Reaktorsicherheit [Federal Ministry of the Environment, Nature Conservation and Nuclear Safety (Germany)]
BPA	Bisphenol A
Br_2CA	cis-3-(2,2-dibromo-vinyl)-2,2-dimethylcyclo-propanecarboxylic acid
BTBPE	1,2-bis(2,4,6-tribromophenoxy)ethane
Ca	Calcium
CALUX	Chemically activated luciferase gene expression assay
CATI	Computer-assisted interviews
Cd	Cadmium
CDC	Centers for Disease Control and Prevention (USA)
CEF	The Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (EFSA)
CF	Consultative Forum
CHMS	Canadian Health Measures Survey
CI	Confidence Interval
cis-Cl_2CA	cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
CNAF	Caisse nationale des allocations familiales [National Family Allowance Office (France)]
CNAMTS	Caisse nationale d'assurance maladie des travailleurs salaries [National Health Insurance Fund for Salaried Workers (France)]
Co	Cobalt
CONTAM	The Panel on Contaminants in the Food Chain (EFSA)
COPHES	Consortium to Perform Human biomonitoring on a European Scale
CORDIS	Community Research and Development Information Service (European Commission)
Cr	Chromium
Cs	Cesium

Cu	Copper
CV-AAS	Cold Vapour Atomic Absorption Spectrometry
DAP	Dialkylphosphate
DBNC	Danish National Birth Cohort
DBNPG	2,2-bis(bromomethyl)-1,3-propanediol
DBP	Disinfection by-products
DCHP	Di-cyclohexyl phthalate
DCP	Dichlorophenol
DDD	Dichlorodiphenyldichloroethane
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethanes
DEDTP	Diethyl dithiophosphate
DEHP	Di(2-ethylhexyl) phthalate
DEMOCOPHES	Demonstration of a Study to Coordinate and Perform Human Biomonitoring on an European Scale
DEP	Diethylphosphate (organophosphate) or Diethyl phthalate (phthalate)
DETP	Diethylthiophosphate
DiBP	Di-iso-butyl phthalate
DiDP	Di-iso-decyl phthalate
DINCH	Di(isononyl) cyclohexane-1,2-dicarboxylate or Diisononylcyclohexanoate
DiNP	Di-iso-nonyl phthalate
DL	Dioxin-like
DMA	Direct mercury analyser
DMDTP	Dimethyl dithiophosphate
DMEL	Derived Minimal Effect Level
DMP	Dimethylphosphate (organophosphate) or Dimethyl phthalate (phthalate)
DMTP	Dimethyl thiophosphate
DNA	Deoxyribonucleic acid
DNBC	Danish National Birth Cohort Study
DnBP	Di-n-butyl phthalate
DNEL	Derived No Effect Level
DnOP/DOP	Di-n-(Octyl) phthalate
DnPeP	Di-n-pentyl phthalate
DPHP	Di-propy-heptyl phthalate

ECD	Electron Capture Detector
ECHA	European Chemicals Agency
ECNI	Electron Capture Negative Ion
ECNIS	Environmental Cancer Risk, Nutrition and Individual Susceptibility (Europe)
EDEN	French cohort study on early live determinants for neurodevelopment and children's health (Etude de cohorte généraliste, menée en France sur les Déterminants pré et post natals précoces du développement psychomoteur et de la santé de l'Enfant)
EDI	Estimated Dietary Intakes
EFSA	European Food Safety Authority
EHA	Environmental Health Act (Korea)
EHAP	Environment and Health Action Plan (EU)
EHBMI	European HBM Initiative
EHMS	Environmental Health Monitoring System (Czech Republic)
ELFE	Étude longitudinal française depuis l'enfance (France)
ELISA	Enzyme-linked immunosorbent assay
ENNS	Étude nationale nutrition santé [National Nutrition and Health Survey (France)]
EPA	Environmental Protection Agency (USA)
EQUAS	External Quality Assessment Schemes
ERI	Emerging Risk Identification
ESB	Environmental Specimen Bank (Germany)
ESBHum	Environmental Specimen Bank for Human Tissues (Germany)
ESBIO	Expert Team to Support Biomonitoring in Europe
ESTEBAN	Étude de santé sur l'environment, la biosurveillance, l'activité physique (France)
ET-AAS	Electrothermal Atomic Absorption Spectroscopy
EtP	Ethylparaben
Et-PFOSA-AcOH	2-(N-ethyl-perfluorooctane sulfonamido) acetic acid
EU	European Union
EU MS	European Union Member State
EWAS	Exposome-Wide Association Study
FAO	Food and Agriculture Organization of the United Nations
F-AAS	Flame Atomic Absorption Spectroscopy
Fe	Iron

FEEDAP	The Panel on Additives and Products or Substances used in Animal Feed (EFSA)
FFQ	Food Frequency Questionnaire
FIP	Food Ingredients and Packaging Unit (EFSA)
Fl	Fluoride
FLEHS	Flemish Environment and Health Study
FP	Framework Programme (European Commission)
F-PBA	4-fluoro-3-phenoxybenzoic acid
FUGE	Functional Genomics Programme(Norway)
GC	Gas Chromatography
GC-MSD	Gas Chromatography-Mass Spectrometer Detector
GerES	German Environmental Survey
GF-AAS	Graphite Furnace Atomic Absorption Spectroscopy
GIS	Geographic Information Systems
GM	Geometric Mean
GMO	Genetically Modified Organisms
GP	General Practitioner
GWAS	Genome-Wide Association Study
Hb	Haemoglobin
HBB	Hexabromobenzene
HBCD/HBCDD	Hexabromocyclododecane
HBGV	Health-Based Guidance Value
HBM	Human Biomonitoring
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
HEALS	Health and Environment-wide Associations based on Large Population Surveys (Europe)
HELIX	The Human Early Life Exposome (Europe)
Hg	Mercury
HG-AAS	Hydride Generation Atomic Absorption Spectroscopy
HpBDD	Heptabromodibenzo-p-dioxin
HpBDF	Heptabromodibenzo-p-furan
HpCDD	Heptachlorodibenzo-p-dioxin
HpCDF	Heptachlorodibenzo-p-furan
HPLC	High Performance Liquid Chromatography

HRGC	High Resolution Gas Chromatography
HRMS	High Resolution Mass Spectrometry
HxBDD	Hexabromodibenzo-p-dioxin
HxBDF	Hexabromodibenzo-p-furan
HxCDD	Hexachlorodibenzo-p-dioxin
HxCDF	Hexachlorodibenzo-p-furan
IARC	International Agency for Research on Cancer
IC	Ion Chromatography
ICI	Interlaboratory Comparison Investigations
ICP	Inductively Coupled Plasma
ID-ICP-MS	Isotope Dilution Inductively Coupled Plasma Mass Spectrometry
IEHIAS	Integrated Environment Health Impact Assessment System
IgE	Immunoglobulin E
IMI	Imidacloprid
INED	Institut national d'études démographiques [National Institute for Demographic Studies (France)]
INMA	Infancia y Medio Ambiente (Spain)
INSEE	Institut national de la statistique et des études économiques [National Institute for Statistics and Economic Studies (France)]
INSERM	Institut national de la santé et de la recherche médicale [National Institute for Health and Medical Research (France)]
INTARESE	Integrated Assessment of Health Risks from Environmental Stressors in Europe
InVS	Institut de Veille Sanitaire [Institute for Public Health Surveillance (France)]
Ir	Iridium
ISCIII	Instituto de Salud Carlos III [National Institute of Health Carlos III (Spain)]
ISS	Istituto Superiore di Sanità [National Institute of Health (Italy)]
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
JECS	Japan Environmental and Children's Study
K	Potassium
KCDC	Korea Centers for Disease Control and Prevention
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (German Health Interview and Examination Survey for Children and Adolescents)
KNHANES	Korea National Health and Nutrition Examination Survey
KorEHS-C	Korean Environmental Health Survey in Children and Adolescents

KorSEP	Korea National Survey for Environmental Pollutants in the Human Body
LC	Liquid Chromatography
LC/LC	Multidimensional Liquid Chromatography
Li	Lithium
LOAEL	Lowest-Observed-Adverse-Effect Level
LOD	Limit of Detection
LOQ	Limit of Quantitation
MBRN	Medical Birth Registry of Norway
MBzP	Mono-benzyl phthalate
MCHP	Mono-cyclohexyl phthalate
MCNP	Mono-carboxy-isononyl phthalate
MCOP	Mono-carboxy-octyl phthalate
MCP	Monochlorophenol
MCPP	Mono-3-carboxypropyl phthalate
MDA	Malondialdehyde
MDI	Mental Developmental Indices
MeHg	Methyl mercury
MEHP	Mono(2-ethylhexyl) phthalate
MeP	Methylparaben
MEP	Mono-ethyl phthalate
Me-PFOSA-AcOH	2-(N-methyl-perfluorooctane sulfonamido) acetic acid
Mg	Magnesium
MHNCH	Mono hydroxyisononyl ester
MiBP	Mono-iso-butyl phthalate
MiNP	Mono-iso-nonyl phthalate
MIREC	Maternal-Infant Research on Environmental Chemicals (Canada)
MMP	Mono-methyl phthalate
Mn	Manganese
MnBP	Mono-n-butyl phthalate
MnOP/MOP	Mono-n-(octyl) phthalate
Mo	Molybdenum
MoBa	The Norwegian Mother and Children Cohort Study
MOCEH	The Mother's and Children's Environmental Health Study (Korea)
MOE	Margin of Exposure (risk assessment) or Ministry of the Environment (Japan)

MS	Mass Spectrometry
MS/MS	Tandem Mass Spectrometry
Na	Sodium
NAAP	N-acetyl-4-aminophenol
NAS	National Academy of Sciences (USA)
NBAS	Neonatal Behavioral Assessment Scale
NCHS	National Center for Health Statistics (USA)
NCI	Negative Chemical Ionisation
NDA	The Panel on Dietetic Products, Nutrition and Allergies (EFSA)
NDL	Non-dioxin like
NEHAP	National Environmental Health Action Plan (Korea)
NHANES	National Health and Nutrition Examination Survey (USA)
Ni	Nickel
NIEHS	National Institute of Environmental Health Sciences (USA)
NIER	National Institute of Environmental Research (Korea)
NIH	National Institute of Health (USA)
NINDS	National Institute of Neurological Disorders and Stroke (USA)
NIPH	Norwegian Institute of Public Health
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NOAEL	No-Observed-Adverse-Effect Level
OCDD	Octachlorodibenzo-p-dioxin
OCDF	Octachlorodibenzo-p-furan
OCP	Organochlorine pesticide
OECD	Organisation for Economic Co-operation and Development
OELV	Occupational Exposure Limit Values
OP	Organophosphate
OR	Odds Ratio
P	Phosphorus
P90	90th Percentile
P95	95th Percentile
PAH	Polyaromatic hydrocarbon
PANCAKE	Pilot Study for Assessment of Nutrient Intake and Food Consumption among Kids in Europe (EFSA)
Pb	Lead

PBDE	Polybrominated diphenyl ethers
PBPK	Physiologically based pharmacokinetic
PBT	Persistent bioaccumulative and toxic chemicals
PCB	Polychlorinated biphenyls
PCDD	Polychlorinated dibenzodioxins
PCDF	Polychlorinated dibenzofurans
PCP	Pentachlorophenol
Pd	Palladium
PDI	Psychomotor Developmental Indices
PeBDD	Pentabromodibenzo-p-dioxin
PeBDF	Pentabromodibenzo-p-furan
PeCDD	Pentachlorodibenzo-p-dioxin
PeCDF	Pentachlorodibenzo-p-furan
PEM	Personal Exposure Monitoring
PFAS	Perfluoroalkylated substance
PFBuS	Perfluorobutane sulfonate
PFC	Perfluorinated compound
PFDA/PFDeA	Perfluorodecanoic acid
PFDoA	Perfluorododecanoic acid
PFHpA	Perfluoroheptanoic acid
PFHxS	Perfluorohexane sulfonate
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonate
PFOSA	Perfluorooctanesulfonamide
PFUA/PFUDA	Perfluoroundecanoic acid
PHIME	Public Health Impact of Long-Term, Low-Level Mixed Element Exposure in Susceptible Population Strata (Europe)
PLM	Post-Launch Monitoring
PM(E)M	Post-Market (Environmental) Monitoring
PMS	Post-Market Surveillance
PMTDI	Provisional Maximum Tolerable Daily Intake
PNNS	Programme national nutrition santé [National Programme on Health and Nutrition (France)]
POP	Persistent Organic Pollutant

PPR	The Panel on Plant Protection Products and their Residues (EFSA)
PROBE	Programma per il biomonitoraggio dell'esposizione della popolazione generale [Programme for Biomonitoring of the Exposure (Italy)]
PSA	Prostate-Specific Antigen
PSU	Primary Sampling Unit
Pt	Platinum
PVC	Polyvinyl chloride
QA/QC	Quality Assurance/Control
Rb	Rubidium
RDA	Recommended Dietary Allowance
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
Rh	Rhodium
RKI	Robert Koch Institute (Germany)
(m/mi/r/t) RNA	(messenger/micro/ribosomal/transfer) Ribonucleic acid
ROC	Receiver Operating Characteristic
RP	Reference Point
RSD	Relative Standard Deviation
RV	Reference Value
S	Sulfur
Sb	Antimony
SCALE	Science, Children, Awareness, Legal instrument, Evaluation (EU)
SCOEL	Scientific Committee on Occupational Exposure Limit Values
Se	Selenium
SEBIOREC	Epidemiological biomonitoring study on persistent organic pollutants in mothers milk in the Campania region (Studio epidemiologico sullo stato di salute e sui livelli d'accumulo di contaminanti organici persistenti nel sangue e nel latte materno in gruppi di popolazione a differente rischio d'esposizione nella Regione Campania)
SES	Socioeconomic status
SF-ICP-MS	Sector Field Inductively Coupled Plasma Mass Spectrometry
SHS	Secondhand Smoke
Sn	Tin
S/N	Signal-to-noise ratio
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
SPE	Solid Phase Extraction

Sr	Strontium
SVHC	Substances of Very High Concern
TBBPA	Tetrabromobisphenol A
TBDD	Tetrabromodibenzo-p-dioxin
TBDF	Tetrabromodibenzo-p-furan
TCDD	Tetrachlorodibenzo-p-dioxin
TCDF	Tetrachlorodibenzo-p-furan
TCP	Trichloropyridinol
TDI	Tolerable Daily Intake
TEF	Toxic Equivalent Factor
TEQ	Toxic Equivalent Quantity
TIS	Turbo Ion Spray ionisation
Tl	Thallium
trans-Cl_2CA	trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
TWI	Tolerable Weekly Intake
U	Uranium
UBA	Umweltbundesamt [Federal Environment Agency (Germany)]
UNEP	United Nations Environment Programme
UPLC	Ultra Performance Liquid Chromatography
USA	United States of America
UV	Ultraviolet
V	Vanadium
VCI	Verband der Chemischen Industrie [Chemical Industry Association (Germany)]
VOC	Volatile Organic Compound
W	Tungsten
WHO	World Health Organisation
WWF	World Wildlife Fund
Zn	Zinc