Scoping paper on the development of an indicator on chemical exposure in the European population

Deliverable Report

D 5.3

WP 5 – Translation of results into policy

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The delivery date of the present deliverable was modified on a request sent to the HBM4EU Coordinator by EEA on behalf of VITO and UBA. The original delivery date was September 2019. The Coordinator informed Task 5.4 on 19 September 2017 that the extension was accepted with one request from the HBM4EU EC scientific project officer, i.e. to present the work as described in to the EU Policy Board on 13 December.

The current deliverable should be regarded as a concept note for the development of HBM based indicators. It builds on preparatory work done at EEA, UBA and VITO prior to HBM4EU. It also adds to this by proposing an indicator for combined exposures and risk at the population level (sections 2.3 and 3.2). How this combined extent of exceedance indicator at population level can be interpreted and relates to the foreseen mixture indicators at individual level (developed in WP15 Mixtures) should be discussed and further elaborated in connection with WP5.2 Development of Health Based Guidance values, WP5.3 Risk assessment and WP15 Mixtures.
Development of European HBM-based indicators to inform policy and monitor progress towards policy objectives

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Summary

Indicators are a tool to condense complex scientific information into a few key descriptors representing the studied system, with the purpose to communicate to a non-expert audience. The audience may be policy and decision makers, scientists, various stakeholders or the public, representing different fields and with different levels of education. The choice of the descriptors is closely linked to the objective or the question, which the indicator is aiming to answer. In the case of human biomonitoring (HBM) of chemicals, relevant questions could be whether an implemented policy to reduce chemical exposure has had an effect over time, if the health of people in specific regions or subpopulations are at risk, or whether the body burden of chemicals (the internal exposure), varies with time, country, sex or age.

This study proposes a methodology to develop human biomonitoring chemical exposure indicators for the European HBM4EU research project. Criteria for selecting chemicals to make the indicators for are presented. The chemicals may be single substances (e.g. Bisphenol A, BPA) or groups of substances, which may have common chemical/physical structures (e.g. per- and polyfluorinated substances, PFAS), common toxicities (e.g. endocrine disruptors, EDCs) or similar technical functions (e.g. pesticides). The criteria include considerations of EU policy and societal relevance, health relevance, data availability and robustness across Europe, chemical characteristics in relation to excretion, interoperability with other international environmental and health indicators, and transparency and ease of communication.

BPA and PFAS were selected using the criteria above, starting from the nine groups of initially prioritised substances in the HBM4EU project, and considering EU policy and societal relevance, such as endocrine disruptors, mixtures, persistency and support to the development of the non-toxic environment strategy.

Two main types of indicators with some subgroups are proposed:

1) Result indicators, referring only to HBM exposure concentrations. For a group of substances the ‘Exposure indicator’ can sum the individual concentrations of substances (e.g. on a molar basis) to give an idea on the total chemical pressure. The result indicators, do not provide information on health risk. Rather their purpose is to survey exposure patterns in time and space, and thereby help decision makers to prioritise which chemicals that need further attention, such as monitoring, risk assessment or risk management.
a. The ‘exposure indicator’ shows the internal chemical exposure (body burden) of measured chemicals.

b. The indicator showing the exposure in combination with a statistically-derived background internal exposure for the general population not specifically exposed.

2) Impact indicators, referring to a normative internal exposure level, i.e. the health-based HBM guidance value (HBM HBGV), or a health-based legal limit. These indicators link information of exposure to the health risk of the exposure to the selected chemicals:

a. The ‘percentage of exceedance’, describes the percentage of a population which have exposure levels which exceeds a HBM HBGV, or a legal health-based limit. When compared with a legal health-based limit, the indicator can show how the degree of compliance is with set limits.

b. The ‘extent of exceedance’ compares a percentile of the distribution of HBM measurements to an HBM HBGV. For single substances, this indicator may give information on the risk status, or the degree of compliance with a legal limit. For a group of substances, this indicator represents how the chemicals included in the indicator may create an overall health impact, or chemical stress, at the population level. This indicator cannot be used to assess the risk of individuals. Rather, the indicator may serve to help policy and decision makers to prioritise groups of substances, sub-populations, or regions for which further information may be needed to make full risk assessments.

The choice of whether to use individual or aggregate exposure data, and in the case of the latter, what percentile of the distribution of internal concentrations to use, depends on the purpose of the indicator, on the available data sets, and involves value judgement.

It is proposed to use \( P_{50} \) and \( P_{95} \), which to some extent allows inclusion of aggregated data from existing datasets. Depending on the level of disaggregation of the data, each of the indicators can be further split up (stratified) to explore how the chemical exposures and impacts, vary across e.g. age, gender, spatial regions of Europe or socio-economic status.

We have applied the methodology on published data from a) the DEMOCOPHES project (BPA, PFOA and PFOS) to illustrate extent and percentage of exceedance indicators and stratification according to countries, age and gender, and b) Swedish data (PFOA, PFOS, PFNA, PFHxS) to illustrate time trends for the extent of exceedance and exposure indicator. To increase visibility, we plan to submit this study as a peer-reviewed publication by early 2018, after addition of a few more datasets. It is expected that we at least over the duration of the HBM4EU project will continue to populate the HBM4EU indicators with new data. We will therefore continue to collaborate both within the HBM4EU project and externally with EU agencies (e.g. Eurostat), and international partners such as US NHANES, UNEP, WHO and OECD to ensure a long term relevance and use of the HBM4EU indicator, with the overall purpose to evaluate and support of chemical policies in the EU.
1 Introduction

1.1 General introduction

Indicators are a tool to illustrate complex scientific information by a few and carefully selected variables, and thereby communicate the main messages to a non-expert audience. Indicators can be an important tool to translate scientific information into knowledge, which can guide policy makers to take actions in order to achieve goals set by policies or demanded by society. In relation to chemicals, some of the key societal and political questions are how chemicals may impact our health, what their sources are, if subpopulations or geographic regions are impacted differently, and how policies or other risk management options may be designed to prevent risk from chemicals. This study proposes a methodology for how HBM indicators can inform the public and policy makers on what the levels are of various chemicals in our bodies, and which ones that may require further attention or actions to prevent risk.

Human biomonitoring (HBM) is a broad field situated at the intersection of environment and human health, which measures and interprets biomarkers of exposure or effects in humans. Most often samples of blood, urine or breast milk are analysed, but samples of faeces, hair and lipid biopsies may also be analysed. More specifically this study focuses on biomarkers of exposure to exogenous chemicals, and subsequently we will use the term HBM to refer only to the biomonitoring of exogenous chemicals in humans, also called the internal chemical exposure. The measured chemicals may be the chemical of interest and/or its metabolised transformation products (metabolites). The internal exposure may stem from different sources of exposure, be absorbed via various media (e.g. food, water, air, consumer products), and be caused by various activities (e.g. background, consumption vs. occupational exposures). Internal concentrations may stem from multiple sources, and the resulting internal exposure is then the aggregate exposure. In addition, different chemicals present in the same individual and at a given point of time, may have a combined impact on human health, which is called mixture effect. This topic is being dealt with in WP15 of the HBM4EU project. In both cases by studying the relationship between internal dose and prevalence of diseases, HBM can play an important role in assessing the overall health impact of chemicals on humans, from both known and unknown sources. Internal exposures of chemicals and their metabolites may be correlated to sources of external exposure combined with knowledge of the routes of external exposure, e.g. intake via ingestion, inhalation or uptake over the skin. This is the work of HBM4EU WP12.

The HBM4EU (Human biomonitoring for Europe) is a Horizon2020 Framework Project, which started as a European Joint Project (EJP) for the development of a sustainable European-wide HBM network (2017-2021). It currently has 28 participating countries. HBM4EU aims to coordinate and advance human biomonitoring in Europe. HBM4EU will provide better evidence of the actual exposure of citizens to chemicals and the possible health effects to support policy making (https://www.hbm4eu.eu/about-hbm4eu/). The purpose of HM4EU is to inform current and future environmental policies and strategies, related to chemicals, environment and human health. This includes both existing EU and national chemical polices as well as future activities highlighted in the European Union’s 7th Environmental Action Programme (EAP) and the strategy for a non-toxic environment, with the overall aims to assess and minimise environmental health risks from the use

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of hazardous substances by 2020\(^2,3,4\). The HBM4EU project will also contribute to international activities and commitments made by EU to e.g. WHO, OECD, the Stockholm convention on POPs and the UN SAICM process. To ensure interoperability with other indicators and initiatives, both within HBM4EU, Europe and globally we consulted with experts in the development of the HBM4U indicator methodology. This was done during an expert workshop held in June 2017 in Copenhagen at the European Environment Agency, where we also got informed about previous work in the field such as the BRIDGE project, The Flemish projects (VMM and Flemish Center of Expertise on Environment and Health) and the EEA ETC work on chemicals and waste. After developing a draft of the methodology we presented it and got feedback on it during two HBM4EU meetings (Consortium meeting in Berlin, Sept 7\(^\text{th}\) 2017, and WP5 meeting in Antwerp, Nov 14-15\(^\text{th}\) 2017) when participants from outside Task 5.4 provided comments.

1.2 Indicators in general

The purpose of indicators is to provide insight and clarity with respect to a specific question, implied in for instance a quantitative policy target or qualitative policy objective. The indicator is therefore influenced by the value judgement of the posed question. For instance, if a high degree of physical health is perceived to be desirable, impacts that deteriorate health will be considered to be undesirable. In this case, a policy objective then could be ‘to reduce the negative health impacts caused by exposure to chemicals’. Trends showing a decrease in the negative impacts would in this case be interpreted as progress towards the target. The value judgement is therefore not objective, but is related to societal norms of what is ‘desirable’ or ‘undesirable’, which may be affected by political or cultural preferences and related ethical reasoning.

The key function of indicators is to establish a connection between a normative statement (e.g. political goals) about a desirable state of a system, and the scientific, empirical data describing that system. Indicators thereby link the empirical information to the normative question, so that it can be used to measure progress toward the normative goal, which may be a political target or objective to achieve. An example of empirical information is the measured internal chemical concentrations in human blood, or information on the age, sex, habits, and spatial information on the people studied.

Indicators have two essential features: on the empirical side, an indicator has to be based on an appropriate model of the system from which the empirical data are taken so that the data are used in a way that correctly represents key features of the system. The indicator should therefore contain information of the main descriptors of the system, which affect the outcome we are interested in. For instance, to describe PFAS levels in human blood, age, sex, or time may be relevant descriptors, whereas whether an individual drive by car or bicycles to work may be an irrelevant descriptor. By representing only key features, an indicator aggregates empirical information and reduces the complexity of all the data, that may be generated from the empirical system. In relation to the value judgement implied in the question asked (or the set goals), an indicator has to have a transparent connection with a normative statement. Such a statement, which speaks about desirable and undesirable states of the system, needs to be supported by a

\(^2\) Council, 2016, Outcome of the Council meeting, 3512nd Council meeting, Environment, Brussels, 19 December 2016, Council of the European Union, 15703/16.


reasoning that explains why a certain state is more desirable than another. This reasoning can be provided, for example, by ethical arguments. Ethical arguments, such as ‘we should protect vulnerable groups, such as children’, can guide choices in how to construct the indicator: A policy maker may for instance decide to use input data representing also pregnant women and children, rather than using input data only representing the overall average population.

Indicators are generally quantitative so that differences in the system’s state can be measured and compared. Because of their normative meaning, indicators – although expressed in quantitative terms – are substantially different from data obtained from measurements or model calculations. Importantly, empirical data do not speak for themselves, but their relevance and broader meaning – in particular in the political context – is created when they are fed into indicators; by virtue of their normative component, indicators define the meaning of the data. The normative component of indicators should be as explicit and transparent as possible. In practical terms, this means that a measured (empirical) value in itself has little meaning (it is not an indicator according to the definition used above). By contrast a plot of a series of empirical values (at least two) over time can have important policy meaning and therefore is an indicator.

Indeed, indicators need to nourish a clear objective. Presenting HBM data in the form of an indicator informs strategy development in the area of chemicals management, while it may serve to check progress towards policy targets (normative statements). The use of HBM indicators may provide valuable information on the progress of national and international activities on environment and health, including those led by the EEA, Eurostat, WHO, OECD and WHO. They may also provide knowledge on the progress on the UN sustainable development goals (SDGs) no. 3 (good health and well-being), no. 6 (clean water and sanitation), no. 10 (reduced inequalities) and no. 12 (responsible consumption and production), see Table A1 in Annex for some examples. Their objectives differ, but the protection of human health is a common and primary goal. Indeed, human health and safety is an important driver under the horizontal EU chemicals legislation REACH, and is also a priority for the OECD Environment Directorate within the context of sustainable development of regions. In the EU, HBM indicators could also be a tool to assess the objective of creating a non-toxic environment in the complicated context of a circular economy: The overall efficiency of existing limits and restrictions could be evaluated, and exposures to both currently used and legacy chemicals, as well as their substitute chemicals could be surveyed.

The typology of indicators varies in the fields they are applied. We have chosen to follow the terminology used by Eurostat, which differentiates between ‘result’ and ‘impact’ indicators. A result indicator measures a state, such as the concentration of a substance in blood. Without giving information on the hazard of the chemical, or at which level an effect will occur, no judgement can be given on risk, or possible links to diseases. An impact indicator, on the other hand, provides information on effects that a state may have on health for instance. An example may be when an internal concentration of a chemical measured in blood (the result indicator) is compared with the levels at which an effect will occur.

Depending on the objective of the indicator, different quality criteria may be applicable. Of course, the lower the uncertainty of the HBM data (i.e. the higher the accuracy and precision), the higher the chance of finding significant variations, which can be explained by e.g. exposure to different sources of contamination. In practice, when aggregating data from different studies (e.g. using different sampling protocols) the variations will be larger, than when comparing data collected within a study that applied e.g. similar sampling protocols. In order to make use of existing data

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from different studies, it is therefore necessary to consider which quality criteria are essential for different types of indicators. If an indicator is used directly to measure a quantitative progress towards a mandatory target (e.g. a legal limit), the input data must be of high quality and be harmonised to make the comparison fair. An example are the indicators for 'Exceedance of air quality standards in urban areas', for Benz(a)pyrene, nitrogen dioxide (NO$_2$), ozone (O$_3$) and particulate matter (PM$_{2.5}$). Here the concentration of the substances are compared against legal (health based) limits and reported by each European country to the EEA$^6$. Comparable and high quality data is also needed if the indicator will be used as a quantitative input to risk assessment. In other cases the indicators may rather serve to prioritise which substances to further characterise in terms of their hazard or exposure patterns across the EU or for certain subpopulations.

1.3 HBM-Based indicators

The aim of this task, and the current deliverable, is to describe a methodology to develop indicators on chemical exposure in the European population based on HBM data. Two main groups of indicators are distinguished in this respect:

1. Those that provide information on the variation of internal chemical exposure levels:
   a. Internal exposure levels vs. e.g. time, age, sex, spatial differences.
   b. Internal exposure levels compared to ‘HBM Reference Values’ (describing the background levels of a population$^7$), to highlight exposure in specific subpopulations vs. the population as a whole.

2. Those that have incorporated knowledge about ‘no concern’ exposure levels (defined by HBM health-based guidance values - HBM HBGVs$^8$)

One of the objectives for generating HBM data, and HBM-based indicators, is to display changes in the aggregate exposure to mixtures of chemicals, i.e. the overall levels and patterns of chemical body burdens. It would be beneficial if e.g. spatial and temporal trends in chemical body burden could be correlated with differences and trends in environmental contamination and occupational exposures. Such comparisons between HBM-based indicators and environmental indicators can be facilitated by harmonisation of the way chemicals are grouped in different indicators and how HBM indicators are calculated. The grouping used in existing indicators is to some extent is linked to the policies they support. For consistent use, it is beneficial to harmonise the time intervals and the spatial resolution applied across datasets. Typical environmental chemical indicators are reported as single substances expressed as mass (tonnes) of production/consumption/emission per year/area/economic activity or are normalised to a baseline year where changes are shown in percent (e.g. POPs emissions at country level; EEA, 2017$^9$).

The current deliverable discusses and suggests options to develop HBM indicators, illustrated by a few case studies. Within Task 5.4 of HBM4EU, criteria were defined for situations and substances when the development of an HBM indicator would be appropriate or needed. The HBM indicators should be based on existing criteria of other indicator lists, such as the European Core Health Indicators (ECHI), the Norman Networks indicators for chemicals in water, and the Environmental indicators of the European Environment Agency (EEA).

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$^7$ Developed by task 10.3.
$^8$ A methodology for how to develop these is described in deliverable D5.2.
Inspired by this and existing work on HBM and other indicators, we developed a set of criteria for how to select substances to develop HBM-indicators, see Table 1. The criteria were presented and discussed during an expert HBM indicator workshop in June 2017 in Copenhagen (Denmark) organised by the EEA and HMB4EU Task 5.4 partners. Participants of the workshop were experts experienced in indicator development or policy interpretation: Martin Scheringer (ETH, Zurich), Dorota Iwona Jarosinska (WHO, ECEH), Federico Antognazza (EEA), Angela Fehr (Robert Koch Institute, Berlin), Marleen De Smedt (Eurostat), Aantti Kaartinen (EEA), Dries Coertjens (University of Antwerp) and Greet Schoeters (VITO).

Overall, the initial outcome was that indicators should have policy relevance, data should be available, that exposure burden from the chemical is linked to certain health effects, and the indicator should be unique, comparable at international level, and be clear and easy to interpret. However, after the workshop, further discussions led to a consensus in the group that the link to specific health effects would be useful for some, but would not be an essential prerequisite for all HBM-indicators. An increase of the concentration of a chemical in a system (human, environment, etc.) may an alarming indication of a build-up of chemicals. With the precautionary principle in mind, the build-up of the chemical concentration can already be an indicator regardless of the presence of health effects. For most chemicals in HBM4EU, and certainly those in the lower categories C, D and E in the scoping documents of HBM4EU, there are no HBM HBGV. Therefore, in order to accommodate also the possibility to develop indicators for those chemicals for which there are human exposure biomarker values, the criterion “exposure burden from the chemical is linked to certain health effects” was dropped. It might be even practically impossible as for many - if not most chemicals studied - it is NOT yet known whether current internal exposure levels may cause health effects.

Subsequently we presented and got feedback on this approach for other HBM4EU members outside the task 5.4 at two occasions: during the HBM4EU consortium meeting held on September 6th-7th 2017, in Berlin, the participants advised to use the simple result indicator for exposure, rather than applying a ‘read-across’ use of HBGVs for substances lacking a hazard characterisation, but belonging to a chemical group. If the result indicator would warrant further investigation of the substances, a proper risk characterisation and development of HBGVs could then be the next step. This approach was supported at the WP5 general meeting held November 14-15th 2017 in Antwerp, Belgium.
Table 1: List of criteria for the selection of chemicals as HBM indicators

| EU policy relevance | • Public health issue, burden of disease  
|                     | • Clear policy question  
|                     | • Preparing policy (chemicals of concern)  
|                     | • Evaluation of policies (implementation)  
|                     | • Clear possibilities for prevention and risk management options  
|                     | • Association to health inequalities and socio-economic status  
| Societal relevance   | • Public demand for more information on a topic  
| Health effects       | • Evidence of exposure  
|                     | • An association with health effects (hazard) exists (not mandatory)  
|                     | • Human BioMonitoring Health based guidance (HBM HBGV) values preferably available (health risk)  
| Data availability    | • HBM data available from European countries  
|                     | • Representative data in relation to goals  
|                     | • Time trends  
|                     | • Availability of standardised analytical method  
| Comparability        | • Providing benchmark for international comparison  
| Indicator type       | • No overlap/strong correlation with other indicators (e.g. from same source)  
|                     | • Interpretability: simple interpretation in relation to policy question  
| Communication        | • Easy to communicate to non-experts and the public  

Within the HBM4EU project nine priority groups of environmental chemicals were selected for the years 2017-2018: phthalates and phthalate alternatives, bisphenols, per-/polyfluorinated compounds (PFAS), flame retardants, cadmium and chromium VI, PAHs and air pollutants, aniline compounds (primary aromatic amines and their precursors), chemical mixtures, and emerging chemicals. These priority chemicals are classified into three different categories: category A where sufficient data are already available, category B where only insufficient data are available, and category C where no data or very limited data are available.

Two chemical groups (present in category A) were chosen to demonstrate the developed indicators, based on the criteria listed above, representing the bisphenols priority group (bisphenol A) and the per- and polyfluorinated alkyl substances (PFAS), i.e. PFOA, PFNA, PFOS and PFHxS.
Bisphenol A (BPA) is used in certain plastics, epoxy resins and thermal papers and is among the highest volume of chemicals produced worldwide. Studies have indicated that BPA could be associated with increased risk for cardiovascular disease, miscarriages, decreased birth weight at term, breast and prostate cancer, reproductive and sexual dysfunctions, altered immune system activity, metabolic problems and diabetes in adults, and cognitive and behavioural development in young children and that particular exposure during foetal development may be critical. There is a large literature on the toxicity of bisphenol A including at low doses, and in addition a solid evidence for a large majority of the human population is being exposed to BPA (see Scoping Documents from HBM4EU10). BPA represent a single substance, with a fairly short half-life, and aggregate and potentially mixture toxicity characteristics. BPA has high EU policy and societal relevance, mainly due to its endocrine disrupting properties11. BPA has been listed as a substance of very high concern (SVHC) in the EU under REACH12; limit values for BPA have been set by the EU and by member states; criteria for EDCs are currently being debated in the EU; and the EC is preparing the non-toxic environment strategy also addressing chemical exposure of vulnerable groups such as children (http://ec.europa.eu/environment/chemicals/non-toxic/index_en.htm). Data availability is large, including harmonised studies across Europe in the DEMOCOPHES project, but time trends lack in the EU. Due to high societal awareness on BPA we judge that communication to the public will be easy and appreciated.

2. Per and polyfluorinated alkyl substances (PFAS): PFOA, PFNA, PFOS and PFHxS

PFAS is a large group of thousands of highly persistent chemicals which are widely used for industrial and consumer goods such as surfactants, in detergents, lubricants, textiles, carpets, fire-fighting foams, in creams and cosmetics, and in food packaging. Studies have associated exposure to PFAS with increased risk for testicular cancer, impaired immune system, impaired thyroid function, increased cholesterol, decreased birth weight at term, obesity, decreased fertility in men and women, and some indication of breast cancer and risk of miscarriages. Particularly exposure during foetal development may be critical. Because of their global occurrence in different environmental media, their high persistency and their potential to bioaccumulate in humans make them of high toxicological and public concern (Vökel et al., 2008)13. The PFASs chosen represent a group of substances with extremely long half-lived of several years, and aggregate and potentially mixture toxicity characteristics. Since the uses of PFAS are widely spread, and consumer articles and mixtures containing these substances are placed on the market in all EU Member States, high exposure burden from PFAS is a relevant health issue for whole Europe (see Scoping Documents from HBM4EU10). PFAS has a high degree of attention and policy relevance at national, EU and international level. Several PFAS are listed by ECHA as substances of very high concern (SVHCs)12; there is a REACH restriction of PFOA and its precursors14; short chain PFAS restrictions under REACH are being currently being proposed by

11 ECHA 2017b: ECHA/PR/17/14: One new substance added to the Candidate List, several entries updated.
https://echa.europa.eu/-/one-new-substance-added-to-the-candidate-list
12 ECHA 2017: Candidate List of substances of very high concern for Authorisation (published in accordance with Article 59(10) of the REACH Regulation). https://echa.europa.eu/candidate-list-table
Germany and Norway; EFSA is re-evaluating the tolerable daily intake of PFOA and PFOS; limit values for PFAS have been set by EU and member states in water, soil and food contact materials; UNEP has PFOS and its derivatives, and PFHxS listed as POPs; OECD has a dedicated working group on PFAS; and finally the non-toxic environment strategy of the European Commission specifically addresses very persistent substances which mostly consist of PFAS. For the group of PFAS, PFOA, PFNA and PFOS were selected for the indicator development as HBM HBGVs (Human BioMonitoring Health Based Guidance Values) are available from Germany and from the US, and because time trends were available from a longitudinal study. Despite PFHxs being classified as an SVHC (vPvB) substance\textsuperscript{12,15} no HBM HBGV is currently available in Europe or elsewhere. Instead the group of PFOA, PFNA, PFOS and PFHxS were included in the result indicator on PFAS exposure. Data availability on PFOA and PFOS is large and of high quality, particularly in Northern Europe, and is expected to increase both in terms of number of measured PFAS and countries. Currently EU-wide time trends for PFAS, but are available in some countries such as Germany, Sweden and in Flanders. Due to campaigns on PFAS by NGOs, business and in member states – particularly in Northern Europe - we expect that the communication to the public would be manageable, even though it is for a group, and appreciated.

\textsuperscript{12} ECHA 2017b: ECHA/PR/17/14: One new substance added to the Candidate List, several entries updated. \url{https://echa.europa.eu/-/one-new-substance-added-to-the-candidate-list}
2 Methodology development

2.1 HBM data used for indicator calculation

DEMOCPHES was a European-wide HBM pilot study on some phthalates, metals and cotinine which was performed in 2011 among 1844 children and their mothers in 17 European countries (EU-FP7). Urinary BPA data from 6 European countries were collected in 639 mothers (<45 years old) and their children (5-12 years old) (Covaci et al., 2015)\(^\text{16}\). Selected countries comprised Belgium, Denmark, Luxembourg, Slovenia, Spain and Sweden (Frederiksen et al., 2013)\(^\text{17}\). BPA data was used to illustrate a HBM-based indicator for a single substance.

Additionally to BPA, Denmark decided to measure also PFOA and PFOS in 143 mothers and their children (Morck et al., 2015)\(^\text{18}\). PFOA and PFOS data was used to present the impact indicator ‘Extent of Exceedance’ (and the result indicator ‘PFAS exposure indicator’) for a group of substances. The data were stratified for countries and for age (mothers and children).

Sweden has since 1996 run a health related environmental monitoring programme in which they have measured PFAS belonging to the groups of perfluorocarboxylic acids (PFCA, C4, C6-C12, C14, C16, C18) and perfluorosulfonic acids (PFSA, C4, C6, C8, C10). Blood (serum) has been measured for young men and women (18 years old), women (20-41 years old) and children (3-12 years old) for various years, and been reported in ng/g, corresponding to ng/mL according to the data provider. The P50 and P95 percentiles of the data for PFOA (C8 PFCA), PFNA (C9 PFCA) and PFOS (C8 PFSA) and PFHxS (C6 PFSA) were used to generate indicator time trends for the studied Swedish population for a) Extent of exceedance of PFAS (for PFOA, PFOS and PFNA) and b) PFAS exposure indicator (for PFOA, PFNA, PFOS and PFHxS). Data are available in reports from the Swedish website. The HBGVs used for the calculation of the Extent and the percentage of exceedances were taken from the German HBM-1 values (ref) (PFOA: 2 ng/mL, PFOS: 5 ng/mL in blood plasma), and from the US (PFNA: 4.9 ng/mL in serum)\(^\text{19}\). The Target Human Serum Level for PFNA has been developed by the New Jersey Drinking Water Quality Institute and New Jersey Department of Environmental Protection for PFNA.

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\(^{19}\) The basis for this value (PFNA: 4.9 ng/mL in serum) is shown on numbered pages 71-75 (PDF pages 75-79) of the NJ Drinking Water Quality Institute Health-based MCL Support Document at http://www.nj.gov/dep/watersupply/pdf/pfna-health-effects.pdf and on pages 44-48 , and on pages 44-48 of the NJDEP Interim Ground Water Quality Criterion Technical Support Document http://www.state.nj.us/dep/dsr/supportdocs/pfna/PFNA%20FINAL%20%20interim%20GW%20criterion%206_26_15.pdf.
2.2 Methodology to calculate HBM indicators for single substances

Starting from the HBM data, two main types of indicators were derived.

1. Results indicators
   a) Exposure indicator
   b) Exposure compared to reference group indicator

2. Impact indicator (risk indicator)
   a) Extent of exceedance
   b) Percentage of exceedance

Exposure indicators

The first group (results indicators) represents exposure levels in the population, mostly reported as the Xth percentile (P_x) of a population.

For the Exposure indicators (group 1a) the P_x concentration values (e.g. in ng/mL) are plotted against for instance time (producing a time-trend) or a spatial variation (producing a map). The case of 1b, the exposure indicator may also be compared to a typical background level of the general population, such as a statistically-derived reference value (usually P50) called the HBM Reference Value (HBM RV)). The indicator would then be P(x)/(HBM RV) can then again be plotted against time or spatial dimensions. An example how this could look like is presented in Table 2 first row (“Is there a time-trend?”). For this HBM4EU methodology there was consensus to make indicators for both P50 and P95 values. These values are typically also reported in scientific studies. All of the indicators can be further stratified into descriptive parameters (depending on relevance and data availability), which may indicate likely sources, or show subpopulations at particular risk. Typical stratifications could be age, gender, occupational exposures, or vicinity to a contaminated site.

If individual data are not available, the data providers would have to generate the percentiles according to the selected parameter, and share it with those making the indicator.

Impact indicators

The second type of indicators are so-called ‘impact indicators’, which compare HBM exposure data with a concentration level, which is considered safe or at least low risk for humans. In HBM4EU we have used HBM Health Based Guidance Values (HBM HBGV), which gives an idea of the possible presence or absence of health risks based on current knowledge. The impact indicators may as before be varied over time and space (e.g. country level), and be stratified according to e.g. gender and age as described above.

For the HBM4EU we propose two impact indicators: The first one is the ‘Percentage of population exceeding the HBM HBGV’, (called P) and the second is the ‘Extent of exceedance’ (called E) and are described below.

Percent of exceedance indicator

The percentage of the population exceeding the HBM HBGV is given as:

\[ P = \frac{n}{N} \times 100\% \]

where,

n is the number of samples which have HBM-exposure levels above the HBM HBGV and

N is the total number of samples.
This type of indicator is also proposed in the BRIDGE Health project\(^{20}\) and the NORMAN network\(^{21}\). As the outcome of this indicator is largely influenced by the number of samples studied, the advice was given to provide the value of \(N\) together with the indicator. In the NORMAN network (http://www.norman-network.net/?q=Home), the term frequency of exceedance is used, but in that case for each individual sample the ratio of measured environmental concentration/predicted no-effect concentration is calculated and the frequency of samples with a ratio larger than 1 is counted. However, currently the HBM4EU database is not yet populated with individual data The indicator term “percentage of population exceeding the HBM HBGV” can be derived based on aggregated HBM data (known distribution percentiles). In fact, \(P\) can be expressed as the percentile \(P_z\) where the HBM HBGV value intersects the percentile distribution (which can be generated from aggregated data as described in section 2.4). Since \(P_z\) is equal to the number at \(z\%\) of the total number of samples,

\[
n = N - (z/100)*N = N(1-z/100), \text{ and thereby implies that} \\
P = (1-z/100)*100\%
\]

If for instance the HBM HBGV is equal to the HBM-exposure level at the P85, then \(z=85\), and the percentage of exceedance is \(P = 15\%\). When individual HBM data become available, the term ‘percentage of the population exceeding the HBM HBGV’ could be replaced by ‘frequency of exceedance’ conform the term used in the NORMAN network.

**Extent of exceedance indicators**

The extent of exceedance (\(E\)) describes how by much the HBM HBGV is exceeded. It’s calculated by selecting a specific reference value \(P_x\) and dividing this value by the HBM HBGV:

\[
E = \frac{P_x}{\text{HBM HBGV}}
\]

A value > 1 means that for the percentile \(P_x\) the HBM HBGV is exceeded. Below 1, there is no exceedance for the \(P_x\). Comparison with a limit of exceedance value of “1”, makes intuitive sense for a single substance indicator. For a group of substances the choice of the limit of exceedance depends on the level of protection wanted, and therefore should be set by the policy or decision makers, since it involves value judgement.

The choice of the percentile \(P_x\) used to calculate the \(E\) also involves a value judgement, which may depend on the policy question as well as on more scientific issues. Whereas a lower percentile would ‘neglect’ too many individuals, which would not be represented in the \(E\), a percentile which is very high might on the other hand include persons with extreme habits or even with genetic/biological diseases. Altogether, some examples of issues that could be considered in making the choice for a specific (higher or lower) percentile, are:

- chronic character of health outcomes (which also affect the HBM HBGV)
- biological half-life in humans\(^{22}\), with short-lived metabolites, possibly leading to excretion peaks
- focus on highly exposed people, e.g. due to occupational exposures or living at contaminated sites
- availability of the percentiles needed

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\(^{20}\) http://www.bridge-health.eu/

\(^{21}\) NORMAN, Network of reference laboratories and related organisations for monitoring and biomonitoring of emerging environmental substances, Prioritisation framework for emerging substances, 2013. Website: (http://www.norman-network.net/?q=Home)

In the NORMAN Network, the \( P_{95} \) of the distribution of measured values is preferred over \( P_{90} \), to avoid 10\% of the population not being represented in the E.

Consensus was found in calculating the extent of exceedance indicator of single substances for \( P_{50} \) and \( P_{95} \). Whatever \( P(x) \) is selected for use in the extent of exceedance indicator, more information on how the distribution of the HBM data (including other percentiles) relate to the HBM HBGV can be given in the background.

**Choice of health based guidance values (HBM HBGV).**

Over time the HBM HBGVs may decrease as the chemical is better characterised for its toxicity. This has happened for e.g. Vinylchloride and lead, and what a safe level is for various PFAS substances are currently being discussed\(^{23},^{24} \). Over time there may therefore be a need to revise the HBGVs, and hence the indicators.

We have used one single value as HBM HBGVs, and used HBM-I levels derived by Germany for BPA (in urine), and PFOA and PFOS (in blood) and PFNA (in blood) from the US\(^19 \). HBM4EU task 5.2 has developed a methodology to generate new HBM HBGVs. In the future it may enable the generation of HBGVs for chemicals, which have been selected to make HBM4EU indicators for.

### 2.3 Methodology for HBM indicators for combined chemical exposures at population level

**Exposure indicators**

For a group of substances like PFAS, the simplest form is the result (group exposure) indicator being the sum of HBM exposure levels. Scientific studies often report such simple sums of ng/mL. A more correct way could be to add the molar concentrations of each single substance. The disadvantage of summing chemical concentrations would be that the information on the individual substances may be lost: is the concentration of substance x going up and substance y going down over time? The indicator just simplifies a kind of total chemical exposure which can be followed over time, and which may warrant further investigations or risk management options. The group exposure indicator has the advantage that it can include substances, which have replaced phased-out, but which lack HBM HBGVs. This indicator may therefore be used to survey regrettable substitution, e.g. in the group of bisphenols and PFAS. In some cases substances have also been classified under REACH as an SVHC due to its vPvB characteristics, which does not require information of toxicity. HBM HBGVs may therefore not be available. An example is PFHxS.

To calculate the ‘group exposure indicator’ for a group of substances at population level, we used the \( P_{50} \) values, though the \( P_{95} \) or some other \( P_x \) also could be used:

\[
\text{Sum exposure} = P_{x,\text{PFAS,1}} + P_{x,\text{PFAS,2}} + \ldots + P_{x,\text{PFAS,n}}
\]

where \( P_{x,\text{PFAS,n}} \) is the x'th percentile of the HBM concentrations (levels) of the n'th substance at population level.

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Extent of exceedance indicators

In the case that an impact indicator is used to assess a general impact of chemicals on human health, the Extent of exceedance (E) for a group, e.g. $E_{PFAS}$ could be calculated as the sum of

$$E_{PFAS} = E_{PFAS,1} + E_{PFAS,2} + \ldots + E_{PFAS,n} = \left(\frac{P_x}{HBM \ HBGV}\right)_{PFAS,1} + \left(\frac{P_x}{HBM \ HBGV}\right)_{PFAS,2} + \ldots + \left(\frac{P_x}{HBM \ HBGV}\right)_{PFAS,n}$$

The HBM HBGVs could be based on different lead toxicities, such as liver toxicity for one, cancer the second and immunotoxicity for the n’th substance. This is indeed the case for various PFAS-types, which share some, but not all toxicological endpoints, and which do not have the same lead toxicities.

This type of approach is well established for the assessment of mixture toxicities, usually called the “Hazard Index” (HI), and is described in the state of the art report on mixture toxicity for the EU Commission\textsuperscript{25}, in the guidance documents by the US EPA\textsuperscript{26}, in WHO reports\textsuperscript{27}, the EU’s scientific committees\textsuperscript{28} (SCHER, SCENIHR & SCCS, 2012) and the EU Joint Research Centre (Kienzler et al., 2014). A conceptually similar approach is used in the form of PEC/PNEC sums, used for the environmental assessment of chemical mixtures\textsuperscript{21,29,30}.

It should be noted that the final value of E (or the hazard index) is not a direct measure of expectable risk, as the individual HBM HBGV values might be based on different data types, might use different safety factors and might be driven by different critical effects (“lead toxicity”). However, E can be considered a conservative first tier approach (see references above). A value of E exceeding the critical value of 1 therefore simply indicates a potential for concern. For higher tier (more realistic) assessments, additional data are needed, which might require to produce substantial amounts of new toxicological information.

For a group of substances the sum of extent of exceedances can be seen as a combined chemical pressure that may affect the overall health of a population. It does however not provide information, and is not supposed to do so, on the risk for individuals. The reason is that an individual may not have the $P_{95}$ for PFOA, and $P_{95}$ for PFOS and $P_{95}$ for PFNA and $P_{95}$ for PFHxS, all at the same time. The limit of exceedance does therefore not relate directly to a risk of getting a specific disease. Rather, the limit of exceedance serves to indicate to policy/decision makers that there is a need to have increased focus on a specific group of chemicals, a sub-population or a region. Actions may include asking for actual risk assessments on mixtures of chemicals in


\textsuperscript{28} Scientific Committee on Health and Environmental Risks Scientific (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and Scientific Committee on Consumer Safety (SCCS) (2012) Final opinion on: Toxicity and Assessment of Chemical Mixtures.


individuals and, to further develop/review HBM HBGVs. It is up to the decision makers to decide if they want to set a limit of exceedance, and in that case, what the limit should be. The choice of where to set the limit of exceedance depends on the level of protection wanted. The chosen protection level, and hence extent of exceedance, is a value judgement, and should be set by policy or decision makers.

In the case, that the exposure indicator raises reason for concern, a response may be to generate missing information on e.g. risk characterisation of individual substances, or to develop HBM HBGVs. If it turns out, that a group of chemicals affect the same toxicological endpoint, and by the same mode of action, it would be possible to generate a *mixture risk indicator*, but which would require individual data. Methodologies using the Hazard Index (HI) \(^{32}\), the ‘concentration addition’ model (CA), and the ‘independent addition’ model (IA) \(^{33}\), are approaches that may be applied to mixtures at an individual level. This is the topic of WP15, and will not be further described in this report. The impact indicators proposed in this report, could thereby serve to trigger the need to generate mixture risk indicator, such as those being developed in WP15.

In general, if a progress towards a policy objective is found to be unsatisfactory, the policy makers could decide to take various actions, such as:

- request in-depth risk assessments,
- request a review or to develop new HBM HBGVs for substances which do not have them
- provide risk adaptation measures for instance by guiding the public on eating/consumer behaviour habits for the whole or for the more vulnerable sub-populations (e.g. limit the intake of top predator fish)
- initiate risk prevention measures such as restricting the use of hazardous substances.

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\(^{31}\) Which may include getting individual data, and to use methods such as concentration addition to assess the risks for individuals based on the actual chemical profiles in their bodies.


2.4 Visualisation of indicators

At the EEA workshop we decided to use a layered system with additional information (distribution of HBM data) in the background.

HBM Health Based Guidance Values, HBM Reference Values, the percentage of the population exceeding the HBM HBGV (P) and the extent of exceedance (E) can be displayed in number format, to which geographical and temporal dimensions can be added. These data can further be stratified by exposure determinants like age and gender. To create an overview, the indicators can be presented in table and/or figure format (e.g. map of Europe). The visualisation depends mainly on the policy question and which type to use for the visualisation has to be decided on a case by case basis (Table 2).

Table 2: Examples of different types of visualisation of indicators

<table>
<thead>
<tr>
<th>Policy question</th>
<th>Visualisation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there a time trend?</td>
<td>Line graph or bar graph showing time trend; just P50 or P90 levels for the result indicator (exposure levels) and impact indicators (E, P) for single or groups of substances; or box plots for every subsequent year.</td>
<td><img src="image1.png" alt="Line graph" /></td>
</tr>
<tr>
<td>Are there geographical differences?</td>
<td>Map of Europe with colours for different levels.</td>
<td><img src="image2.png" alt="Map of Europe" /></td>
</tr>
<tr>
<td>Is there variation by e.g. sex, age?</td>
<td>Stratification of data by selected variables.</td>
<td>Examples above stratified by studied variables.</td>
</tr>
<tr>
<td>Etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Provided trhat the sampling is randomised over the country and representative
3 Case studies illustrating a few HBM indicators

3.1 Democophes data for BPA, PFOA and PFOS

First a general description of the results is given. The proportion of values >LOQ was 90% in 5 out of the 6 studied countries (Table ; see Annex). For Luxembourg, the country with the highest LOQ (i.e. 1 µg/L), it was around 50%. In general, there was a low inter-individual variability in urinary BPA levels: i) the inter-individual variability within a country was small; ii) levels were quite similar in children and mothers; and iii) the average levels were close together in the different countries (Covaci et al. 201516).

Results indicator BPA

Although the inter-individual variability in urinary BPA levels was low, significant differences were observed between the studied countries. In order to compare the BPA levels between the countries, the overall differences were tested in multiple regression models (based on F-test). When values were compared to the European geometric mean (1.97 µg/L), significantly (P<0.05) higher values were observed in Slovenian children (2.63 µg/L) and significantly lower levels were found in Swedish children (1.48 µg/L). For the mothers, significantly higher concentrations were observed in Belgium (2.55 µg/L) and Denmark (2.0 µg/L), while in Sweden (1.30 µg/L) and Slovenia (1.37 µg/L) levels were significantly lower. Conclusions in both age groups are thus to some extent consistent (e.g. for Sweden), but also contradictory (e.g. for Slovenia).

In children, the weighted geometric mean (95% CI) for urinary BPA equalled 1.97 µg/L (1.81-2.15) in the total European study group. In mothers, it equalled 1.78 µg/L (1.62-1.94), suggesting a tendency for higher levels in children compared to their mothers.

Impact indicator BPA

For BPA do exist different HBM HBGVs: 1) the German HBM-I-value for children and the German HBM-I-value for adults35, 2) the BE value based on one hand on the pTDI from Health Canada and on the other the BE value based on the US EPA RfD and EFSA TDI36. The German HBM-I value was used here as primary health based guidance value seeing the absence of an EU HBM HBGV. The use of the German HBM-I-value indicated that in <5% of the Danish children and in <5% of the mother-child pairs in Belgium the measured urinary BPA concentrations exceeded the German HBM-I-guidance value. Exceeding the HBM-I-value implies that the occurrence of a certain health risk cannot be excluded with sufficient certainty. As the percentage of the population exceeding the HBM HBGV was <5% in Danish mothers, Belgian children and mothers, the extent of exceedance indicator, based here on the ratio of the 95% percentile over the HBM-I-guidance value, was <1. None of the participants in the six European countries did exceed the BE values for urinary BPA which are older and higher than the HBM-I. The BE value corresponding to the oral provisional tolerable daily intake (pTDI) of 25 lg/kg-d from Health Canada is 1 mg/L (1.3 mg/g creatinine); value corresponding to the US EPA reference dose (RfD) and EFSA tolerable daily intake (TDI) estimates (both of which are equal to 50 lg/kg-d) is 2 mg/L (2.6 mg/g creatinine36).

**Graphical visualisation BPA indicator**

As only percentiles were available from the published data, the $P_{50}$ and $P_{95}$ were visualised for the DEMOCOPHES data from BPA (Figure 1 and Figure 2). Results were benchmarked against the German HBM-I-value.

![Graph 1](image1)

*Figure 1: Urinary levels (µg/L) BPA-equivalents in mothers (50th and 95th percentile) in xix EU countries (DEMOCOPHES, 2011) benchmarked against the German HBM-I guidance value below which no adverse effects are expected according to current knowledge.*

![Graph 2](image2)

*Figure 2: Urinary levels (µg/L) BPA-equivalents in children (50th and 95th percentile) in six EU countries (DEMOCOPHES, 2011) benchmarked against the German HBM-I guidance value below which no adverse effects are expected according to current knowledge.*
Results indicator PFOS and PFOA DEMOCOPHES

DEMOCOPHES data showed that PFOS is more abundant than PFOA in the plasma samples of both mothers (for P<sub>50</sub> factor 4.8) and children (for P<sub>50</sub> factor 2.9). The levels were significantly higher in children compared to their mothers for PFOS (for P<sub>50</sub> factor 1.1) and PFOA (for P<sub>50</sub> factor 1.9) (Table 3).

Impact indicators PFOS and PFOA DEMOCOPHES (single substance and group)

Further the data showed that for both PFOA and PFOS a substantial amount of the Danish population exceeded the German HBM-I-values and especially children over 50% did exceed the German HBM-I-values for both substances. The German HBM-I-values for the general population of PFOA: 2 µg/L (2 ng/mL) and PFOS: 5 µg/L (2 ng/mL) were used here as guidance values given the absence of an EU HBM HBGV. Extent of exceedance indicators showed that based on P<sub>50</sub> for PFOA and PFOS the HBM-I-value was exceeded 1.5-1.7 times while based on P<sub>95</sub> for PFOA and PFOS the exceedance was 1.7-3.2 times. Highest exceedance was for PFOS for children in Denmark and Belgium (P<sub>95</sub>/HBM-I-value = 3.2).

The total chemical pressure, based on the sum of P<sub>50</sub> values expressed at molar basis, was equal to 0.019 µmol/L for mothers and 0.025 µmol/L for their children. This shows that concentrations for the group of PFOS and PFOA in children are larger than in adults (mothers).

For those PFAS which have the same mode of action, it would be possible to make mixture toxicity indicators, which could consider various approaches using e.g. concentration addition, independent action and hazard indices to express the combined risk of exposure. This would however require individual data. Depending on future agreements between the data owners and HBM4EU about data use and data transfer, and assuming that individual data will become available, development of such a mixture indicator could be considered in collaboration with WP15 on mixtures.

Table 3: Impact indicators based on DEMOCOPHES data for PFOA and PFOS in blood plasma from Danish mothers and their (school) children and the HBM-I value

<table>
<thead>
<tr>
<th>Country</th>
<th>Substance</th>
<th>Study group</th>
<th>Number of people</th>
<th>AM (µg/L)</th>
<th>P50</th>
<th>P95</th>
<th>HBM-I-value [µg/L]</th>
<th>Percentage of population exceeding HBM-I value [%]</th>
<th>Extent of exceedance (P50/German HBM-I value)</th>
<th>Extent of exceedance (P95/German HBM-I value)</th>
<th>Total chemical pressure : sum of P50 [µmol/L]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DK</td>
<td>PFOA</td>
<td>children</td>
<td>116</td>
<td>3.2</td>
<td>3.02</td>
<td>5.21</td>
<td>2</td>
<td>&gt;50</td>
<td>1.51</td>
<td>2.61</td>
<td>0.025</td>
<td>Morck et al. (2015)&lt;sup&gt;18&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PFOS</td>
<td>children</td>
<td>116</td>
<td>9.02</td>
<td>8.63</td>
<td>16.06</td>
<td>5</td>
<td>&gt;50</td>
<td>1.73</td>
<td>3.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFOA</td>
<td>mothers</td>
<td>143</td>
<td>1.8</td>
<td>1.59</td>
<td>3.38</td>
<td>2</td>
<td>&lt;50</td>
<td>&lt;1</td>
<td>1.69</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PFOS</td>
<td>mothers</td>
<td>143</td>
<td>8.3</td>
<td>7.57</td>
<td>16.18</td>
<td>5</td>
<td>&gt;50</td>
<td>1.51</td>
<td>3.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AM: arithmetic mean, P: percentile

<sup>18</sup>: percentage of population exceeding the HBM HBGV estimated by comparing P<sub>50</sub> with HBM-I-values. When the whole data distribution would be known a more precise number could be given.
Graphical visualisation indicators PFOS and PFOA indicators DEMOCOPHES

As only percentiles were available from the published data, the $P_{50}$ and $P_{95}$ were visualised for the DEMOCOPHES data from PFOS and PFOA (Figure 3 and Figure 4). Results were benchmarked against the German HBM-I-value. Time trends and geographical coverage could not be displayed seeing the limited dataset.

![Graphical visualization of PFOS and PFOA indicators DEMOCOPHES](image)

**Figure 3**: Benchmarking HBM results for PFOA in women and children ($50^{th}$ and $95^{th}$ percentile) (DEMOCOPHES, 2011) against German HBM-I guidance value. At concentrations below the HBM-I-value no adverse effects are expected to current knowledge

![Graphical visualization of PFOS and PFOA indicators DEMOCOPHES](image)

**Figure 4**: Benchmarking HBM results for PFOS in women and children ($50^{th}$ and $95^{th}$ percentile) (DEMOCOPHES, 2011) against German HBM-I guidance value. At concentrations below the HBM-I-value no adverse effects are expected to current knowledge
3.2 Swedish study of PFAS time trends

Table 5 shows the data for the PFAS exposure indicator and for the PFAS extent of exceedance indicators measured in the serum of the Swedish population (men, women and children), from the SEPA Health related environmental monitoring programme. Both types of indicators give a picture of the combined chemical pressure at the population level.

Data have been aggregated from several Swedish studies, which have been conducted under the Swedish SEPA Health related environmental monitoring programme, which is published in several reports and are available online\(^\text{37, 38, 39}\). The proportion of values >LOQ was 100% in the three studies. Method quantification limits (MQLs) were: PFOA (0.8), PFNA (0.08), PFHxS (0.01), PFOS (0.01) ng/mL. PFOS was quantified for the linear PFOS (branched PFOS was not included which is a small bias). PFHxS was for total PFHxS (linear+branched). To generate averages, concentrations <MQL were set to MQL/√2.

**Time trend of the Exposure indicator for PFAS (PFOA, PFNA, PFOS, PFHxS)**

To illustrate a time-trend for a group, a result indicator was made for PFAS, based on Swedish PFAS time trend data, called the PFAS exposure indicator. \(P_{50}\) (ng/mL) of PFOA, PFNA, PFOS and PFHxS were first summed for each year, in each of the categories for women (18-41y), men (17-18 y), for teenagers (12-16 y), for children (6-11y) and toddlers (3-5y). The age groups were chosen to be as consistent as possible with those suggested by the HBM4EU statistical work package to be sampled in the years to come (6-11y, 12-19y, 20-40y), adopted by the management board in November 2017. The average exposure (result) indicator representing available Swedish data, was then calculated by taking a simple average of the age groups, without weighing the subgroups for the reasons described in the methodology. For simplicity we only included four PFAS, but it would have been perfectly fine to add other PFAS to this sum exposure indicator. Table 5 shows the data, which are plotted in Figure 5. The figure shows a steady decrease in the time trend since 1996 for the PFAS exposure indicator. Since these four PFAS are highly bioaccumulative and bind to proteins in the blood (half-lives of 3.8 - 8.5 years), HBM-levels serum levels typically rise with age. The decrease might therefore be somewhat confounded by that no older people (women 20-41y, average 29y) were included in the years 2012-2015.


\(^\text{39} \) http://www.diva-portal.org/smash/get/diva2:711698/FULLTEXT01.pdf
Table 4: Time trends of PFOA, PFOA, PFNA and PFHxS for the Swedish population (men, women and children ($P_{50}$ and $P_{95}$) against German HBM-I guidance values (PFOA and PFOS) and the New Jersey PFNA value. Both indicators (sum of PFAS level in blood and extent of exceedance) give an idea on the total chemical or combined pressure at population level. Data have been aggregated from several studies.

<table>
<thead>
<tr>
<th>Year</th>
<th>PFAS Exposure indicator in serum ($P_{50}$) ng/mL</th>
<th>$E_{PFAS, P50}$</th>
<th>$E_{PFAS, P95}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>24.2</td>
<td>5.3</td>
<td>8.6</td>
</tr>
<tr>
<td>1997</td>
<td>21.7</td>
<td>4.8</td>
<td>10.2</td>
</tr>
<tr>
<td>1998</td>
<td>24.2</td>
<td>5.3</td>
<td>8.9</td>
</tr>
<tr>
<td>1999</td>
<td>23.4</td>
<td>5.1</td>
<td>9.3</td>
</tr>
<tr>
<td>2008</td>
<td>8.3</td>
<td>1.7</td>
<td>2.9</td>
</tr>
<tr>
<td>2009</td>
<td>5.0</td>
<td>1.1</td>
<td>2.1</td>
</tr>
<tr>
<td>2010</td>
<td>5.3</td>
<td>1.4</td>
<td>2.4</td>
</tr>
<tr>
<td>2011</td>
<td>4.3</td>
<td>0.9</td>
<td>1.7</td>
</tr>
<tr>
<td>2012</td>
<td>2.8</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>2013</td>
<td>4.4</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>2014</td>
<td>3.3</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>2015</td>
<td>2.1</td>
<td>0.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Time trend of the Extent of exceedance indicators for PFAS (PFOA, PFNA and PFOS)

Table 5 also shows the Extent of exceedances ($P_{50}$ and $P_{95}$), $E_{PFAS}$, which is a sum of the individual ‘extent of exceedances’ (as described in the methodology) for PFOA, PFOS and PFNA over time. These were the only PFAS we could find guidance values for, and we used the German HBM-I guidance values for PFOA (2 ng/mL in blood plasma) and PFOS (5 ng/mL in blood plasma), and the New Jersey ‘Target human serum level’ for PFNA (4.9 ng/mL in serum). The data are visualised in Figure 5. Such a sum of Extent of exceedances can be seen as the combined chemical pressure from the group, which may affect the overall health of a population.

This $E_{PFAS}$ impact indicator could be used to get a picture of the total chemical stress from the group of PFAS at population level. The indicator could not directly be used for risk assessment of mixtures at an individual level. It might however rather warrant further risk management actions for this particular group of chemicals, including the development of more HBM HBGVs.
Figure 5: Time trend Exposure indicator of PFOA, PFOA, PFNA and PFHxS for the Swedish population (men, women and children, $P_{50}$), and Extend of Exceedance indicators ($E_{P50}$ and $E_{P95}$) using German HBM-I guidance values for PFOA and PFOS and US PFNA value. The time trend shows a steady decrease since 1996 for both the total PFAS HBM exposure levels and for the extent of exceedances.
4 Discussion

4.1 Choices and uncertainties in the data and $P_x$, used to generate indicators

Since indicators aggregate information from several data sources, they will also accumulate uncertainties from each part of the study.

In comparison with the use of averages, percentiles have the advantage that they are not affected by the value assigned to measurements below LOD or LOQ\(^4\). When calculating the percentiles, it is important to include all measurements, i.e. also those having values <LOQ and LOD. As described in the introduction, the choice of which $P_x$ to use, is a value judgment and may vary between different regulatory institutions and for different purposes. EFSA for instance may use $P_{50}$, $P_{75}$ or $P_{95}$ depending on the substance and its type of toxicity. In some cases, risk assessors may need other percentiles, e.g. $P_{75}$, $P_{90}$ or $P_{99}$, and we have therefore suggested that if individual data are not available, that the distributions be reconstructed based on aggregated data. During the consortium meeting it was proposed in the future that IPCHEM for aggregated data bring in the $P_1$, $P_5$, $P_{10}$, $P_{20}$, $P_{30}$, $P_{50}$, $P_{60}$, $P_{70}$, $P_{80}$, $P_{90}$, $P_{95}$, $P_{99}$. This will allow to reconstruct the distributions with a fairly high resolution, while avoiding to make individual data discernible. The statistical group in the HBM4EU is currently developing an R-script, which they will ask the data-providers to use to generate the percentiles with. This will ensure a harmonised generation of the percentiles.

If different studies on subpopulations are available, the data sets may need to be combined to obtain a value for the whole population in a country (e.g. men, women and children). More than one study of a subpopulation, e.g. for women, pregnant women\(^4\) and elderly women, may also need to be aggregated. If individual data are available the datasets can be combined to one large dataset and the percentiles can be taken. However, if only aggregated data available for the data sets, the percentiles must be combined in some way. If the studies are representative of a population, it would be possible to weigh the study, using the sample size in proportion to the whole population. This is for instance done for environmental monitoring in the EU, when only a fraction of lakes have been monitored for their chemical concentration.

In many cases studies, have not been designed to be representative for a population. Rather, they have been designed to study a specific and often vulnerable group. In this case it would be incorrect apply weighing factors to scale up the study, since it will introduce a bias on the $P_x$ value\(^4\). In such cases, it would therefore be more transparent to take the simple average between the $P_x$ values of each study, without having to make assumptions of unknown distributions of e.g. how age affect the HBM levels. To calculate the $P_x$ for the Swedish population, simple averages were therefore taken for the (PFAS sum) $P_x$ values for each of the differently designed study. In the future, these biases could be avoided if the same sampling design (representative of a population, or the relevant subpopulation at risk) was applied across the studies. Other biases, on the $P_x$ between different studies, could in the future also be minimised, if a high degree of harmonisation was applied to everything from sample protocols, time of sampling (particularly relevant for substances with short half-lives < 5 hours), correction factors (e.g. for hydration level in urine, or lipid content in blood), use of similar analytical methods incl. the use of (the same) internal

\(^4\) As long as $>x\%$ (here 50\%) of the values are above LOQ

\(^4\) While taking into account that pregnancy has an influence on the biomarker levels due to changed metabolism and physiology

\(^4\) unless it is known how the subpopulations $P_x$ levels compares with other population groups, and how big a fraction of the whole they each represent.
standard(s), and by giving specific guidance on whether and how to include metabolites in the reported levels.

The laboratories in DEMOCOPHES that analysed the samples, had been selected through a strict quality assurance process, comprising Inter-laboratory Comparison Investigations (ICI) and External Quality Assessment Schemes (EQUAS). In this way it was ensured that the data was comparable between the countries\(^43\). Statistical analysis and interpretation of the results had been performed for each country as well as at EU level after having transferred the cleaned national databases to a European central database. As a result the variation in the data was minimised, which strengthens the interpretation of the results.

### 4.2 Results indicator

Most HBM campaigns are cross-sectional studies with focus on the measurement of exposure biomarkers, their surveillance over time and the generation of reference values. As HBM HBGV only exist for a limited amount of substances, results indicators (only HBM measurements) or ‘results with reference to statistically-derived reference values’ are the primary type of HBM-based indicator.

Results indicators may build a picture about the actual body burden of a chemical in the human body. Based on this information differences between the countries, age groups and sexes can be drawn. Concentrations of urinary BPA were measured in 6 European countries and different age groups, like mothers and children. Generally it shows that BPA exposure burden was quite similar in children and in mothers\(^44\). With HBM data from different years, time trends might have shown the development of the exposure burden in the population over time. As DEMOCOPHES data were gathered only in 2011, no time trends are available.

For PFOA and PFOS only data for one country (Denmark) in one period was available. The results showed that the internal exposure was larger for PFOS than PFOA and that the burden in children was larger than in mothers, for PFOS and PFOA individually as well as for the group of substance indicator (sum of concentrations on molar basis). Stratification between age categories (children versus mothers) was possible. Spatial and temporal dimensions can be added to the indicator when more data become available.

The result indicator for the group of PFAS (PFOA, PFNA, PFOS, PFHxS) from the Swedish study showed a steady decline since 1996 to 2015. It may also be relevant to include other PFAS into this group, since PFOA and PFOS largely have been substituted with other and often rather similar PFAS. The environmental trends of PFOA and PFOS are thus decreasing, whereas e.g. PFNA is increasing in some areas. In recent years the perfluoropolyethers (PFPEs) and their carboxylates and fluorotelomer alcohols and thio-ethers and (polymer) derivatives thereof have substituted many of the PFAS uses which generated PFOA and PFOS\(^44\). They are estimated to be however similarly persistent, and from the little toxicological information available they may pose many of the characteristics of the chemicals they substituted\(^45\). Currently PFOA, PFNA, PFOS and PFHxS contribute most to the measured PFAS (mainly PFCA and PFSA) in human blood, so though the exposure indicator may increase some, it will likely not change markedly for now. However, in the

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\(^43\) [http://www.eu-hbm.info/democophes](http://www.eu-hbm.info/democophes)


future the PFAS profile in humans may change. Recently the GenX (a PFPE carboxylate) which is the substitute for PFOA in the Teflon production, was found together with other PFAS in the soil and water surrounding a Teflon plant in the Netherlands\textsuperscript{46}, as well as in the US\textsuperscript{47, 48, 49}. This warrants that the group of PFAS be followed both by an exposure (result) indicator to track possible regrettable substitution. An example of a follow-up action in case the exposure (result) indicator was found to raise concern, could be to prioritise selected PFAS for further risk characterisation and development of HBM HBGVs.

The time trend for this PFAS exposure indicator shown in Figure 5 is simple to communicate, but it does not provide information on the relative contribution of the individual PFAS. Such information might however be conveyed if stacked bars were used instead of one number, but would at the same time make the indicator more complicated to look at. Such a visualisation would therefore be suited to be put at a ‘layer’ behind the main indicator, which then could be consulted by experts.

4.3 Impact indicator

In the previous section we described how the result indicator could be calculated using $P_x$ values, and the uncertainties associated with it. Since the impact indicators combine $P_x$ or $n$, with the HBM HBGVs, we will also discuss how HBGVs may be derived and their influence on the impact indicators. Methodologies and actual HBM HBGVs are being developed in a different part of the HBM4EU, which in the future may feed into new HBM impact indicators.

4.3.1 Development of HBM HBGVs

The possibilities to interpret biomonitoring data in relation to adverse health effects are still limited. For this, HBM HBGV are pivotal but yet available only sparsely. The evidence of being highly exposed to a chemical, combined with the fact that exposure burden is associated with relevant health effects, supports the necessity of tracking the indicator. At the same time there should be the possibility for policy measures.

HBM data on its own does not provide information on the possible associated health risks. Generally, different countries may have different procedures to derive guidance values. We have focused on the two main systems used in Europe, which are used to interpret HBM data for the general population in a health risk context: the German system with health based guidance values\textsuperscript{50} and the biomonitoring equivalents (BE) of Summit Toxicology\textsuperscript{51}. The German HBM-I value is defined as the concentration below which there is no or a negligible risk for adverse health effects. The German HBM-II value is defined as the concentration above which there is an

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\textsuperscript{48} Sun, M.; Arevalo, E.; Strynar, M.; Lindstrom, A.; Richardson, M.; Kearns, B.; Pickett, A.; Smith, C.; Knappe, D. R. Legacy and Emerging Perfluoroalkyl Substances Are Important Drinking Water Contaminants in the Cape Fear River Watershed of North Carolina


\textsuperscript{51} www.summittoxicology.com
increased risk for health effects and immediate action is wanted. The HBM-I value is not equal but conceptually similar with the biomonitoring equivalent (BE) of Summit Toxicology (Hays et al. (2008)) representing an internal concentration consistent with a defined external exposure guidance value (e.g. tolerable daily intake, reference dose) below which no adverse health effects are expected.

The BEPOD (Point of Departure) of Summit Toxicology corresponds with a human equivalent concentration (HEC) based on the no-effect level in animals (if starting from animal toxicity data) and if values are > than the BEPOD, priority for risk assessment follow-up is high. Both systems (German and Summit Toxicology) are dual with two assessment levels (German: HBM-I and HBM-II; Summit Toxicology: BE and BEPOD). For the increased or unacceptable risk level (HBM-II and BEPOD) there could be discussion on the definition and the use of such a level whereas for the no or negligible risk level (HBM-I and BE) this is more straightforward. Therefore experts attending the EEA workshop, decided to focus on an indicator only on the zero or negligible risk value (HBM-I and BE). Different institutions (USEPA, EFSA, JECFA, etc.) may derive different values for tolerable daily intake, and reference doses which results in different values for BE. There is thus uncertainty on the level of no adverse health effects (depending on amongst others, when starting from external dose in animal studies, the critical study, the assessment factors used and conversion to body burden). This uncertainty can be taken up in the indicator, which would be relevant to show in the indicator for reasons of transparency, but makes the indicator more difficult to interpret for a non-expert audience. The proposition during the workshop discussion was to go for a single value (Px) to which exposure data can be benchmarked. It was also discussed whether there should be bars of uncertainties around the P_x values, which would be scientifically correct, but which may be harder to communicate.

Within the HBM4EU project for each of the priority substances one uniform EU HBM HBGV, below which no adverse effects are expected, will be derived if possible, taking into account information on e.g. existing values and derivations. When available, the EU HBM HBGV can be used in the calculation of the HBM indicator. In case no guidance value can be derived, HBM data can be compared using the reference values.

Another concern regards the increasing evidence that toxicity (potency) may not be the same for all ages. This point was brought up during the WP5 meeting in November 2017, in Antwerp. For substances, which affect foetal development, various critical time of exposures exist. This may be for endocrine disruptors, and for chemicals, which have immuno-development or neuro-development toxicities. Another case are the substances which have non-monotonic dose-response curves and may cause effects at low-doses, but no (or different) effects at higher doses. BPA is one such example. Also for bioaccumulative chemicals, it could be argued that the HBM HBGVs change with age: The protective level for a child is likely lower (in order to prevent high levels of bioaccumulated chemicals later in life), than for an elderly person, who will have fewer years to accumulate the chemical, and therefore might have a higher HBM HBGVs. PFAS which typically have very long half-lives in humans (up to 8.5 years for PFHxS) are such examples. At this point varying HBM HBGVs cannot be addressed for the indicators, but it is important to make the information available to the policy makers and risk assessors and managers, both for

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transparency reasons and since the question may arise (from NGOs and scientists) when communicating the indicator to the society.

### 4.3.2 Discussion of BPA results

From the data it could be seen that the exposure burden from BPA was relatively low in the participating countries. Only <5% of Danish children and Belgian children and mothers did exceed the German HBM-I-value of 100 µg/L in children and 200 µg/L in mothers (German Human Biomonitoring Commission, 2012\(^53\)). By measuring the percentage of the population exceeding the HBM HBGV it could be shown that for a small number of children and mothers in Denmark and Belgium health damage cannot be excluded with sufficient certainty. For these people preventive actions could be taken by risk managers to minimise the exposure burden from BPA. The HBM-I-values were adapted after a revision of the EFSA TDI in 2015. Based on the BE values, no exceedance could be observed, but as the BE values were derived in 2010 based on relatively ‘old’ TDIs, it can be concluded that the use of the German HBM-I-values for BPA gives a more realistic picture.

### 4.3.3 Discussion of PFAS results

Since PFOA and polyfluorinated PFOA precursors have been widely used in both industrial and consumer products in all EU Member States, EU wide action is necessary to retrace emissions of PFOA. In 2010 PFOS was added to the regulation on persistent organic pollutants under the Stockholm Convention\(^54\), but is still present in human bodies and the environment. For this purpose the development of an HBM indicator was favoured to track changes and political decisions in chemical exposure burden of the European population. For PFOS the HBM-I value was exceeded with >50% for Danish mothers and children, while for PFOA this was only valid for children and not for mothers. The extent by which the P95 exceeded the HBM-I value was 1.7 to 3.2 times. Spatial and temporal dimensions can be added to the indicator when data becomes available. As PFOA and PFOS are also bioaccumulative, persistent substances and PFOA is listed as carcinogenic (Cat 2) these results are alarming.

Therefore it can be summarised that both the Exposure indicator, and the Extent of exceedance for PFAS are valuable HBM indicators, which gives a picture of the PFAS exposure burden and likely associated health impacts in the European population. Regarding the high exposure burden of PFOA and PFOS in the mothers and children from Denmark it can be recommended to follow-up the development of exposure burden from PFOA and PFOS in all of Europe.

The time-trend of the Swedish PFAS data in Figure 5 shows that a substantial amount of the Swedish population had HBM-levels, which were above HBGVs. It is however reassuring to see a decreasing time-trend from 1996-2015, and that \(E_{PFAS, P95}\) drops from 8.6 (1996) to 0.84 (2015). This might indicate that policy measures to limit the use of particularly PFOS and PFOA have worked. The \(P_{95}\) is on average higher by a factor of 2.2 than the \(P_{50}\) (from 1.7 to 3.3). If HBGVs were present for more PFAS they could be added. It would likely increase the \(E_{PFAS, P95}\) a bit, particularly due to PFHxS, which is present in the 1-5 ng/mL range. However, the majority of other PFAS are currently present in very low levels, so their contribution would generally be minor. However close to hotspot contaminated sites, they might add significantly to the indicator. As PFAS toxicity data continuously is getting more abundant, there has been a tendency that the safe levels have decreased after re-evaluation of the limit values, e.g. in the US\(^23,24\). This could in the future have the consequence that the HBGVs will be revised (lowered) and the EPFAS therefore

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\(^{54}\)http://www.pops.int/
would rise – however the E\textsubscript{PFAS} should then be done for the whole time period to provide a proper trend.

This E\textsubscript{PFAS} impact indicator could be used to get a picture of the total chemical stress from the group of PFAS at population level. It could not directly be used for risk assessment of mixtures at an individual level. It might however rather warrant further risk management actions for this particular group of chemicals, including the development of more HBM HBGVs.

As for the PFAS exposure indicator, the time trend for this PFAS exposure indicator is simple to communicate, but it does not provide information on the relative contribution of the individual PFAS. Such information might however be conveyed if stacked bars were used instead of one number, but would at the same time make the indicator more complicated to look at. Such a visualisation would therefore be suited to be put at a ‘layer’ behind the main indicator, which then could be consulted by experts.

4.4 Indicator visualisation

An indicator can be seen as a road sign for policy making. It’s a simplification which helps users to absorb information quickly, but this also means that it increases the amount of context needed to interpret the information in a correct way. De-contextualisation is one of the most common and yet complex risks in the use of indicators\textsuperscript{55}. The workgroup agreed that the indicator should contain a clear and easy to understand description and in case a graph is displayed, it should be clarified with text (and references), in order to avoid being taken out of the interpretation context. Including the policy context of the HBM data is of additional value towards different stakeholders. The policy questions also largely determines the type of presentation.

Generally, the indicator can be expressed in number format or infographics to increase the readability. Exposure reference values can be displayed on a map to show geographical variation. Time trends can be shown by a line, or alternatively by stacked bars for to show the individual contribution of single substances to the groups of substances. For the health impact indicator, the example of BPA doesn’t lend itself well for displaying the percentage of the population exceeding the HBM HBGV and the extent of exceedance as the exceedance is limited.

\textsuperscript{55} Eurostat, Towards a harmonised methodology for statistical indicators – Part 3: relevance of indicators for policy making, 2017
PFAS on the other hand can be shown as the percentage of the population in different countries, which exceeds the HBM HBGV for a single or groups of substances, for instance using e.g. a pie diagram (Figure 6) on the map of Europe. The time trend in relation to a baseline year, or over several years, can be given in the form of an arrow within the pie.

**Figure 6: Hypothetical example of spatial visualisation of HBM indicator in health risk context based on EEA publication (2010).** The figure presents the % of the population above (below) an EU HBM HBGV. No adverse health effects are expected below this value to current knowledge.

Behind the indicators, or even the single numbers of reference values, percentage of population exceeding the HBM HBGV and extent of exceedance, more information on the distribution of the individual HBM data can be given, if available. When evaluating single substances, a histogram can be used presenting both the percentage of the population exceeding the HBM HBGV and extent of exceedance (see Figure 7).

The time trend can be shown by displaying histograms of different monitoring campaigns next to each other. Not only relative values (% of population exceeding the HBM HBGV) but also absolute values (geometric mean; x% of the population having a concentration y) can be given. Absolute numbers are useful and can easily be interpreted by experts. Relative numbers (percentage of population exceeding a threshold) are more relevant for policymakers. Data availability (raw data, aggregated data) largely influences its presentation.

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4.5 European HBM indicators in the European indicator field

In the field of environment and health, there are three European Core Indicator lists, namely the Environmental Core Indicators of the European Environmental Agency (EEA)\(^57\), the WHO European Region ENHIS\(^58\) (Environment and health information system) list and the European Core Health indicators (ECHI)\(^59\). The EEA is one of several EU-level bodies that produce environmental indicators, in cooperation with Eurostat, the Directorate-General (DG) for the Environment and the Joint Research Centre (JRC). At international level, the OECD, the United Nations Statistical Division (UNSD) and United Nations Economic Commission for Europe (UNECE) regularly publish environmental indicators (for which internationally comparable data exist) and/or environmental performance reviews.

Comparing trends in the HBM-indicators with environmental indicators would in the future be valuable to better understand routes of exposures. A pre-requisite is that the same substance(s) is(are) measured and grouped in the same way. This may be a challenge, because environmental indicators typically are linked to specific policies, which may group chemicals differently. For instance the emissions regulations (E-PRTR) groups fluorochemicals in a larger group, which is different from the F-gas grouping, which again is different from how PFAS are regulated in products (PFOA and PFOA precursors in the REACH restriction), or in food (PFOA and PFOS).

Depending on the substance and its suspected sources and routes of exposure it would be relevant to compare different types of environmental indicators. If a major source of contamination is the environment (e.g. via aerial deposition of the lipophilic Dioxins from incineration) it would be relevant to correlate with emission indicators and e.g. for food and feed if available. When the sources are more varied, such as for PFAS and BPA, it would be relevant also to correlate with indicators from products, water, air and the Artic (for POPs) to mention some. Unfortunately we lack measurements and consequently also indicators for chemicals in most articles and products in

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\(^{58}\) https://ec.europa.eu/health/indicators/indicators_en
the EU. IPCHEM does however have a fourth module for Products and Indoor Air, which currently is being populated with existing research data for products. Links are also being set up to other international databases, such as the US EPA and the OECD. Over time IPCHEM may therefore become the tool of choice, which may allow comparison of HBM data with other data, which should help to identify sources of exposures and e.g. sub-populations and regions at risk. This information could then be communicated to the risk managers to mitigate or prevent future risks of prioritised chemicals.

If this search for sources and their relative relevance should be effective it might require a combination with a modelling tool. In this respect it might be highly relevant to investigate if the tools being developed in the HBM4EU WP12 could be applied to the indicators. If successful, ideally such tools should be made part of or made compatible with IPCHEM. It would also be relevant to explore the correlation with the health indicators developed in the HBM4EU, by Eurostat and by WHO.

During the workshop at the EEA, in Copenhagen, June 2017, WHO and Eurostat expressed a clear interest in using European HBM chemical indicators. These indicators could be used to measure progress towards qualitative objectives to reduce negative health impacts from chemicals on humans, but could also elucidate the role of chemicals in the SDGs. WHO was rather interested in knowledge on occupational exposures, since this is a major source of chemical exposure and related diseases particularly in developing countries. Eurostat shared their experience with how long time (> 10 years) it had taken to harmonise the questionnaires used to produce the core health indicators, and urged HBM4EU to harmonise sampling design, protocols, questionnaires and analytical methods as much as possible from the start. They also offered to provide disaggregated health data (to a few certified experts) which could be used in combination with HBM-indicators, e.g. to stratify according to socio-economic status. This may be a timely and highly relevant stratification to pursue in the years to come, both from a policy and societal point of view. The relevance is connected to its possible link to (health) inequalities, some of which may be caused by exposure to chemicals, being one of several stressors, which decrease people’s resilience. EEA also expressed interest to include HBM-indicators, which could support the measurement of progress on the 7th EAP objective to reduce impacts of hazardous chemicals on human health and the environment.

The three angles: going downstream to describe the health effects of the measured levels of chemicals in humans, going upstream to identify environmental and other sources which can be reduced, and digging deeper to understand if certain groups are at risk, lend itself well to create a compelling narrative of chemicals impact on human lives. Throughout the work with indicators and their construction, it is therefore essential to keep in mind, whether one or another representation facilitates or hampers the communication to the target audience. The hope is that such stories will help to raise awareness across Europe, and will make more people interested in making smart choices in relation to chemicals: Whether it be which products they buy, or which politician they vote for. How well the HBM4EU HBM-indicators serves in the communication of this rather complex topic of the chemical burden of people could also be explored in collaboration with HBM4EU task 5.5, which investigates the societal dimension of HBM in Europe.
5 Conclusions and outlook

Human biomonitoring (HBM) indicators are easily interpretable tools to monitor internal exposure to (a) chemical substances in various dimensions in absolute sense (temporal scale, spatial scale, subpopulations) or in relative sense, e.g. referred to statistically-derived reference level in the general population or normalised to some ‘regarded as safe levels’ such as the HBM HBGV (health based guidance value). As such, they can convey messages to policy makers on positive or negative developments in different fields of actions, such as chemical exposure burden in a population or population subgroup and can highlight success or failure of regulative actions that have been taken. Consequently HBM indicators can be used as a governance instrument to deliver information about the progress that has been made in reaching policy objective, such as minimising the exposure burden and the health impact of chemicals on the European population. For observing changes in chemical exposure burden it is necessary to collect data periodically that reflect the current status and historical time trends of the exposure to environmental chemicals. Finally, the use of HBM indicators will allow to follow-up exposure burden from chemicals in Europe and may inform policy regulations in the future.

The methodology for creating HBM exposure indicators was developed for exposure to single substances and to a group of substances at population level. For a single substance primary indicators are those taking into account the measured exposure which may or may not be benchmarked against HBM reference values (HBM RV) for the general population. Time trends, spatial trends, stratification by age and gender, socioeconomic status, etc. can be displayed related to the data availability and policy goal, if already present. Secondly when HBM health based guidance values (HBGV) are available, measured exposure can be benchmarked against these and inform on the risk status. The percentage of the population exceeding the HBGV can be calculated. However, HBGV are sporadically available when compared to the number of chemicals people can be exposed to. For a group of substances the sum of concentrations (molar basis) or the sum of extent of exceedances can be used as a proxy for total chemical pressure but not for making statements on risk status.

In the further course of HBM4EU new HBM HBGVs will be derived and more data will be collected and made available for creating new indicators. Therefore it is envisaged to further strengthen the exchange with task 5.2 to get further insight into the derivation of HBM HBGVs and how to illustrate best fitted and easy interpretable indicators. With the use of individual data made available through IPCheM and WP10 the calculation of the percentage of the population exceeding the HBM HBGV will be anticipated. These indicators will illustrate how many people in the participating European countries may exceed an HBM HBGV for a certain chemical and be at risk. In addition to indicators for chemical pressure at the population level, WP15 will deal with the effect of mixtures at the individual level, this may give rise to new mixture indicators.
# 6 Annex

Table 5: Impact indicators based on DEMOCOPHES data for urinary BPA using existing HBM HBGV: German HBM-values and US BE values.

<table>
<thead>
<tr>
<th>Country</th>
<th>Study group</th>
<th>Number of people</th>
<th>AM (µg/L)</th>
<th>GM (µg/L)</th>
<th>P50</th>
<th>P95</th>
<th>MAX</th>
<th>LOQ</th>
<th>%LOQ</th>
<th>German HBM-I value [µg/L]</th>
<th>Percentage of population [%] exceeding the German HBM-I</th>
<th>Extent of exceedance [P95/German HBM-I GV]</th>
<th>BE value [µg/L] based on US EPA RfD and EFSA TDI</th>
<th>Percentage of population [%] exceeding the BE values</th>
<th>Extent of exceedance [P95/BE values]</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEMOCOPHES – 6 countries</td>
<td>children 653</td>
<td></td>
<td>1.97 (1.81-2.15)</td>
<td>1.96</td>
<td>13.14</td>
<td>821.90</td>
<td>0.11-1.00</td>
<td>91.1</td>
<td>100</td>
<td>0</td>
<td>1000 (1300 µg/g creatinine)</td>
<td>2000 (2600 µg/g creatinine)</td>
<td>0</td>
<td>&lt;1</td>
<td>Covaci et al. (2015)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mothers 639</td>
<td></td>
<td>1.78 (1.62-1.94)</td>
<td>1.94</td>
<td>11.13</td>
<td>455.62</td>
<td>0.11-1.00</td>
<td>90.5</td>
<td>200</td>
<td>0</td>
<td>1000 (1300 µg/g creatinine)</td>
<td>2000 (2600 µg/g creatinine)</td>
<td>0</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denmark</td>
<td>mothers 145</td>
<td></td>
<td>4 (0.06-1.106)</td>
<td>2.00 (1.6-2.47)</td>
<td>2.10</td>
<td>11.45</td>
<td>105.84</td>
<td>0.12</td>
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<td>Frederiksen et al. (2013)</td>
</tr>
<tr>
<td></td>
<td>children 142</td>
<td></td>
<td>9 (0.06-822)</td>
<td>1.87 (1.53-2.29)</td>
<td>1.71</td>
<td>7.9</td>
<td>821.90</td>
<td>0.12</td>
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<td>100</td>
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<td>1000 (1300 µg/g creatinine)</td>
<td>2000 (2600 µg/g creatinine)</td>
<td>0</td>
<td>&lt;1</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Study group</td>
<td>Number of people</td>
<td>AM (µg/L)</td>
<td>GM (µg/L)</td>
<td>PS5</td>
<td>PS5</td>
<td>MAX</td>
<td>LOQ</td>
<td>%LOQ</td>
<td>German HBM-1 value (µg/L)</td>
<td>BE value (µg/L; based on pTDI from Health Canada)</td>
<td>BE value (mg/L; based on US EPA RfD and EFSA TDI)</td>
<td>Percentage of population [%] exceeding the BE values</td>
<td>Extent of exceedance [P95/BE values]</td>
<td>Reference</td>
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<tr>
<td>Belgium</td>
<td>mothers</td>
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<td>2.55</td>
<td>2.3</td>
<td>11.63</td>
<td>455.62</td>
<td>0.2</td>
<td>100</td>
<td>200</td>
<td>≤5*</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>Covaci et al. (2015)</td>
<td></td>
<td></td>
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<tr>
<td>Luxembourg</td>
<td>children</td>
<td>125</td>
<td>2.35</td>
<td>2.27</td>
<td>13.44</td>
<td>445.24</td>
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<td>96.8</td>
<td>100</td>
<td>≤5*</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>Covaci et al. (2015)</td>
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<td>Slovenia</td>
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<td>&lt;1</td>
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<tr>
<td>Country</td>
<td>Study group</td>
<td>Number of people</td>
<td>AM (µg/L)</td>
<td>GM (µg/L)</td>
<td>P50</td>
<td>P95</td>
<td>MAX</td>
<td>LOQ</td>
<td>Percentage of population [%] exceeding the German HBM-1</td>
<td>Extent of exceedance [P95/German HBM-1]</td>
<td>BE value [µg/L] based on pTDI from Health Canada</td>
<td>BE value [mg/L] based on US EPA RfD and EFSA TDI</td>
<td>Percentage of population [%] exceeding the BE values</td>
<td>Extent of exceedance [P95/BE values]</td>
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<td>Spain</td>
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<td>112</td>
<td>2.63 (2.15-3.22)</td>
<td>3.3</td>
<td>18.86</td>
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<td>x1</td>
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<tr>
<td></td>
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<td>113</td>
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<td>2.26</td>
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<td>96.5</td>
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<td>x1</td>
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<td>x1</td>
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<td>118</td>
<td>1.83 (1.50-2.24)</td>
<td>1.91</td>
<td>9.84</td>
<td>21.6</td>
<td>0.20</td>
<td>95.8</td>
<td>100</td>
<td>0</td>
<td>x1</td>
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<td>2000 (2600 µg/g creatinine)</td>
<td>0</td>
<td>x1</td>
<td></td>
</tr>
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<td>Sweden</td>
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<td>1.29</td>
<td>5.02</td>
<td>6.34</td>
<td>0.15</td>
<td>100</td>
<td>200</td>
<td>0</td>
<td>x1</td>
<td>1000 (1300 µg/g creatinine)</td>
<td>2000 (2600 µg/g creatinine)</td>
<td>0</td>
<td>x1</td>
<td></td>
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<tr>
<td>Country</td>
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<td>Number of people</td>
<td>AM (µg/L)</td>
<td>GM (µg/L)</td>
<td>P50</td>
<td>P95</td>
<td>MAX</td>
<td>LOQ</td>
<td>%LOQ</td>
<td>German HBM-I value (µg/L)</td>
<td>Percentage of population (%) exceeding the German HBM-I value</td>
<td>Extent of exceedance [P95/German HBM-I value]</td>
<td>BE value (mg/L) based on pTDI from Health Canada</td>
<td>Percentage of population (%) exceeding the BE values</td>
<td>Extent of exceedance [P95/BE values]</td>
<td>Reference</td>
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<td>-----------</td>
</tr>
<tr>
<td>children</td>
<td>children</td>
<td>97</td>
<td>1.48</td>
<td>1.31</td>
<td>6.24</td>
<td>32.4</td>
<td>0.15</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>&gt;1</td>
<td>&lt;1</td>
<td>1000 (1300 µg/g creatinine)</td>
<td>0</td>
<td>&lt;1</td>
<td></td>
</tr>
</tbody>
</table>

**AM:** arithmetic mean, **GM:** geometric mean, **P:** percentile, **LOQ:** limit of quantification, **LOD:** limit of detection, **MAX:** maximum

`: based on comparison of the MAX and P95 with the German HBM-I-value. When the data distribution is known in detail a more precise number could be given.
Table A1: Frameworks and organisations in which environmental health and HBM indicators are valuable.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Frame/Organisation</th>
<th>Objectives</th>
<th>HBM or HBM indicators included?</th>
<th>Data sources</th>
<th>Policy target</th>
</tr>
</thead>
</table>
| National | CDC Centre for Disease control (NHANES) | Protecting the health and safety of people at home and abroad, providing credible information to enhance health decisions, and promoting health through strong partnerships. | **HBM:** NHANES surveys all over US population  
**HBM indicators:** see ROE indicator below for USEPA | - Find out which environmental chemicals actually get into people  
- Measure how much exposure a person has  
- Assess exposure for health studies of certain groups of people such as children or women of childbearing age.  
- Determine which population groups, such as minorities, people with low incomes, children, or the elderly, are at high risk for exposure and adverse health effects.  
- Assess the effectiveness of public health interventions.  
- Monitor trends in exposure levels over time | |
## Domain: USEPA

**Frame/Organisation:** USEPA

**Objectives:** a.o. protect all Americans from significant risks to human health and the environment where they live, learn and work.

**HBM or HBM indicators included?**

- **HBM:** exposure assessment survey, source investigations, occupational investigations, risk characterisation, etc.

**HBM indicator:** ROE indicators do  

- a) Allow EPA and the public to assess whether the Agency is succeeding in its overall mission to protect human health and the environment;  
- b) Provide valuable input to EPA in developing its strategic outlook and priorities.

**Data sources:**

- Cadmium in blood  
  (https://cfpub.epa.gov/roe/indicator.cfm?i=61)
- Cotinine in serum  
  (http://cfpub.epa.gov/roe/indicator.cfm?i=26)
- Lead in blood  
  (http://cfpub.epa.gov/roe/indicator.cfm?i=63)
- Mercury in blood  
  (http://cfpub.epa.gov/roe/indicator.cfm?i=64)
- Pops in serum  
  (http://cfpub.epa.gov/roe/indicator.cfm?i=65)
- Pesticides in urine  
  (http://cfpub.epa.gov/roe/indicator.cfm?i=66)
- Phthalates in urine  
  (http://cfpub.epa.gov/roe/indicator.cfm?i=67)

**Policy target:**

- HBM time trends

For example, population data on blood lead concentrations associated with adverse health effects provided impetus for the U.S. Environmental Protection Agency’s (EPA’s) regulatory reduction of lead in gasoline.
<table>
<thead>
<tr>
<th>Domain</th>
<th>Frame/Organisation</th>
<th>Objectives</th>
<th>HBM or HBM indicators included?</th>
<th>Data sources</th>
<th>Policy target</th>
</tr>
</thead>
<tbody>
<tr>
<td>National</td>
<td>Health Canada</td>
<td>Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health.</td>
<td><strong>HBM</strong>: Surveys</td>
<td>HBM time trends 2007-2013 geometric mean (µg/l in blood or urine)</td>
<td>Aid in assessing the exposure to environmental chemicals and assessing policies to reduce exposure to chemicals for the protection of the health of Canadians.</td>
</tr>
</tbody>
</table>

**HBM indicators**: CESI indicator is used to measure progress towards **Target 4.8**: Chemical Management – Reduce risks to Canadians and impacts on the environment and human health posed by releases of harmful substances.

**Indicators on:**
- cadmium in blood
- lead in blood
- mercury in blood
- BPA in urine
- PBDE-47 in blood plasma
- PFOS in blood plasma

<table>
<thead>
<tr>
<th>Domain</th>
<th>Frame/Organisation</th>
<th>Objectives</th>
<th>HBM or HBM indicators included?</th>
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<th>Policy target</th>
</tr>
</thead>
</table>
| National | UBA | - to protect and maintain natural resources, also as an act of responsibility towards future generations,  
- to advance sustainable development,  
- to promote environmental protection as a matter of course in the thinking and action of everybody. | HBM: surveys  
HBM indicators: In the studies on data on the environment (2002, 2009) two indicators (blood lead and blood organochloro compounds) are given.  
These indicators were not selected in 2013, 2015 reports. | HBM time trends 1985-2006 geometric mean (µg/l in blood) | HBM provides scientific data for informed decision making by regulators, policy makers and the general public. Moreover it allows to control the success of reduction measures and to identify areas for priority action. |
| National | FLEHS | Generating information on the distribution of biomarker values for a large number of environmental pollutants in a representative sample of the Flemish population.  
Find temporal and spatial patterns.  
Monitor policy interventions.  
Follow-up of exposure and effects in hot spots etc. | HBM: surveys  
HBM indicators: indicators developed for - As in urine of adolescents⁴  
- Cd in blood of adolescents⁵  
- PF0A in cord blood of newborns⁶  
- PCBs in serum of adolescents⁷  
- Pb in cord blood of newborns⁸  
- HCB in serum of adults⁹  
Since April 2017 available on following website http://www.milieurapport.be/nl/feitencijfers/gevolgen-voor-mens-natuur-en-economie/milieu-mens-en-gezondheid/ | HBM time trends (µg/l in blood or urine) and risk analysis | Awareness-raising activities and implementation of measures (pesticides, POPs, asthma and allergies, hot spots, PAHs, cadmium, lead) |
<table>
<thead>
<tr>
<th>Domain</th>
<th>Frame/Organisation</th>
<th>Objectives</th>
<th>HBM or HBM indicators included?</th>
<th>Data sources</th>
<th>Policy target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>WHO, Parma Declaration on Environment and Health 2010</td>
<td>Increase efforts CEHAPE: Goal1: safe water &amp; sanitation Goal 2: safe environment &amp; healthy diet Goal 3: improved air quality Goal 4: prevent disease from physical, biological and chemical environment (e.g. endocrine disruptors, bio-accumulating chemicals).</td>
<td><strong>HBM:</strong> - <strong>HBM indicators:</strong> See WHO indicators below on blood lead in children and dioxins in human milk. Other HBM indicators: need for being developed expressed in declaration</td>
<td></td>
<td>Commitment to act. Health promotion in all policies. Supporting environment and health information system. Development of internationally comparable indicators. Contribution to develop a consistent and rational approach to human biomonitoring as a complementary tool to assist evidence-based public health and environmental measures, including awareness-raising for preventive actions.</td>
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<tr>
<td>Domain</td>
<td>Frame/Organisation</td>
<td>Objectives</td>
<td>HBM or HBM indicators included?</td>
<td>Data sources</td>
<td>Policy target</td>
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</tbody>
</table>
| Global | WHO European Centre for Environment and Health (ECEH), 2012 | a.o. coordinating the development of biomonitoring-based indicators for efficient monitoring of Parma Declaration commitments. | **HBM**: Focus on children/pregnant women. List of high priority biomarkers composed.  
**HBM indicators**: ENHIS indicators about blood lead in children and persistent organic pollutants (POPs) in human milk which were already implemented. Need for other indicators being developed.  
Other environmental health indicators not using HBM:  
- PM10 in outdoor air  
- Exposure to chemical hazards in food  
- Exposure of children to second-hand tobacco smoke (SHS) | HBM time trend for dioxins 1988-2007 (pg/g fat)  
HBM geometric mean for lead in blood (µg/dl)  
Time trends 1992-2012 for PM10 Annual mean (µg/m³)  
Intake of heavy metals through food in 2004 (µg)  
Time trends of children exposed to SHS 2002-2007 (Percentage) | - develop biomarker selection criteria  
- include these criteria to identify HBM indicators for inclusion in survey  
- testing efficiency of approaches for biomonitoring-based surveillance in support of risk reduction measures. |
### Domain | Frame/Organisation | Objectives | HBM or HBM indicators included? | Data sources | Policy target |
--- | --- | --- | --- | --- | --- |
**International** | OECD - Organisation for Economic Co-operation and Development | a.o. reduce health inequality; consumer product safety aims to improve co-operation amongst jurisdictions; stimulating innovation | HBM: use of HBM data e.g. assessing the risk of chemicals to children's health: an OECD-wide survey | | Safe product innovations, safe packaging; Safe circular economy as Europe is not rich in raw materials; Follow-up clean technologies. |
| UNEP - United Nations Environment Programme | Coordinates worldwide actions to reduce emissions and exposure levels | HBM: - Minamata convention: mercury - Stockholm convention: POPs - blood lead | | e.g. ban on leaded petrol. HBM was instrument in stimulating policy actions and demonstrating their effectiveness. |
**Global** | UN Sustainable development goals | a.o. - ensure healthy lives and promote well-being for all at all ages: an important target is to substantially reduce the number of deaths and illnesses from pollution-related diseases. - reduce inequality | HBM: - HBM indicators: - | | e.g. Poverty reduction |
<table>
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<tr>
<th>Domain</th>
<th>Frame/Organisation</th>
<th>Objectives</th>
<th>HBM or HBM indicators included?</th>
<th>Data sources</th>
<th>Policy target</th>
</tr>
</thead>
</table>
| EU     | SOER (EEA) - State and Outlook European Environment – European Environment Agency | Assessment of European environment’s status, trends and prospects, and placement in a global context. | **HBM:** Current activities to streamline existing information on chemicals in the environment, including human biomonitoring data, should improve the knowledge base.  
**HBM indicators:** - | - | It informs European environmental policy implementation and analyses the opportunities to modify existing policies. |
| EU     | ECHI - European Core Health indicators | Presenting relevant and comparable information on public health at European level | **HBM:** -  
**HBM indicators:** -  
Only two environmental health related indicators available: regular smokers, PM10 in air | Proportion (%) of people reporting to smoke cigarettes daily for 2008  
Annual average of PM10 1998-2012 (µg/m$^3$) | Consolidate and expand the ECHI indicator system towards a sustainable health monitoring system in Europe. |
<table>
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<tr>
<th>Domain</th>
<th>Frame/Organisation</th>
<th>Objectives</th>
<th>HBM or HBM indicators included?</th>
<th>Data sources</th>
<th>Policy target</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU</td>
<td>EU Strategy for a non-toxic environment</td>
<td>Non-toxic products and material cycles</td>
<td>Identify gaps, deficits and related improvement opportunities in the management of chemicals in material cycles in order to decrease unwanted effects from chemicals, such as toxic emissions or material stream contaminations.</td>
<td><strong>HBM:</strong> coordinated HBM efforts at EU level should bridge science and policy by generating targeted evidence on human exposure and associated health outcomes to directly address current policy questions. <strong>HBM indicators:</strong> -</td>
<td>Consumer protection. Safety first as guiding principle. Avoid contaminations in product chain. Information on actual exposure (bridging gap between real exposure and exposure estimation).</td>
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<td>Early warning systems (environment, worker, consumer protection &amp; food safety)</td>
<td>Set on the hazards posed by chemicals to human health and the environment in an early stage</td>
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<td></td>
<td>HBM can provide the first examples needed to give action and be used to assess the exposure to new contaminants in the population (Norden, 2015). The longer it takes to identify a problem with a chemical, the longer it will continue to be used. Science moves forward and often finds new toxicity (and often exposures) which hadn’t previously been demonstrated. In reality we are always dealing with ‘currently estimated toxicity’ (CET). Also the identification of new emerging contamination issues at level</td>
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<tr>
<td>Domain</td>
<td>Frame/Organisation</td>
<td>Objectives</td>
<td>HBM or HBM indicators included?</td>
<td>Data sources</td>
<td>Policy target</td>
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| EU     | REACH             | SVHC Substances of Very High Concern | Improve the protection of human health and the environment from the risks that can be posed by chemicals, while enhancing the competitiveness of the EU chemicals industry. It also promotes alternative methods for the hazard assessment of substances. | HBM: application of HBM data in dossiers (e.g. phthalates, BPA)  
HBM indicators: - | Systematic environmental monitoring and surveillance to track presence and to be aware of any build-up. Follow-up of possible phase out of certain SVHC and substitution. Enhance the application of the substitution principle in the policy context.  
Given the potentially serious health and environmental problems screening is necessary e.g. PFAS |

**Abbreviations used in the table above:**

- **CDC:** Centre for Disease Control
- **CEHAPE:** Children's Environment and Health Action Plan for Europe
- **CET:** Current Estimated Toxicity
- **CESI:** Canadian Environmental Sustainability Indicators
- **ECEH:** WHO European Centre for Environment and Health
- **ECHI:** European Core Health indicators
- **EEA:** European Environment Agency
- **EFSA:** European Food Safety Agency
- **ENHS:** Environment and Health Information System
- **FLEHS:** Flemish Environment and Health Study
- **NERC:** New or Emerging Risks of Chemicals
- **OECD:** Organisation for Economic Co-operation and Development
- **PFAS:** Per and PolyFluoroAlkyl Substances
- **REACH:** Registration, Evaluation, Authorisation and Restriction of Chemicals
- **ROE:** Report On Environment
- **SOER:** State and Outlook on the Environment Report (European Environment Agency)
- **SVHC:** Substance of Very High Concern
- **UBA:** Umweltbundesamt
- **UN:** United Nations
- **UNEP:** United Nations Environment Programme
- **USEPA:** United States of America - Environmental Protection Agency
- **WHO:** World Health Organisation