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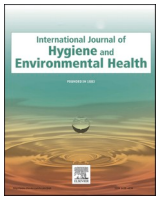

HBM4EU results support the Chemicals' Strategy for Sustainability and the Zero-Pollution Action Plan

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ABSTRACT

One of the major goals of the European Human Biomonitoring Initiative (HBM4EU) was to bridge the gap between science and policy by consulting both policy makers and national scientists and generating evidence of the actual exposure of residents to chemicals and whether that exposure would be suggest a potential health risk. Residents' perspectives on chemical exposure and risk were also investigated.

HBM4EU's research was designed to answer specific short-term and long-term policy questions at national and European levels, and for its results to directly support regulatory action on chemicals. A strategy was established to prioritise chemicals for analysis in human matrices, with a total of 18 substances/substance groups chosen to be investigated throughout the five-and a -half-year project. HBM4EU produced new evidence of human exposure levels, developed reference values for exposure, investigated determinants of exposure and derived health-based guidance values for those substances. In addition, HBM4EU promoted the use of human biomonitoring data in chemical risk assessment and developed innovative tools and methods linking chemicals to possible health impacts, such as effect biomarkers. Furthermore, HBM4EU advanced understand of effects from combined exposures and methods to identify emerging chemicals. With the aim of supporting policy implementation, science-to-policy workshops were organised, providing opportunities for joint reflection and dialogue on research results. I, and indicators were developed to assess temporal and spatial patterns in the exposure of European population. A sustainable human biomonitoring monitoring framework, producing comparable quality assured data would allow: the evaluation of time trends; the exploration of spatial trends: the evaluation of the influence of socio-economic conditions on chemical exposure. Therefore, such a framework should be included in the European Chemicals' Strategy for Sustainability and the data would support the Zero Pollution Action Plan.

1. Introduction

The European Green Deal aims to protect the health and well-being of residents from environment-related risks, through a just and inclusive transition (European Commission, 2019). The strategy for sustainable use of chemicals is part of the Green Deal. With over 100,000 chemicals circulating in products on the European market, chemicals are found in the bodies of men, women, children of all age groups including new-borns across Europe (Choi et al., 2017; EUROSTAT, 2021; Gennings et al., 2012).

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The Human Biomonitoring Initiative in Europe (HBM4EU) was an effort of 30 countries, plus the European Environment Agency and the European Commission. It was co-funded under Horizon 2020. The HBM4EU project aimed at coordinating and advancing human biomonitoring in Europe. HBM4EU (2017–2022) generated evidence of the actual exposure of residents to chemicals and the possible health effects to support policy making.

HBM4EU has established a European Union-wide human biomonitoring programme to generate knowledge on human internal exposure to chemicals and their potential health impacts., One of the main goals was to provide evidence to support policy measures to ensure chemical safety and improve health in Europe. It developed and implemented a chemical prioritisation strategy that set out the steps to identify substances of priority concern to be the subject of research and surveys and policy needs (Ougier et al., 2021a). The prioritisation strategy identified specific substances or groups of substances, which were chosen to answer specific policy-related questions and needs in support of legislation.

HBM4EU knowledge will be used to assess progress under several key strategies of the European Green Deal. Evidence on human exposure to pesticides, as well as chemicals used in food contact materials and food contaminants, will be used to assess progress towards the objectives of the Farm to Fork Strategy (Farm to Fork Strategy, 2020). Under the Circular Economy Action Plan, implementing circularity creates new pathways through which humans can be exposed to hazardous chemicals in contaminated material flows (European Commission, 2020a). As an example of how human biomonitoring can add value, HBM4EU collaborated with the e-waste recycling industry to assess workers' exposure to hazardous chemicals and identify opportunities to improve occupational health and safety. The Zero Pollution Action Plan aims to create a toxic-free environment and reduce the burden of premature death and disease driven by pollution in Europe, typically more borne by children, the elderly, persons with disabilities, and those living in poorer socio-economic conditions (European Commission, 2021a). Later in 2022, the European Environment Agency will deliver a first assessment using HBM4EU indicators to establish a baseline on population exposure to chemicals against which to measure progress towards zero pollution. Indicators can be used to assess the effectiveness of current EU chemicals regulations and to identify the need for additional action to protect t the environment and human health.

The Chemicals' Strategy for Sustainability (CSS) provides a progressive approach to managing chemical risks, through upstream measures to ban or restrict the most harmful chemicals and allow essential uses only (European Commission, 2020b). The one substance, one assessment approach promoted under the strategy mirrors the reality of human exposure as captured by human biomonitoring, which measures total internal exposure from multiple sources across legislative silos. HBM4EU data has been made openly accessible via the European HBM dashboard. This allows for the visualization of summary statistics from data collections obtained through HBM4EU, where it is possible to look at exposure levels and trends in chemical exposure of European Residents. HBM data was also generated in the HBM4EU Aligned Studies,[1] and exposure levels can be compared with currently available health-based guidance values. The data included in the dashboard were obtained in a standardized and comparable way. Another platform where the HBM4EU metadata and descriptive statistics is included, is IPCHEM, the Information Platform for Chemical Monitoring, available for risk assessors and researchers to use, so multiplying the added value of this new evidence base. HBM4EU work to assess population exposure against health-based guidance values allows regulators to judge the effectiveness of existing risk management measures and identify those substances for which further efforts are needed to reduce exposure, in particular for vulnerable groups (Apel et al., 2020).

Recognising the observation that in some cases a banned chemical is substituted by another with similar or even unknown properties through regrettable substitution, HBM4EU tackled chemicals in groups (Blum et al., 2019; Buekers et al., 2021; Carvaillo et al., 2019; Lemke et al., 2021; Molina-Molina et al., 2019; Rugard et al., 2020; Sackmann et al., 2018; Trasande, 2017). Grouping of substances is advocated under the chemical strategy as a means of speeding up the risk assessment and management process, for example with per- and polyfluoroalkyl substances (PFAS). HBM4EU has shown that humans are simultaneously exposed to many substances of different chemical classes that enter the human body once these substances are introduced into the environment. HBM4EU has made it very clear that innovative tools to identify human exposure to these new chemicals of emerging concern need to be further developed as well as new approaches for addressing combined exposure assessment and risk assessment dealing with potential mixture effects of these chemicals (Reina-Pérez et al., 2022; Rodríguez-Carrillo et al., 2021; Socianu et al., 2022; Vinggaard et al., 2021; Zare Jeddi et al., 2021). Also methods addressing combined exposure assessment should be targeted in order to find out which groups are higher or lower exposed to multiple chemicals (Willey et al., 2021). The newly generated HBM data on biomarkers of exposure and effect will support a science-based derivation of a Mixture Assessment Factor (MAF) proposed under the CSS strategy. A MAF is an additional safety factor, addressing mixture effects potentially caused by unintentional chemical mixtures.

HBM4EU has created a strategy and of scientific excellence across Europe focusing on translating evidence to knowledge for policy making. It built on a foundation of existing human biomonitoring programmes, the EU co-funded EU-projects COPHES and DEMOCOPHES, and initiatives at national level, to make the whole greater than the parts. It was the first EU chemical-based research project that had a unique two-way open dialogue between policymakers and researchers to prioritise chemical substances and research activities in relation to policy demands, leading to input from the policy perspective for use of results. This relationship reduced the gap between science and policy, with the following underlying principles:

- the need for multi- and transdisciplinary cooperation in the context of complexity.
- the need for opportunities to interact and for dialogue between scientific-, policy- and societal stakeholders.
- the creation of mutual ownership, transparency and a well-structured process architecture with attention to a diversity of relevant perspectives.
- a diversity of policy instruments, policy domains and policy levels.

Human biomonitoring (HBM) delivers a new type of knowledge that resonates with residents, who donate samples to learn about their body burden from chemicals in consumer products and the environment. Responding to their concerns, HBM4EU has produced materials to guide residents in how to change behaviours to minimize exposure to hazardous chemicals, in parallel to channelling evidence into regulatory processes to move forward to a zero-pollution environment.

With the closure of HBM4EU in June 2022, research on human biomonitoring and chemical exposure in support of legislation will be carried out under the Horizon Europe Partnership for the Assessment of Risks from Chemicals (PARC) (European Commission, 2022a). PARC builds on HBM4EU and on its legacy, with the added aspect of strengthening the connection between environmental pollution, effects on the environment and on human health. Therefore, it also follows a more systemic perspectives approach, recognising that humans are an integrative part of their environment. This will support understanding interlinkages between the environment, society and the economy, and

[1] The HBM4EU Aligned Studies are a survey aimed at collecting HBM samples and data as harmonized as possible from (national) studies to derive current internal exposure data representative for the European population/citizens across a geographic spread.

understanding how policies could respond to them (EEA, 2020).

2. Material and methods

2.1. Chemical prioritisation

HBM4EU developed a participatory approach to prioritise substances addressing the most important needs of both policy makers and risk assessors at EU level and in the participating countries and of a broad range of stakeholders, including industry and non-governmental organisations (NGOs). This methodology has been widely endorsed, it is transparent and has been published (Ougier et al., 2021a).

In summary, this strategy consisted of three mains steps:

1) Mapping of knowledge gaps and nomination of substances
2) Prioritisation of substances using a scoring system
3) Listing of priority substances reflective of the scoring, as well as of public policy priorities and available resources

For the first step, a survey was done in which relevant ministries and agencies at European and national levels, as well as members of the Stakeholder Forum, which consists of NGOs, industry and trade unions, each nominated up to 5 substances/substance groups of concern. These nominations were collated and subsequently shortened to another list based on the number of nominations. This initial step, prioritised the substances/groups of substances nominated by the EU Policy Board (with the objective of meeting EU knowledge needs for policy support), followed by substances nominated by two or more National Hubs, or by at least one National Hub and one member of the Stakeholder Forum.

For the second step, substances/substance groups were scored against several prioritisation criteria, namely hazardous properties, exposure characteristics, and societal concern. The scores were used to rank the substances/substance groups. The aim was to understand how much information was already available on substances and to identify the need for new evidence, to ensure that HBM4EU addressed knowledge gaps.

For the third step, and in addition to the ranking and categorisation of the substances, the need for new evidence to support policy priorities at European Union (EU) level was a strong factor influencing the final list of substances and substance groups. This need was communicated to the HBM4EU partners by EU officials in an intensive dialogue involving several workshops.

2.2. Indicators

Indicators are measures of progress or activity and can be visualized to enable data to be interpreted in an easy and accessible way by a broader audience be it scientists, policy makers or the general public. HBM-based indicators are lacking, and hence an approach to develop these was done in HBM4EU. This type of indicators is designed to be relevant for policy, society, and health, and support chemical policy making by using HBM data collections.

During HBM4EU, indicators were developed to assess time and spatial trends in the exposure of European residents to chemicals and to get a picture of whether the population would be at risk. HBM4EU first developed an approach to producing European HBM indicators and proposed two types of indicators (Buekers et al., 2018):

1) Result indicators, which are indicators of internal exposure derived directly from biomarker concentrations.
2) Impact indicators, which are indicators of health risk comparing exposure concentrations to health-based guidance values, such as human biomonitoring guidance values (HBM-GV).

Result indicators measure the concentration of a substance in blood or urine and present time and spatial trends of HBM exposure data, using exposure percentiles e.g., P50 values (or median values) to which participants are exposed. It does not give information on the hazard of the chemical, at which level an effect will occur (potency) or of the risk of being exposed. However, quantitative, and qualitative analysis will allow for an evaluation on policy effectiveness as spatial and temporal trends can be assessed. These indicators are descriptive and allow to respond the question "What are current internal exposures?" and are a good way to track policy efficacy "Are the policy measures working?".

Impact indicators, using exposure values at the higher end of the exposure distribution, e.g., P95 values or 95th percentiles, place HBM data in a health risk context by including the respective HB-GV (or HBM-GV where available), which were derived under HBM4EU (Apel et al., 2020). HBM data can be compared with a level below which no adverse health effects are expected, such as the HBM guidance value (HBM-GV). They are used to assess health impacts ("Is the chemical exposure burden of health concern?").

Health-based human biomonitoring guidance values provide benchmark values against which to compare exposure in the general population.

To allow for the interpretation of HBM data in a health risk context, HBM4EU's scientists derived HBM-GVs for the public and for workers for a number of substances (Apel et al., 2022). Despite not having a regulatory basis, these health-based guidance values were widely endorsed after a consultation process involving all HBM4EU partners, with the methodology made available to the scientific community (Lamkarkach et al., 2021). *"The HBM-GVs derived for the general population represent the concentration of a substance or its specific metabolite(s) in human biological media (*e.g.*, urine, blood, hair) at and below which, according to current knowledge, there is no risk of health impairment anticipated, and consequently no need for action"* (Apel et al., 2020). Although no public consultation took place, the derived HBM-GVs were also shared with the EU Policy Board for input. The HBM-GVs were endorsed by the HBM4EU Management Board after wide consultation of European experts through the HBM4EU national hubs and the EU policy board which was composed of several European Commission's Directorate Generals. These guidance values have no regulatory status but are based on actual scientific knowledge.

Based on selection criteria discussed and defined on a first workshop, indicators have been produced for bisphenol A (BPA), bisphenol S (BPS) and per- and polyfluoroalkyl substances (PFAS), which both have high policy and societal relevance, as well as for cadmium, phthalates, and DINCH, a non-phthalate plasticizer, pesticides and aprotic solvents (Gerofke et al., 2023; Lobo Vicente et al., 2022a, 2022b).

Two pan-European harmonized datasets were used: those from the HBM4EU Aligned Studies with sampling between 2014 and 2021 and those from the previous European human biomonitoring DEMOCOPHES project with sampling in 2011_2012 (Den Hond et al., 2015; Gilles et al., 2022, 2021; Govarts and et al., 2022). Both datasets met requirements of adequate sample size, a successful quality analysis and quality control (QA/QC) of the biomarker analyses and a uniform data handling. In the recent HBM4EU Aligned studies, HBM samples and data were collected in a harmonized way from existing (national) studies or newly conducted studies to derive current internal exposure data for the European population/citizens across a geographic spread (Gilles et al., 2021). HBM4EU developed a HBM European Laboratory Network to ensure the delivery of quality reliable and trustworthy analytical results (Esteban López et al., 2021; HBM4EU, 2021). Based on this harmonized and quality-controlled data, initial indicators have been developed according to the developed HBM indicators' strategy (Buekers et al., 2018).

This approach is illustrated with the impact indicators developed for PFAS, BPA and BPS. The PFAS indicator was produced with data from the HBM4EU Aligned Studies in teenagers, the BPA in children with data from DEMOCOPHES, and the BPA and BPS in adults with data from DEMOCOPHES and the HBM4EU Aligned Studies.

PFASs are a group of synthetic chemicals, also called "forever chemicals" as they do not break down in the environment due to their

strong carbon-fluorine bond, and therefore accumulate over time. PFASs are toxic to human health and the environment with specific PFAS already regulated by several legislations and cross-regulation activities.

Bisphenols are synthetic chemicals found in many types of products including plastics, thermal paper (BPA excluded in receipts), can liners, flooring. Bisphenols enter the human body mainly via food intake and by dermal contact (e.g., with paper receipts).

2.3. Science to policy workshop

To support the use of HBM4EU results for policy making, several participatory case studies were organised to facilitate the joint interpretation of HBM4EU-results and their translation into policy options, in co-creation between scientists, policy makers and societal stakeholders. The case studies consisted of several iterative steps, including desk research and bilateral consultations leading to a final workshop. This allowed to gradually develop the case, not only in terms of content but also as a learning process for the various partners involved. Timely preparatory meetings with key partners enabled to better align expectations, refine messages, and increase engagement and shared ownership. This kind of explorative meetings turned out to be fruitful. Three participatory case studies were implemented: a first focusing on science-policy aspects of phthalates and bisphenols (2018); a second on PFAS (2020–2021); and a third on HBM4EU indicators for PFAS, phthalates and cadmium (2021–2022). Each time, a diversity of actors was invited to participate, including HBM4EU researchers, representatives from various DGs of the European Commission, EU agencies, representatives of national HBM studies and national authorities, and – if the research context allowed – societal stakeholders (including NGO's and industry representatives.

The consortium always strived for the presence of both researchers with detailed knowledge about the research activities as well as members of the Management Board (with a broad view on project activities and objectives). Representatives for the policy actors and societal stakeholders were invited through the HBM4EU Policy Board and Stakeholder Forum, and invitations extended with the snowball method for additional suggestions. Open calls for participation were not used to maintain sufficient control over the size and composition of the group, paying particular attention to a diversity of perspectives, while also maintaining a manageable group size for the discussions. A closed meeting also allowed to present preliminary results or to share information in a confidential setting. This way of working can lead to a certain bias in the group of participants, for example with a predominance of participants who see added value in human biomonitoring for policy purposes. This was not seen as a problem for the consultations, as their main purpose was to initiate an open-ended dialogue on policy relevance and how to optimize and facilitate it, in the context of a science-to-policy research project, rather than producing binding final conclusions. A relevant diversity of perspectives was certainly aimed for, based primarily on the diversity of representatives in the project boards, and expanded through the snowball method. Relevance was defined here firstly as a diversity of policy domains, to also think transversally about policy integration, and secondly as a diversity of interests (represented mainly in the stakeholder forum). We also reasoned in terms of contrasting viewpoints and for instance invited national voices next to European guest speakers and panel members.

Workshops were always organised on two days, from noon to noon. The first workshop in 2018 was organized in Brussels on the premises of the Directorate General for Research and Innovation (DG RTD) of the European Commission. The other workshops, in 2021 and 2022, took place online due to the Covid-19 pandemic. The workshop programs always aimed at a combination of presentations and sufficient space for discussion (both in plenary sessions and break-out discussion groups). Presentations from the consortium were thoroughly prepared in working groups, with attention to formulating clear key messages and relevant questions for further discussion. In two out of three cases, representatives of the European Commission and Member States were also asked to prepare a presentation or lead a discussion group.

Reports of the case studies, including process design, conclusions and participants' evaluation are available on the HBM4EU website (Coertjens et al., 2019, 2021, 2022; Crabbé et al., 2022).

2.4. Residents' perspectives and outreach

The inclusion of resident perspectives and perceptions was part of a systematic, transparent, and participatory strategy within HBM4EU. To gather qualitative in-depth understanding on resident's perceptions of chemical exposure, trust, and concerns on human biomonitoring initiatives, HBM4EU ran focus groups between 2018 and 2021 hosted in 11 countries, including Austria, Portugal, Ireland, the UK, Cyprus, Hungary, the Netherlands, Denmark, Israel, North Macedonia and Latvia. Participants were selected through purposive, non-probabilistic sampling, in order to ensure a heterogeneous group of people in terms of ages and educational background, which was considered also to provide heterogenous perspectives about Human Biomonitoring related topics. Participants were invited to take part on the focus groups either through face-to-face invitation, by email or telephone; and a more detailed description of the methodology may be found in the peer-reviewed publications (Matisāne et al., 2022a; Uhl et al., 2021a).

As part of the outreach to residents, non-representative surveys were conducted in countries that hosted the focus groups. This survey was initially used for the focus groups to better understand their awareness and concerns regarding chemical exposure and human biomonitoring. Additionally, a European resident online survey (non-representative), which ran from September 2020 until February 2021, was done.

Since the European resident survey was developed in 2020, it was updated to harvest more EU-wide results including chemical exposure during the COVID-19 pandemic. The survey was then implemented on the HBM4EU website with a specific link to the translated survey for each of the countries. The collaboration of the 30 National Hubs (country representatives) was requested for the dissemination of the survey. The questions in the resident survey may be found in the Supplemental Data section. More details on how the survey was implemented may be found in the literature (Joana Lobo Vicente et al., 2021).

3. Results and discussion

3.1. Chemical prioritisation

The nominations by 32 different entities were collated into a preliminary list of 48 substances/substance groups, which was subsequently shortened to a list of 23 after considering the total number of nominations each substance/substance group received and the nature of the nominating entities.

A stakeholder workshop was held to reflect on the priorities and capture the stakeholders' concern. A top-10 list of substances was voted on by the HBM4EU Stakeholder Forum (Uhl, 2018). The list included pesticides authorised in the EU and metabolites, glyphosate, siloxanes, mercury and mercury compound, arsenic acid and its inorganic metabolites, nanomaterials, lead and its compounds, UV absorbers and filters, diisocyanates and mycotoxins.

A dialogue between the HBM4EU Management Board and the EU Policy Board took place to assess resources available for the project and the alignment with the policy priorities at European level. A final priority list of 9 substances/substance groups for research activities and surveys within the framework of the HBM4EU project was produced and presented to the Governing Board for approval.

After the prioritisation round of 2017, some modifications were introduced. The following prioritisation round initiated in 2019 included substances that were ranked according to the number of nominations, but they were not scored against prioritisation criteria (hazard, exposure probability, health concern) by an expert team. This

process will be finalised in the PARC, the follow-up partnership to HBM4EU.

It was crucial to have the EU Policy Board involved in this process, comprising of several directorate generals of the European Commission as well as several EU Agencies, which facilitated the swift uptake of results by EU institutions. Having this opened channel of communication also facilitated communication between the policymakers and the researchers, in which the former could express their needs for certain results to the researchers to influence policy processes.

3.2. Indicators

3.2.1. Per- and polyfluoroalkyl substances in teenagers (PFASs)

In HBM4EU, 12 PFAS were covered by the QA/QC process and could be analysed in the Aligned Studies: PFOS, PFOA, PFPeA, PFHxA, PFHpA, PFNA, PFDA, PFUnDA, PFDoDA, PFBS, PFHxS and PFHpS. The most detected PFAS in human blood of European teenagers (12–19 years) were perfluorohexane sulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). They were a fraction of the PFAS to which the European population is exposed to. In 2020, the European Food Safety Authority (EFSA) set a new safety threshold for intake (Tolerable Weekly Intake) as sum value of these 4 PFAS i.e., sum of PFOS, PFOA, PFNA and PFHxS of 4.4 ng/kg BW per week, which corresponds to an internal blood level of 6.9 μg/L in women of child bearing age; the sum of PFOS and PFHxS (4.9 μg/L); and the sum of PFOA and PFNA (2.0 μg/L) (Schrenk et al., 2020). These guidance values were based on serum levels in females aged 35 years old and effects on immunity[2] of their new-borns.

In all studies, a fraction of the participating teenagers exceeded the EFSA based guidance value of 6.9 μg/L (Fig. 1). In all studies, except BEA (Spain), P95 values (95% of the participants had biomarker levels below this value, and 5% above) exceeded the EFSA based guidance value (Fig. 2). Fig. 2, also gives an indication of the extent of the exceedance. It is noteworthy to mention that, both indicators complement each other. Fig. 1 shows the percentage of exceedance related to EFSA's health-based guidance value for the sum of the 4 PFASs, whereas Fig. 2 shows the P95 for the single studies thus showing the extent of exceedance above EFSA's guidance value of 6.9 μg/L. For example, in Fig. 1 Slovenia had 7.45% of the teenager population exceeding EFSA's guidance value, whereas in Fig. 2, the P95 values showed that the 5% most exposed teenagers had an extent of exceedance (EE) of 1.12 above the HBM-GV. The EE was obtained by dividing the P95 value with the health-based guidance value, therefore 7.74 μg/L/6.9 μg/L = 1.12.

The indicator, based on internal exposure data from European teenagers, showed that combined exposure to PFOS, PFOA, PFNA and PFHxS of teenagers in the EU exceeds the EFSA health-based guidance value. Exceedances in the different studies and locations ranges from 1.34% up to 23.78% of the participants (Fig. 1) with an extent of exceedance (P95 value/6.9 μg/L) varying from 0.74 to 1.78. The studies conducted in Western and Northern Europe had the most teenagers exceeding the guidance value.

The indicator based on HBM4EU aligned study data, clearly demonstrated that a significant fraction of European teenagers was exposed above the health-based guidance values. In some study sites, 5% of the participants exceeded the health based guidance values by 78%. Despite the fact these HBM-GVs do not reflect regulatory measures, these data support a swift action to decrease the exposure of the EU population to these compounds and to carefully study PFAS substituents exposure and health impacts.

In recent years, policy attention for PFAS has increased strongly at various policy levels (from the local, to the national, European and international level). Policy processes have been initiated for which HBM4EU provided relevant input (HBM4EU, 2022a). This applies to regulatory initiatives, policy evaluation, agenda setting and various other complementary policy instruments. The HBM4EU indicators emphasise the need for reducing human exposure from existing environmental sources and to prevent exposure from new sources. The data supports adaptation of the chemical regulation under the Chemicals Strategy for Sustainability, with a set of actions already laid out for phasing out PFAS use, unless it's essential (European Commission, 2020b). This should add up to existing regulations at EU level.

PFAS are regulated by a number of pieces of legislation and cross-regulation activities. These cover i) implementation of international conventions, actions and agreements, and wider chemicals legislation; ii) consumer products; iii) occupational exposure, and iv) the environment (e.g., emissions to air and water). As an example, PFOS is regulated under the EU's Persistent Organic Pollutants (POPs) Regulation; PFOA, its salts and related compounds are regulated under the Stockholm Convention, and it has been banned under the POPs Regulation since 4 July 2020. Perfluorohexane sulfonic acid (PFHxS), its salts and related compounds as well as perfluorinated carboxylic acids (C9-14 PFCAs) are being considered for inclusion in the Stockholm Convention and consequent global elimination. In addition, the Chemicals Strategy for Sustainability includes a specific focus on the risks posed by PFAS. The links to the current legislation may be found in the HBM4EU's substance web page (HBM4EU, 2022a). For example, PFOA is covered by REACH Annex XVII restriction, SVHC Candidate List (PBT, Repr.), CLH (Carc. 2, Repr. 1B, STOT RE 1, Acute Tox. 4, Eye Dam. 1), and are proposed for inclusion in the Stockholm Convention, (European Commission, 2017, 2008a, 2008b; ECHA, 2018; UNIDO, 2004). For PFOS (perfluorooctane sulphonate) Heptadecafluorooctane-1-sulphonic acid (linear and branched isomers), it is covered by restriction, CLH (Carc. 2, Repr. 1B, Lact., STOT RE 1, Acute Tox. 4, Aquatic Chron. 2), PIC regulation, POP Regulation (EG) No. 757/2010, Stockholm Convention, environmental legislation Seveso (European Commission, 2017, European Commission, 2012, European Commission, 2010, 2008b; ECHA, 2018; European-Parliament, 2012; UNIDO, 2004).

HBM4EU has submitted data on several occasions to feed information to this these different regulatory processes, and PFAS indicators will be included in the work being developed for the Chemicals' Strategy for Sustainability and the Zero-Pollution Assessment. Despite these regulations already implemented, the European population continues to be widely exposed and health risks cannot be excluded.

At the national and local level there is a strong interest of policy makers and risk managers on how to deal with already existing contamination and prevent further exposure of residents. HBM4EU has created a network of experts working on PFAS contaminated sites in Belgium, Denmark, the Netherlands, Hungary, Italy and Sweden. A guidance document was developed and published with recommendations on identification, human biomonitoring and risk communication in PFAS hotspots (De Brouwere et al., 2022).

3.2.2. Bisphenols

Former DEMOCOPHES[3] data already showed that urinary BPA concentrations were quite similar in children and mothers (Covaci et al., 2015; Schindler et al., 2014).

Within the HBM4EU project, an HBM guidance value of 230 μg/L was derived for BPA exposure in adults and 135 μg/L for BPA exposure in children (>3 years) (Ougier et al., 2021b). Below these values no adverse health effects were expected according to current knowledge.

[2] Ability to resist a particular infection.

[3] COPHES/DEMOCOPHES was a project funded through the European Environment and Health Action Plan of 2004 to "develop a coherent approach on human biomonitoring (HBM) in Europe". It targeted the collection of specimens from 120 mother-child-pairs in each of the 17 participating European countries. These specimens were investigated at that time for six biomarkers: mercury in hair; creatinine, cotinine, cadmium, phthalate metabolites and bisphenol A in urine.

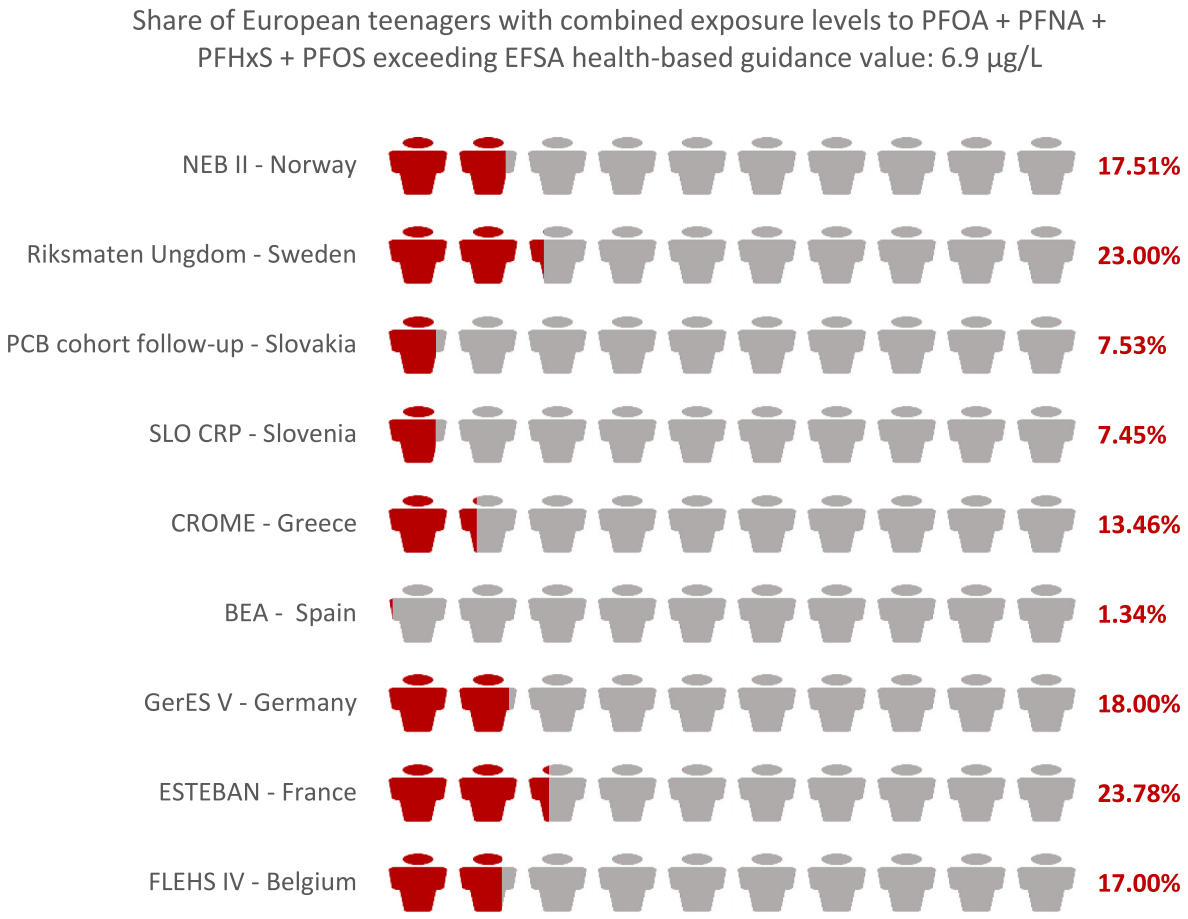

Fig. 1. Share of European teenagers with combined exposure levels to PFOA + PFNA + PFHxS + PFOS exceeding health-based guidance value of EFSA (6.9 µg/L), based on data from the HBM4EU Aligned Studies.

HBM-GV is set at a urinary concentration of total BPA consistent with a steady-state exposure to the temporary TDI of 4 µg/kg bw/day derived by EFSA (2015). A more stringent value was proposed last year. BPA analogues are less studied but data suggest they are also estrogenic (den Braver-Sewradj et al., 2020; Örtl, 2020). BPS is more difficultly removed from the body than BPA, which may lead to relatively higher exposure to a hormonally active substance. For BPS, a HBM-GV of 1 µg/L was derived in HBM4EU, based on animal studies for mammary gland and neurodevelopmental toxicity (Catanese and Vandenberg, 2017; Kolla et al., 2018, 2019; Kolla and Vandenberg, 2019). No reference values have been proposed by EU or non-EU organisations so far. However, there is currently an assessment of BPS ongoing at EU level. Although the safety of BPA substitutes (such as BPS and BPF) is not completely clear at this stage, new text mining/artificial intelligence tools developed in HBM4EU highlighted the health effects of these BPA substituents (Carvaillo et al., 2019; Rugard et al., 2020).

3.2.2.1. BPA in children. This indicator (Fig. 3) illustrated the 95th percentile (P95) BPA values of children from the DEMOCOPHES project (children 5–12 years, 2010–2012, compared to age-dependent HBM-GVs derived before the new EFSA assessment). The observed 95th percentiles in all included EU studies were at least a factor 8 below this HBM-GV derived for children. This will change if EFSA's TDI is updated and the TDI is lowered by a factor of 100,000 (ongoing discussions, pending conclusion). Health concerns remain due to the co-exposure to BPA substitutes with incomplete toxicological data and because of concern for potential mixture effects.

3.2.2.2. BPA in adults. This indicator (Fig. 4) illustrated the 95th percentile (P95) values for urinary BPA compared to the HBM-GVs for adults from specific studies conducted in different geographical areas of Europe. While the observed 95th percentiles in all included EU studies (DEMOCOPHES: 2010–2012; and HBM4EU Aligned Studies in adults: 2014–2021) was below these HBM-GVs, current BPA levels were, however, a reason for concern. These HBM-GVs were based on a tolerable daily intake (TDI) of 4 µg/kg bw/day, set by the European Food Safety Agency (EFSA) in 2015. An increased number of academic studies show adverse effects at current low exposure levels, below the TDI of EFSA (Ougier et al., 2021b). So far, health effects for substitutes BPS and BPF at current exposure levels are still unclear.

In the EU, bisphenol A is regulated under REACH (1907/2006/EC) (European Parliament and European Council, 2006). EU law regulates BPA in plastic materials and articles intended to come into contact with food (European Commission, 2011a), and since 2011, BPA has been banned from infant feeding bottles across Europe (European Commission, 2011b). In 2018, the EU further restricts the use of bisphenol A in certain food-contact materials. A specific migration limit (SML) for BPA in varnishes and coating has been introduced and the specific migration limit (SML) for BPA in the Plastics Regulation has been revised (European Commission, 2018a). Further restrictions are likely to be put in place in the coming years, following the Chemicals' Strategy for Sustainability work, and the Annex XV restriction dossier submission under REACH (European Commission, 2022b).

Several countries have restrictions on the use of BPA in food contact materials and in pacifiers and teething rings (e.g. France, Denmark, Belgium, Austria and Sweden). Occupational exposure limits are also in place in several countries. For a more detailed description of legislation

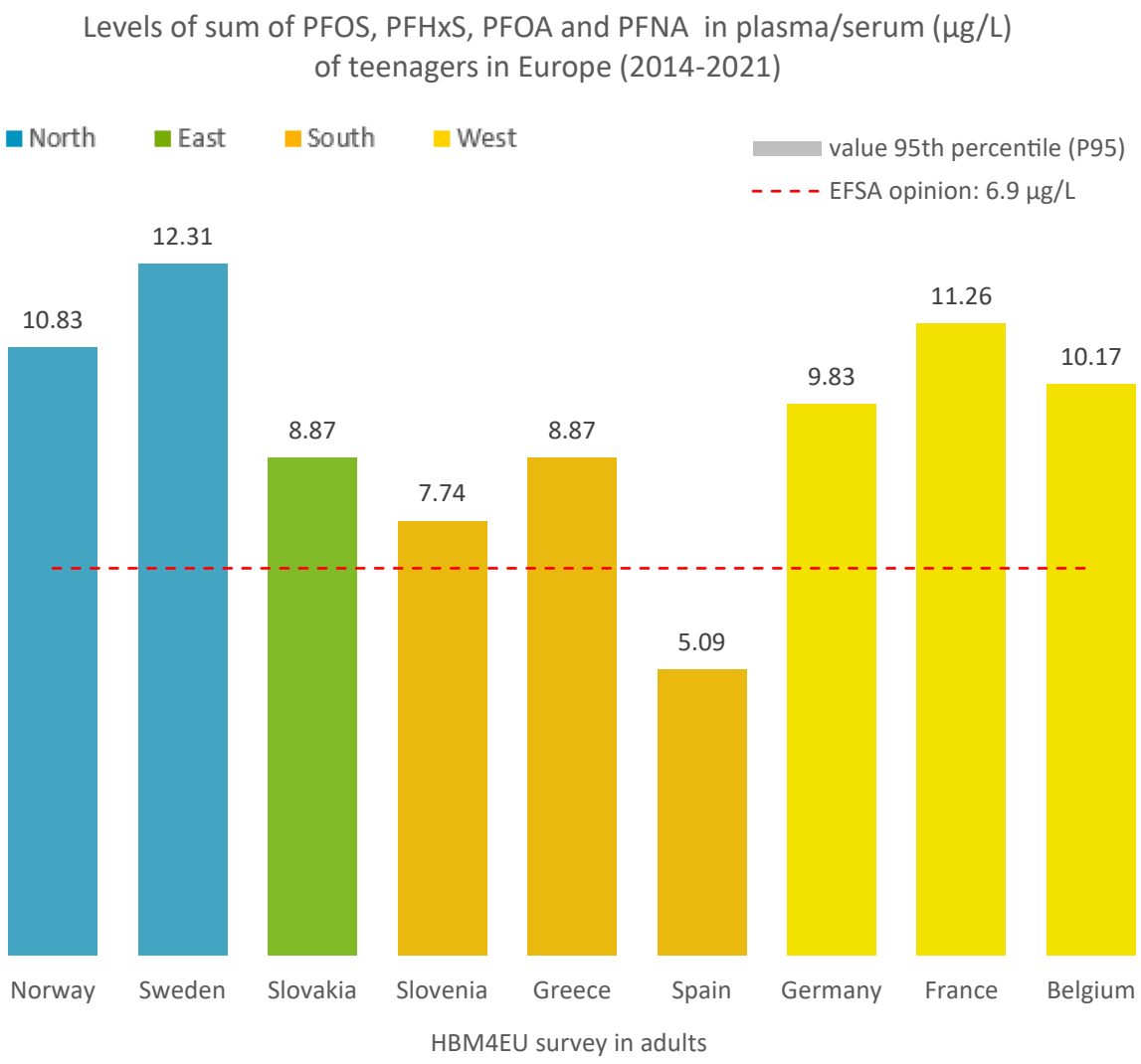

Fig. 2. Indicator showing P95 value of the sum of PFOS, PFHxS, PFOA and PFNA from 9 studies in teenagers (12–18 years) in Europe between 2014 and 2021 compared to EFSA guidance value of 6.9 µg/L. Based on data from the HBM4EU Aligned Studies in teenagers (Norway: NEB II, Sweden: Riksmaten Ungdom, Slovakia: PCB cohort follow-up, Slovenia: SLO CRP, Greece: CROME, Spain: BEA, Germany: GerES V-sub (unweighted), France: ESTEBAN, Belgium: FLEHS IV).

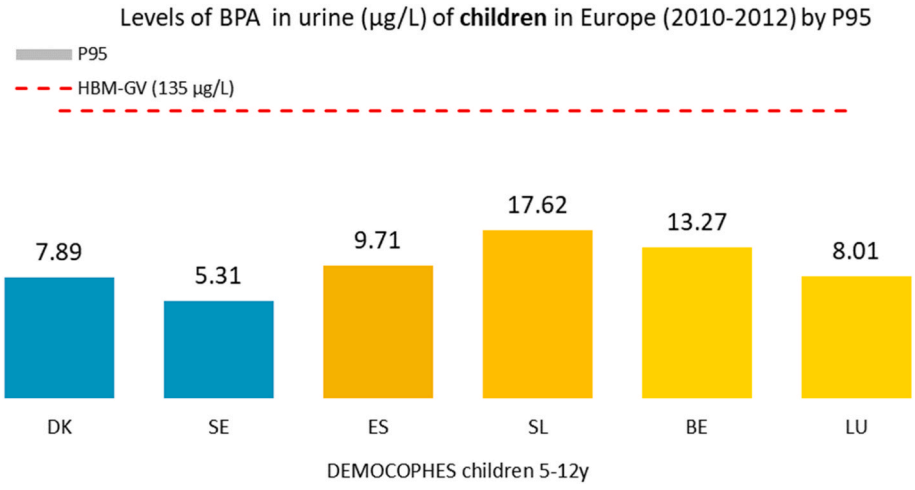

Fig. 3. Impact indicator showing 95th percentile of urinary bisphenol A concentrations of children sampled at 6 different sites in Europe between 2010 and 2012 (DEMOCOPHES project) compared to HBM-GV of 135 µg/L.

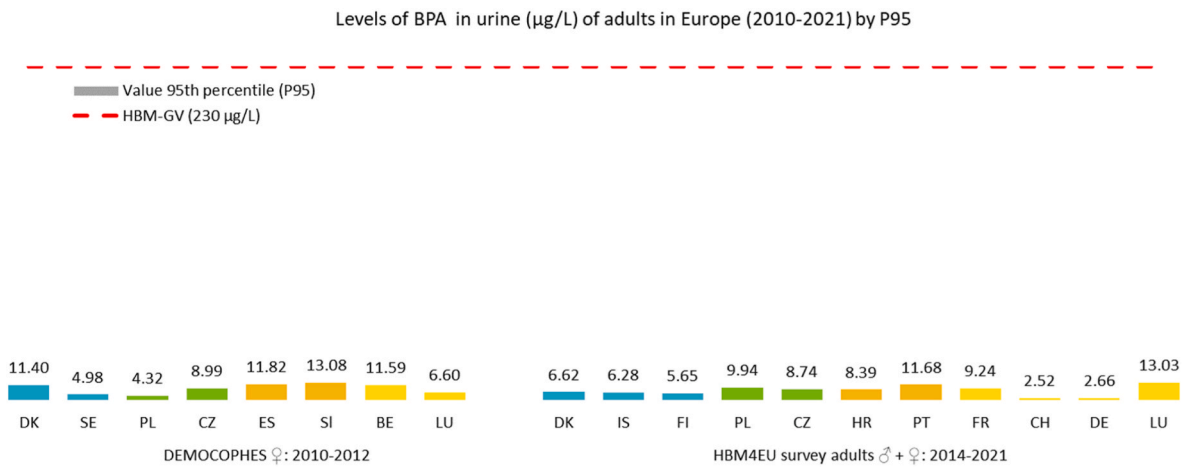

Fig. 4. Impact indicator showing 95th percentile of urinary bisphenol A from 8 studies in adult women (20–59 years) in Europe between 2010 and 2012 (DEMOCOPHES project) and 11 studies in adults (men and women, 20–39 years) in Europe between 2014 and 2021 (HBM4EU Aligned Studies; DK: CPHMINIPUB-parents_DYMS; IS: DIET_HBM, FI: FinHealth; PL: POLAES; CZ: (C)ELSPAC:YA; HR: HBM in adults in Croatia; PT: INSEF-ExpoQuim; FR: ESTEBAN; DE: ESB and LU: Oriscav-Lux2). BPA levels of ESB are measured in 24 h urine samples, all other BPA levels are measured in first morning or random spot urine sample.

at EU-national level, please consult the bisphenol substance page (HBM4EU, 2022b).

HBM4EU results have been provided to different EU-wide consultations including the Chemicals' Strategy for Sustainability, the Zero-Pollution Action Plan, as well as EFSA consultations. These are available in the HBM4EU Science to Policy section (HBM4EU, 2022c). HBM4EU indicator data will also be included in the Zero-Pollution Assessment work due at the end of 2022.

Recently, (December 2021) EFSA's draft opinion proposed lowering the tolerable daily intake (TDI) of BPA from 4 µg/kg of body weight per

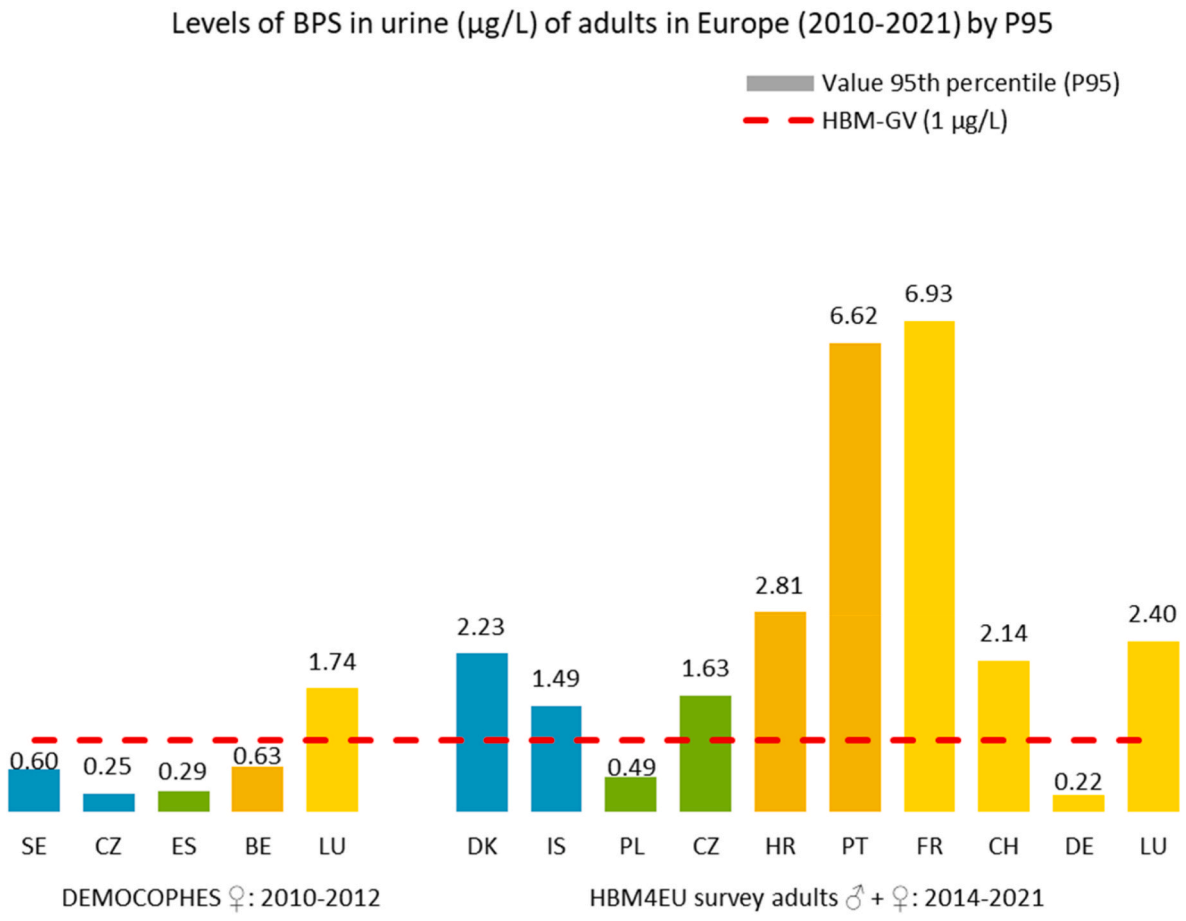

Fig. 5. Impact indicator showing 95th percentile of urinary bisphenol S from 5 studies in adult women (20–59 years) in Europe between 2010 and 2012 (DEMOCOPHES project) and 10 studies in adults (men and women, 20–39 years) in Europe between 2014 and 2021 (HBM4EU Aligned Studies); DK: CPHMINIPUB-parents_DYMS; IS: DIET_HBM, PL: POLAES; CZ: (C)ELSPAC:YA; HR: HBM in adults in Croatia; PT: INSEF-ExpoQuim; FR: ESTEBAN; DE: ESB and LU: Oriscav-Lux2). BPS levels of ESB are measured in 24 h urine samples, all other BPA levels are measured in first morning or random spot urine sample.

day to 0.04 ng/kg body weight per day (European Food Safety Authority, 2021). This is based on immunological parameters instead of on endocrine disrupting chemicals or reprotoxic effects. This value is 100, 000 times lower than the previous one established in 2015. This new TDI value of EFSA was derived taking into consideration new studies on health impacts of BPA; this highlights the importance of such exposure and health research to which HBM4EU has contributed to.

3.2.2.3. BPS in adults. Between 2010 and 2012, only in 1 sampling location the P95 value exceeded the guidance value of 1 μg/L. Between 2014 and 2021, in all sampling locations except POLAES (Poland) and ESB (Germany), the P95 value, exceeded the guidance value of 1 μg/L.

The indicator showed that internal exposure of a fraction of European adults (20–39 years) exceeded the HBM-GV for BPS (Fig. 5). Exceedances in the different studies and locations range from 0.56% up to 19.26% (Fig. 6). The studies with most adults exceeding the HBM-GV were conducted in Southern Europe.

In those sampling sites with >5% of participants exceeding the HBM-GV, the extent of exceedance (P95/2 μg/L) varied from 1.49 to 6.93.

HBM4EU results confirmed that legacy chemicals subject to regulation are in many cases being replaced by substitutes that have entered the human body and that can now be quantified in a large proportion of the EU population. This is a clear case of regrettable substitution, something the European Commission and the Member States are trying to avoid with the implementation of the CSS. To prevent regrettable substitution, it is therefore important to revise the BPS and BPF guidance values following the revision of BPA values by EFSA.

Despite the fact that HBM is an important tool to check policy efficacy, some of the legislation covering PFAS and BPA were put in place whilst HBM4EU samples were being taken, or later and therefore policy efficacy could not always be tracked. However, having indicators that display the chemical exposure of the population in certain periods of time is a good signal in terms of chemical prioritisation for policy making, and will be used as a baseline against which to measure progress in the future.

3.3. Science to policy workshops

Results from the Science to Policy workshops showed a great interest from the side of policy actors and stakeholders into HBM and related scientific results. For the three cases a satisfying diversity of the intended target groups was achieved, and a thoroughly prepared and successful two-day workshop was organized. Evaluation surveys after the workshops showed that most participants were satisfied with the way in which the workshops were organised. Most appreciation went to the opportunities that were offered to provide input and to enter discussion. A big majority of participants indicated that they would use what they have learned in their respective organisations and networks (Dries Coertjens et al., 2022).

The workshops provided an opportunity for an open and in-depth dialogue about HBM4EU results, across the boundaries of science, policy and society, and across policy fields and the interplay of the European and national level. Such processes encourage the further interpretation and evaluation of the statistical and scientific results in terms of policy goals, as the current policy context and specific policy opportunities matter in the formulation of conclusions and key messages. Even in situations where guidance values are available, different interpretations might exist. Thus, these workshops allowed for the identification and transparency on common and divergent views, remaining uncertainties, and obstacles as well as opportunities for policy uptake.

By way of illustration, we summarize here some conclusions from the workshop in 2021 on the HBM4EU results for PFAS, as partly visualized in the previous section on PFAS indicators. These conclusions are, of course, time bound. The measurement results reflect a specific period, just like policy processes that are constantly evolving. Regulatory measures now in place might not have been captured.

In general, all participants seemed to agree that the results clearly support an urgent need for policy action. Concrete opportunities for the use of HBM4EU results were identified, including:

i. The PFAS group restriction that is being prepared and for which HBM4EU results will be important supportive evidence.
ii. Ongoing discussions to set maximal levels in food, as a consequence of EFSA's scientific opinion on for PFAS.
iii. Several legislative changes on the EU agenda with the potential to include limits for PFAS, such as the Water Framework Directive, Groundwater Directive, Environmental Quality Standards Directive, Urban Waste Water Treatment Directive and Sewage Sludge Directive.
iv. Awareness raising of the public and national policy makers, including on the need for preventive health policies, monitoring and remediation, and better enforcement of EU legislation.
v. The current HBM4EU results are also seen as an important baseline to follow up effectiveness of current and future policy measures.

On the other hand, open questions and data needs were identified, including a need to better understand exposure pathways and (local) sources, to act where it is most relevant; to better monitor and study emerging PFAS and PFAS mixtures; and better identification and screening of potential (local) contamination cases as well as exchange of good practices.

A more detailed report is available on the HBM4EU website (Coertjens et al., 2021).

3.4. Residents' perspectives and outreach

The results of the focus groups revealed a level of concern regarding chemical exposure on residents' health and their daily lives (Matisāne et al., 2022b; Uhl et al., 2021b). Residents have an interest in understanding their own chemical body burden and expressed their concern using narratives from their own daily experiences, believing there is a cause–effect relationship between chemical exposure and health. Although the knowledge on human biomonitoring and chemical exposure, varied between participants and different focus groups, residents were aware of potential exposure to chemicals in the environment and how they may enter our bodies. Some identified main exposure pathways to chemicals and made links between sources of exposure and their pathways. For example, car exhaust emissions and car brake dust were linked to chemical exposure through outdoor air. Pesticides used in crops and flavourings, preservatives, and colour additives used in soft drinks production were linked to chemical exposure through food. Environmental reservoirs of antibiotic resistant microorganisms and industrial wastewater discharges were linked to chemical exposure through drinking water.

The mixture effect of combined exposures, a major challenge in the chemical safety field and explored under HBM4EU, is also a concern for residents. Participants were aware that mixtures may influence health, and they suggested that they should be addressed in future human biomonitoring studies.

Another key aspect highlighted by the participants is related to communication. Some highlighted the unintelligibility of the information communicated by scientists and authorities, which is viewed as a barrier to the public understanding of what is being transmitted. Risk information was also pointed out as something that needs to be improved. Furthermore, focus group's participants regarded science as the cornerstone to preventing chemical exposure, allowing scientific information to be better translated into policies and effective protection of human health.

Chemical safety is a matter of public concern. One in four residents

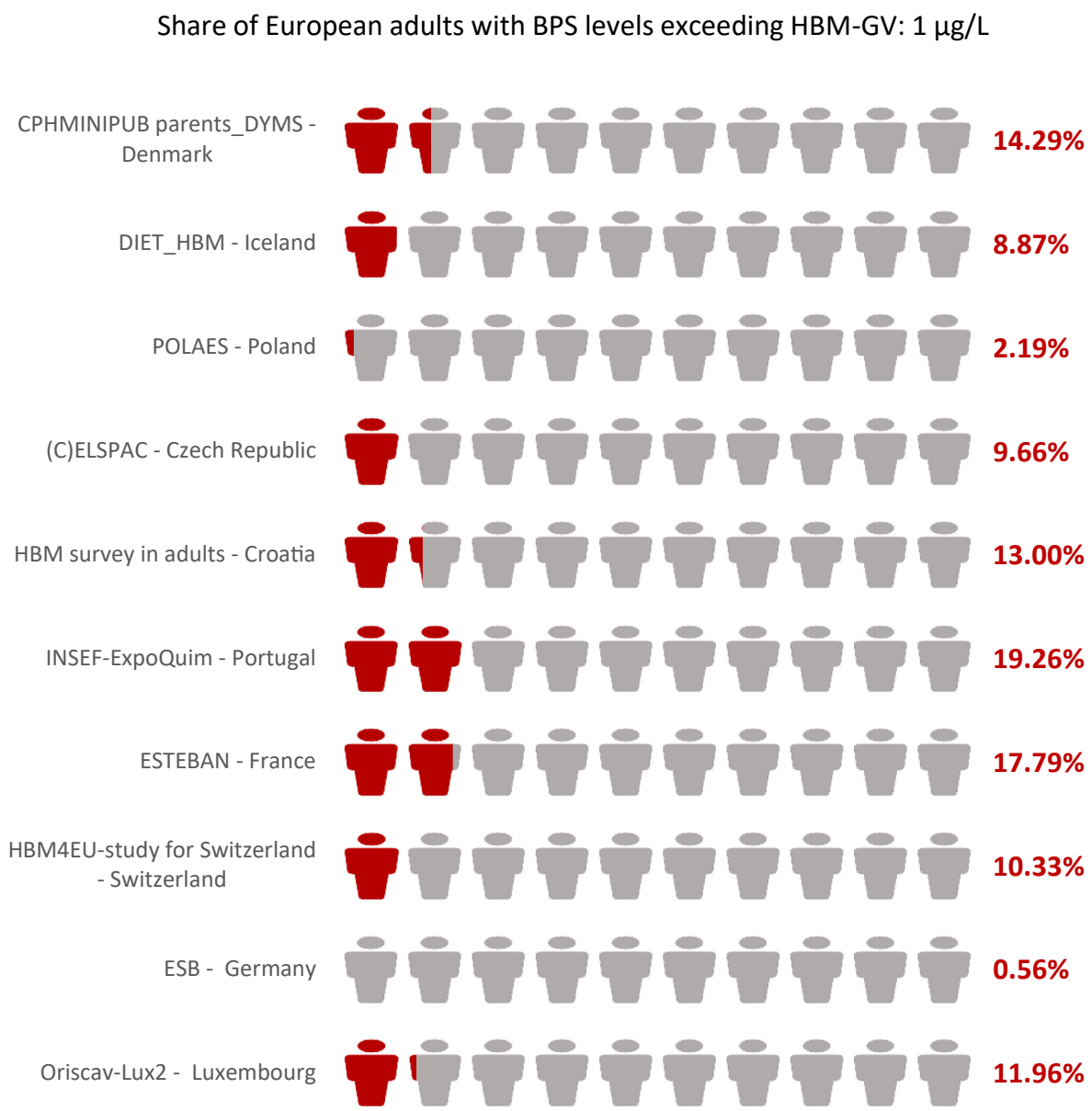

Fig. 6. Share of European adults (20–39 years) with BPS levels exceeding HBM-GV (1 µg/L). Results from the HBM4EU Aligned Studies (2014–2021).

are "very concerned" about exposure to chemicals in their daily life (Matisāne et al., 2022b; Uhl et al., 2021b). Residents want to be sufficiently informed to be able to make targeted decisions. They can choose not to purchase products containing hazardous chemicals and can drive substitution by the competent authorities. Residents also vote and can choose to back parties that promise greater protection for their health and the environment. They feel that they have the right to know what they are exposed to, which chemicals they have in their body and how they should interpret this using the best available science. Informing policy makers and providing science-based information for the public debate is key to this initiative.

Regarding the non-representative resident survey conducted in HBM4EU, it was answered by 5391 residents from 26 of the 30 National Hubs (Joana Lobo Vicente et al., 2021).

For consistency, the same regions as the aligned studies were used, with Israel included in the Southern Europe countries:

- Northern Europe (DK, FI, SE, IS, NO, LV, LT, IE, UK, EE)
- Western Europe (AT, BE, NL, FR, DE, CH, LU)
- Southern Europe (HR, CY, EL, IT, PT, Sl, ES, MK, IL)
- Eastern Europe (CZ, PL, SK, HU).

Based on the above clustering, 30% of the responders resided in "Northern Europe", 33% in "Southern Europe", 12% in "Eastern Europe" and 25% in "Western Europe".

The three main issues that concern the residents in terms of chemical exposure are industrial emissions and pollution, followed by pesticides in food and in the environment, and contaminants in drinking water and food.

European residents were supportive of the use of human biomonitoring as an important and reliable tool on public health policies on chemicals management, that could be used not only at EU level, but also nationally coordinated. These results were also aligned with some of the findings from the HBM4EU focus groups, which included residents' clear articulation on pathways of exposure (Uhl et al., 2021a). Concerning the importance that HBM studies may have, the one sentence most residents totally agreed with was "study the health impacts of chemical exposure", followed by "evaluate chemical exposure of the population" and "the

development of health policy that promote the safe use of chemicals". All these high ranked answers show their opinion on the relevance of HBM studies' contribution to key aspects of health impact and policy.

Although the survey was not representative by design, the results can be used to facilitate decision-making and policy development, and feed into the awareness needs of similar and future projects in Human Biomonitoring. Furthermore, it also brings to light ideas and concepts of residents in shaping collaborative knowledge between residents', experts, scientists, and policy makers on equal terms.

Our results are in line with the Eurobarometer survey on "Chemical Safety", which shows that European residents are concerned by the presence of thousands of chemicals in their environment and in consumer products. According to the Eurobarometer of 2017, around two-thirds of EU residents (65%) are at least a little concerned about being exposed to hazardous chemicals in their daily life, including 26% who are 'very much' concerned. Less than half of respondents (45%) feel well informed about the potential dangers of the chemicals contained in consumer products, and this proportion varies considerably by Member State (Eurobarometer, 2017).

The Eurobarometer survey "Europeans attitudes toward chemicals in consumer products" which assessed the Europeans' attitudes toward chemicals in consumer products, reported that European residents place the greatest trust in the European Union (35%), followed by the national authorities (32%) and the industry (21%) (Eurobarometer, 2010). Public trust towards industry and regulators has been declining since the 1980s, which impairs the risk communication.

Another aspect of resident outreach, was the production of animated videos on specific topics, substance videos, and factsheets and infographics where residents could learn how to reduce their exposure to chemicals, and what type of legislation there is in place to protect them (HBM4EU, 2020).

3.5. Chemicals' Strategy for sustainability

The EU Chemicals Strategy for Sustainability acknowledges the important role chemicals play for human well-being as well as for the green and digital transition in Europe (European Commission, 2020b). It also recognises the urgent need to tackle the health and environmental challenges caused by the most harmful chemicals. Boost innovation for safe and sustainable chemicals and increase protection of human health and the environment against hazardous chemicals is one of the objectives of the Strategy.

To comply with these objectives, the Strategy includes relevant supporting actions:

- Banning the most harmful chemicals from consumer products, such as toys, cosmetics, household items, food contact materials and textiles, unless their use is proven essential for society. Harmful substances include endocrine disruptors, chemicals that affect the immune and respiratory systems, and persistent substances such as per- and polyfluoroalkyl substances (PFAS).
- Minimising and substituting the presence of substances of concern in products, prioritising product categories that affect vulnerable populations and have potential for circular economy;
- Tackling "cocktail effect" i.e., the combination effect of chemicals, by assessing risks from chemicals posed to human health and the environment through daily exposure;
- Establishing a "one substance one assessment" process for the risk and hazard assessment of chemicals
- Promoting the EU's resilience of supply and sustainability of critical chemicals by ensuring that both producers and consumers have access to information on chemical content and safe use (Sustainable Product Policy Initiative).

To support the objectives laid out above, HBM4EU provided data on the priority substances to the consultations on the CSS and the Zero-Pollution Action Plan (ZPAP) and provided input for risk assessment to the HBM4EU EU Policy Board. These included data on bisphenols, PFAS, pesticides and mixtures in general, to name a few, and this will feed directly into the work being developed at EU-level.

Establishing a "one substance one assessment", will support the simplification of coordinating the hazard/risk assessment on chemicals in different legislations by assessing groups of substances instead of individual substances. This will ensure that safety assessments are done in a coordinated manner, that methodologies are harmonized, that decision-making processes are faster and more consistent, as well as reducing the burden on stakeholders.

The indicators generated will be part of the CSS indicator framework and the ZP Assessment which is due in the last quarter of 2022. A report using HBM to understand new chemical exposures in a circular economy has also been produced and explores new pathways through which humans can be exposed to hazardous chemicals as a result of a circular economy (HBM4EU, 2022c).

Another key element of the Strategy is to increase the knowledge base on chemicals and the mention of the importance of human, but also environmental (bio)monitoring. To support this, financial support for EU-wide activities in this field include:

- A research and innovation agenda for chemicals, driven by a EU-level Coordination Group, promoting the regulatory uptake of research findings;
- Fostering multidisciplinary research and digital innovations for advanced tools, methods and models, and data analysis capacities to also move away from animal testing;
- Building an EU early warning and action system for chemicals thus ensuring that EU policies address emerging chemical risks when identified by monitoring and research;
- Developing a framework of indicators to monitor the drivers and impacts of chemical pollution and to measure the effectiveness of chemicals legislation.

HBM4EU results on human exposure to chemicals in products, such as PFAS and bisphenols, highlighted that current human exposure to these substances pose a health risk, and support regulatory action to make products safer. In certain countries, legislations has been put in place after sample collection and hence another sample analysis to check for policy efficacy of new measures would be valuable. Substitutes of the legacy compounds are increasingly detected with scarce knowledge on their potential health effects. Moreover, many of these hazardous chemicals are simultaneously detected in most Europeans without any clear knowledge on the possibility of combined exposure and potential mixture effects. . It has not yet been fully elucidated when and under which circumstances combined exposure leads to a mixture effect.

Evidence of exposure to multiple chemicals at the same time supports efforts to consistently address combined exposure and potential mixture effects in risk assessments, while work to identify chemicals of emerging concern that may pose a health risk through non-target screening provides early warnings of potential risks.

HBM4EU generated scientific knowledge on the exposure of the general population to chemicals and their effects on human health and provided new tools to facilitate the use of these results. These included indicators of chemical exposure, derivation of HBM-GVs, risk assessment analysis, an EU-wide HBM Laboratory Network, and a HBM Dashboard with the data.

3.6. Zero-pollution action plan

The European Union's Zero Pollution Action Plan aims to tackle pollution that causes significant negative impacts on both the environment and human health (European Commission, 2021a). Aligned with the 8th Environment Action Programme, indicators will be part of this process to serve as a political summary to guide policy making, as a way

to summarize and monitor processes, whilst providing information on what has been achieved and the distance to set targets (European Commission, 2022c). It presents a vision for 2050 where pollution is reduced to levels that are no longer harmful to human health and natural ecosystems. The plan aims to deliver on the European Commission's European Green Deal, which recognises that environmental degradation poses an existential threat to Europe and the world (European Commission, 2019).

The use of the terminology 'Zero Pollution' flags the ambitious nature of this action plan and emphasises that systemic changes in key sectors, including transport, energy, agriculture and industry, will be required to deliver on its objectives. The zero-pollution hierarchy (Fig. 7) prioritizes the processes to be used to tackle pollution, with prevention as a first priority, followed by minimising and controlling pollution and finally elimination and remediation of pollution. Previous approaches, such as 'end-of-pipe' treatment of pollution, are now the least favoured option to address pollution.

A key element in delivering on this ambition is the development of a fit-for-purpose "monitoring and outlook framework", proposed by the EU Commission under the Zero Pollution Action Plan (European Environment Agency, 2021). This framework will support delivery of the action plan as follows:

- **Monitoring**: Assess progress in moving towards zero pollution, establish a baseline and measure the distance-to-targets set under the Zero Pollution Action Plan
- **Outlook:** Use future projections based on modelling and forecast approaches to assess the likelihood of achieving the objectives within the 2050 timeframe. This outlook will also identify potential blockers to achieving objectives, considering current and future policies.

The European Commission can then use these assessments to identify policy interventions necessary to deliver zero pollution or to address tensions across policy areas. The monitoring and outlook framework will also feed into the research agenda, identifying areas where new solutions may be required or where new monitoring or modelling techniques are needed in order to develop a more reliable indicator of current status and future outlooks.

The HBM4EU project and the follow-up partnership, PARC, are excellent examples of initiatives to deliver better monitoring data and intelligence to track progress in delivering zero pollution of humans and the environment (ANSES, 2022; European Commission, 2021b).

The role of the European Environment Agency (EEA) is to lead on the development of the 'monitoring' element of the monitoring and outlook framework (European Environment Agency, 2021). The first zero pollution monitoring assessment will be delivered in late 2022, to set a baseline, with the second assessment completed in 2024. EEA will work closely with a range of partners and stakeholders to gather inputs, including the European Environment Information and Observation Network (European Environment Agency, 2022). The assessment will cover the domains of health, ecosystems and production and consumption, based on available indicators and other relevant sources of information from a range of research and knowledge brokers (Fig. 8).

On chemicals and health, EEA will work closely with other HBM4EU partners to showcase HBM4EU knowledge in the baseline assessment report. Robust evidence of European population exposure to chemicals and associated health impacts provides a baseline against which to measure future progress.

As the zero-pollution monitoring report will be an indicator-based assessment, the HBM4EU work to develop indicators of exposure against HBM Guidance Values is particularly valuable.

It is also foreseen that activities planned under the PARC will support future zero pollution monitoring assessments, providing comparable data and analysis to assess the impact of chemicals pollution on human health. Importantly, such data will enable us to map trends in population exposure to chemicals in Europe and tease out the effects of policy interventions on exposure.

3.7. *Bridging science and policy to better protect human health*

To support decision making at European level, HBM4EU generated coherent European-wide datasets on human exposure to chemicals, demanding significant efforts to harmonize methodologies and standardise data collection.

An updated summary mapping relevant HBM4EU results in support of the European Green Deal is available in Table 1.

The HBM4EU Aligned studies have generated new human bio-

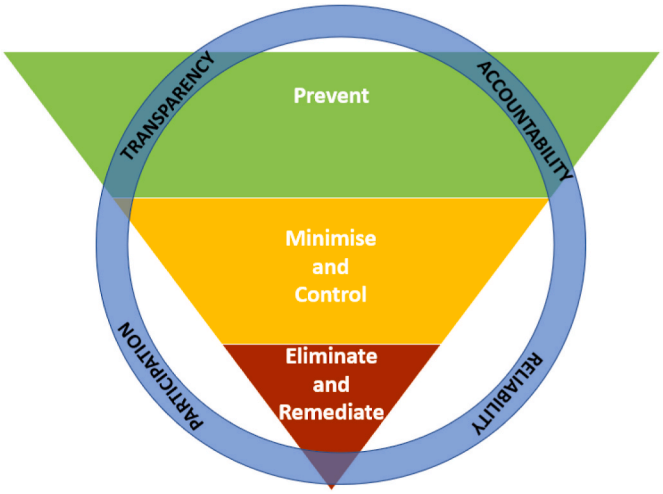

Fig. 7. Zero pollution hierarchy.

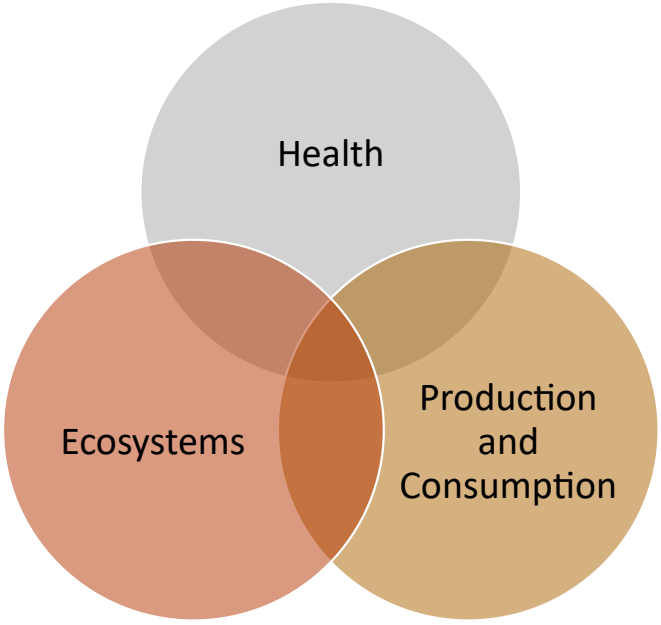

Fig. 8. Domains covered under the zero-pollution assessment.

monitoring data on the current internal exposure of the general population to a selection of HBM4EU priority substances and effect biomarkers in over 10,000 European residents. The data is available in the European Human Biomonitoring Dashboard, which also includes human biomonitoring data from previous studies collated under the HBM4EU project (Gilles et al., 2022, 2021; Govarts and et al., 2022).

Furthermore, aggregate data is included in the Information Platform for Chemical Monitoring (IPCHEM),[4] facilitating the use and reuse of human biomonitoring data in regulatory processes and research (European Commission, 2018b).

A HBM European Laboratory Network was also implemented and it has delivered coherent, robust results on chemical exposure and impacts on health in Europe to support policy making to improve chemical safety for residents (Esteban López et al., 2021; HBM4EU, 2021). HBM4EU has built up scientific capacities for human biomonitoring research across Europe that will continue to serve the public going forward.

HBM4EU has also provided direct input to public consultations on the development of strategies and action plans led by the European Commission under the European Green Deal, the European Chemicals Agency, the European Food Safety Authority, and Secretariat of the Minamata Convention on Mercury at the United Nations Environment Programme (HBM4EU, 2022c). HBM4EU is also supporting regulatory measures addressing priority substances, such as the ongoing proposal to restrict a wide range of PFAS under REACH and the recent EFSA draft opinion on Bisphenol A.

In what concerns chemicals, knowledge has been generated for about 500 out of 100,000 chemical substances on the market, but either little or nothing on most of the others (Fig. 9). Under HBM4EU, work was done on the chemicals of highest concern in terms of risks to health. Research was also done on emerging substances using new screening methods, techniques that HBM4EU sought to harmonize across Europe. The number of substances for which little knowledge is available is so substantial that only a sustained effort over time will allow us to face such a challenge.

One of the major issues addressed in the Strategy is how to identify the most relevant mixtures of chemicals and how to address their impacts. HBM4EU has been carrying out relevant research and contributing to working groups on risk assessment and management of chemical mixtures (Bopp et al., 2018; HBM4EU, 2022d; Socianu et al., 2022). This matter is rather intricate, and long-term research is needed. Yet, there is an urgency to act and, based on the available knowledge, decision makers can already draw some conclusions and take action.

Similarly to the objectives of chemical policy, HBM4EU's objectives cannot be achieved by a single discipline. There is a need for epidemiologists, exposure experts, public health specialists, toxicologists, computational scientists, analytical chemists, social scientists, policy advisers and policy makers working side by side. This multi-disciplinary collaboration happened under HBM4EU, but it is also happening in other EU projects in this field. To further expand this multi-disciplinary collaboration towards the social sciences, attention should be given to other specializations within the social sciences and humanities, such as risk governance, risk perception, communication, policy sciences and evaluation and socio-economic inequality.

Crucial to HBM4EU's success was also the number of countries that were part of this programme and contributed to a functional HBM network. HBM4EU's legacy will be built upon in the next partnership, PARC, with an enlarged scope. It will bring together European risk assessment and regulatory agencies, as well as policy makers, academia, and stakeholders to set a joint research and innovation agenda. This agenda will support EU and national chemical risk assessment and risk management bodies with new data, knowledge, methods, networks, and skills to address current, emerging and novel chemical safety challenges. It will facilitate the transition to next generation risk assessment to better protect human health and the environment, in line with the zero-pollution ambition, and will be an enabler for the EU Chemicals Strategy for sustainability.

[4] IPCHEM is the European Commission's reference access point for searching, accessing and retrieving chemical occurrence data collected and managed in Europe. The platform has been developed to fill the knowledge gap on chemical exposure and its burden on health and the environment.

The Strategy represents the first step towards a zero-pollution ambition for a toxic-free environment. The zero-pollution agenda should start from an understanding of how European residents are exposed to synthetic chemicals and how these accumulated in the body and make the reduction of the chemical body burden and associated health impacts a key priority.

In practice, this can only be delivered through a surveillance system for measuring the exposure burden of environmental pollutants in the European population that is embedded in European Union legislation.

4. Conclusion

HBM4EU results demonstrate that exposure of European residents is too high for some chemicals, with a fraction of the population exceeding health based guidance values. If exposure continues, adverse health effects cannot be excluded anymore. This underlines the need to further develop chemicals regulation and management in the EU as well as the research on risks on humans and the environment. The EU strategies aim at filling this gap by increased emphasis on lowering the impact of environmental pollution on health, in line with the European Green Deal's objectives. This rather ambitious legislative packaged, has a set of goals which include a zero-pollution ambition for air, water and soil thus protecting the health and well-being of Europeans as well as reducing environmental and climate pressures.

Protecting the health of European residents is a priority of the European Union and residents are eager to learn about their chemical body burden. In this context, the science-policy interface of HBM4EU is particularly important, ensuring up-to-date and coordinated science-based information for policy makers responsible for managing risks to human health from chemical exposure. Furthermore, informing the public will give additional support for the policy measures. Analysis of exposure determinants reveals how the internal dose may be attributed to multiple upstream sources, emphasising the need to consistently regulate substances across policy domains.

By assessing the internal dose of chemicals, HBM integrates the intake of chemicals from different sources and from different routes (ingestion, inhalation, dermal). In the exposure science field, this is now referred to as the "Aggregated Exposure Pathways" or AEP. HBM takes into consideration the absorption, distribution metabolism and excretion (ADME), that lead to internal dose. Together with computational tools such as PBPK, HBM studies provide critical information both on the actual level of contamination that can initiate or contribute to adverse health effects, and on the contribution of the different exposure sources and pathways.

HBM data complements exposure modelling which is increasingly complex due to the variety of sources and exposure pathways by which the same chemical can enter the human body. A sector-based decision making is not protective enough as sustainable use of chemicals will result in more complex chemical life cycles. By focusing on a substance approach, HBM is an essential step for the implementation of the "one substance one assessment" promoted by the Chemical Strategy for Sustainability. A straightforward implication of this conclusion is that data on chemicals should be presented both from the perspective of the current legislation/sectors, but also from the perspective of the substances themselves.

One of the overarching goals of HBM4EU was to actively engage with policy makers to translate scientific results into effective policies and make a step forward in protecting residents' health across Europe. As the premier European programme in the field of exposure to chemicals and health, HBM4EU looked at the Chemicals' Strategy for Sustainability as a major opportunity to move forward with the protection of European residents and human biomonitoring is mentioned in the CSS to assess the growing number of different hazardous chemicals in the human body. To attain the zero-pollution objective, it is critical to apply tools to monitor the chemical body burden of European residents and assess whether this would be related with associated health impacts. To ensure

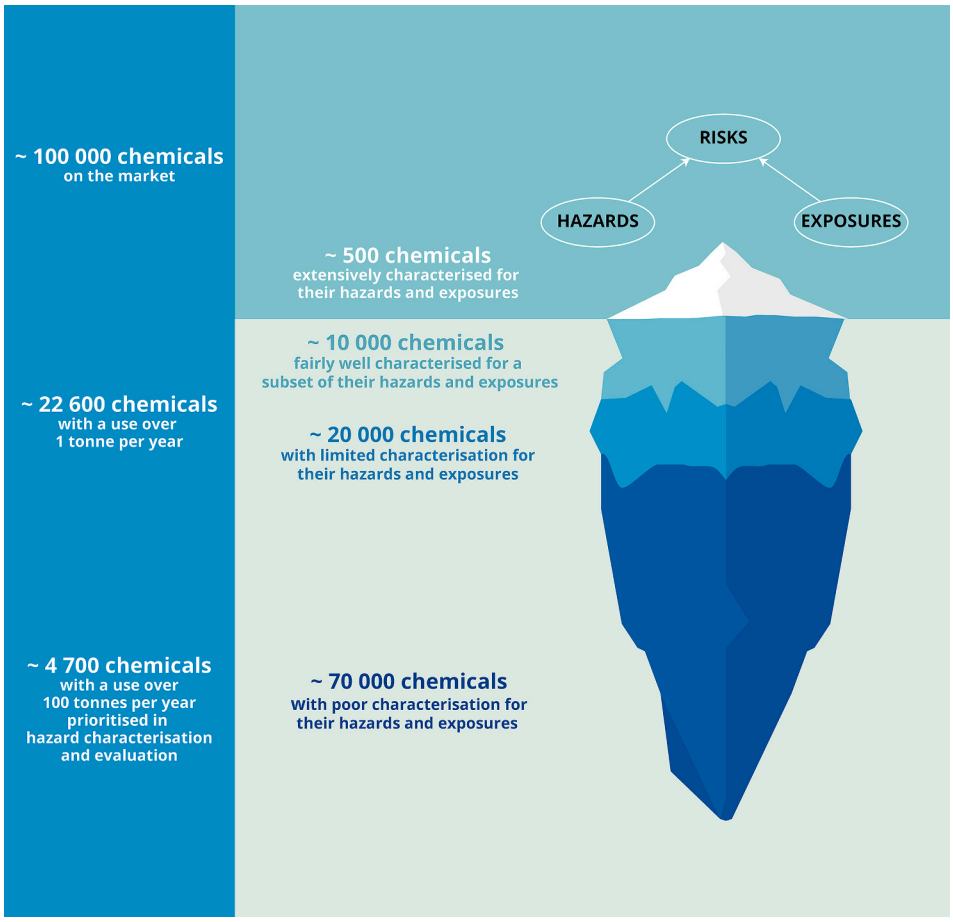

Fig. 9. The unknown territory of chemicals. Note: The numbers in the figure do not include impurities, transformation products or structural variants (isomers) of chemicals placed on the market. ~ 500 chemicals: Chemicals which are considered sufficiently regulated (ECHA, 2019b), typically legacy and well-known chemicals characterised for most known hazards, which have limit values and are regularly monitored by quantitative methods in most media. ~10,000 chemicals: Chemicals on EU or national legislation lists which are characterised for some but not for all known hazards, which have specific limit values, and are monitored quantitatively, but irregularly across time, media, or space. ~20,000 chemicals: Chemicals with hazards characterised mainly by modelling, or where exposure data are based on qualitative screenings done occasionally and in few media. ~70,000 chemicals: typically, low volume chemicals for which usually no or very few hazards characteristics are available and information on uses and exposure is scarce, not characterised or measured in very few media. Source: © EEA, 2020, The European Environment – State and outlook report.

that, HBM4EU established a trust-based cooperation and data-sharing process between all parties to enable the consortium to react on short notice to knowledge needs; partners were actively identifying windows of opportunities in regulatory processes on chemicals where they might feed in evidence; accomplished the vision of a human biomonitoring programme in Europe to support the delivery of chemical safety for Europe's population.

Looking forward, HBM4EU results will be used as baseline against which the success of the EU Chemicals Strategy for Sustainability and Zero Pollution Action Plan supported by the development of indicators. It is therefore crucial that the PARC, the follow-up partnership to HBM4EU, ensures a constant flow of data on priority chemicals to allow for the mapping of trends in population exposure over time at European level and tease out the effects of policy interventions on exposure. Data generated under PARC will also allow to assess progress against objectives in the Zero Pollution Action Plan and the Chemical Strategy for Sustainability and provide comparable data and analysis to assess the impact of chemicals pollution on human health. This will also contribute to estimate the burden of disease from chemical exposure in Europe. Another key element is the development of approaches that are safe and sustainable by design, with the power to fundamentally transform how chemicals are used.

To achieve such an ambitious goal, a sustainable surveillance system is needed, a system embedded in legislation that can be used to measure the chemical burden through human biomonitoring not only to help inform policy actions and environmental health interventions but also to evaluate the efficacy of such actions. This will support sustainable risk assessment, chemical management and legislation in Europe to the benefit of current and future generations.

Another one of HBM4EU's biggest achievements and main drivers was its inclusiveness across the different domains of research and policymaking, as well as capacity building. While this demands time and investment in the short-term, it is certainly more productive in the long-term with the added value of having an open channel between scientists, policy advisers and policy makers acting as a catalyst, and in line with the European spirit.

HBM4EU has contributed to shaping the next research agenda for chemicals at European level, and its legacy with carry on with PARC, as mentioned in the introduction. PARC is an EU-wide research and innovation programme, involving 28 partner countries and three EU agencies, the European Environment Agency (EEA), the European Chemicals Agency (ECHA), and the European Food Safety Authority (EFSA), to cement the link to implementation of the Chemical Strategy for Sustainability. It started in May 2022 and will last for 7 years. It will support EU and national chemical risk assessment and risk management bodies with new data, knowledge, methods, networks and skills to address current, emerging and novel chemical safety challenges. It will facilitate the transition to next generation risk assessment to better protect human health and the environment, in line with the Green Deal's zero-pollution ambition for a toxic free environment and will be an enabler for the EU Chemicals Strategy for sustainability.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2023.114111.

Abbreviations

CLH	Harmonized Classification and Labelling
CLP	Classification, Labelling & Packaging
CSS	Chemicals' Strategy for Sustainability
ECHA	European Chemicals Agency
EEA	European Environment Agency
EFSA	European Food Safety Authority
HBM-GV	Human Biomonitoring guidance value
COPHES/DEMOCOPHES	DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale
HBM	Human Biomonitoring
BPA	Bisphenol A
BPS	Bisphenol S
bw	Bodyweight
Cd	NGOs Cadmium Non-Governmental Organisations
PARC	Partnership for the Assessment of Risks from Chemicals
PBT	Persistent Bioaccumulative and Toxic
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid (sum of all isomers)
PIC	Prior Informed Consent
SVHC	Substance of Very High Concern

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