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HBM4EU Newspaper

European Human Biomonitoring Initiative

HBM4EU science and policy for a healthy future

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Funded by the European Union's Horizon 2020 research and innovation programme, the **European Human Biomonitoring Initiative**, led by the German Environment Agency, was jointly implemented by 120 partners from 30 participating countries – 25 EU member states plus Norway, Switzerland, Iceland, Israel and the UK, and the European Environmental Agency from 2017-2022.

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science and policy for a healthy future

HBM4EU
aims to advance human biomonitoring in Europe by providing evidence of the exposure of EU citizens to chemicals and their effects on human health in order to support policy making.

We are HBM4EU

HBM4EU - a strong network to support human biomonitoring and environmental health policies in Europe

written by The German Environment Agency

The exposure of citizens to chemicals and related health impacts are in the center of public and political concern. Reliable data are the prerequisite on which policies, regulation and information for the general public must be based to safeguard a healthy life in a healthy Europe.

Human Biomonitoring (HBM) is a key tool to investigate the exposure of people, and to inform regulators and citizens about the extent of the pollution of the human body, the sources and meaningful protective measures.

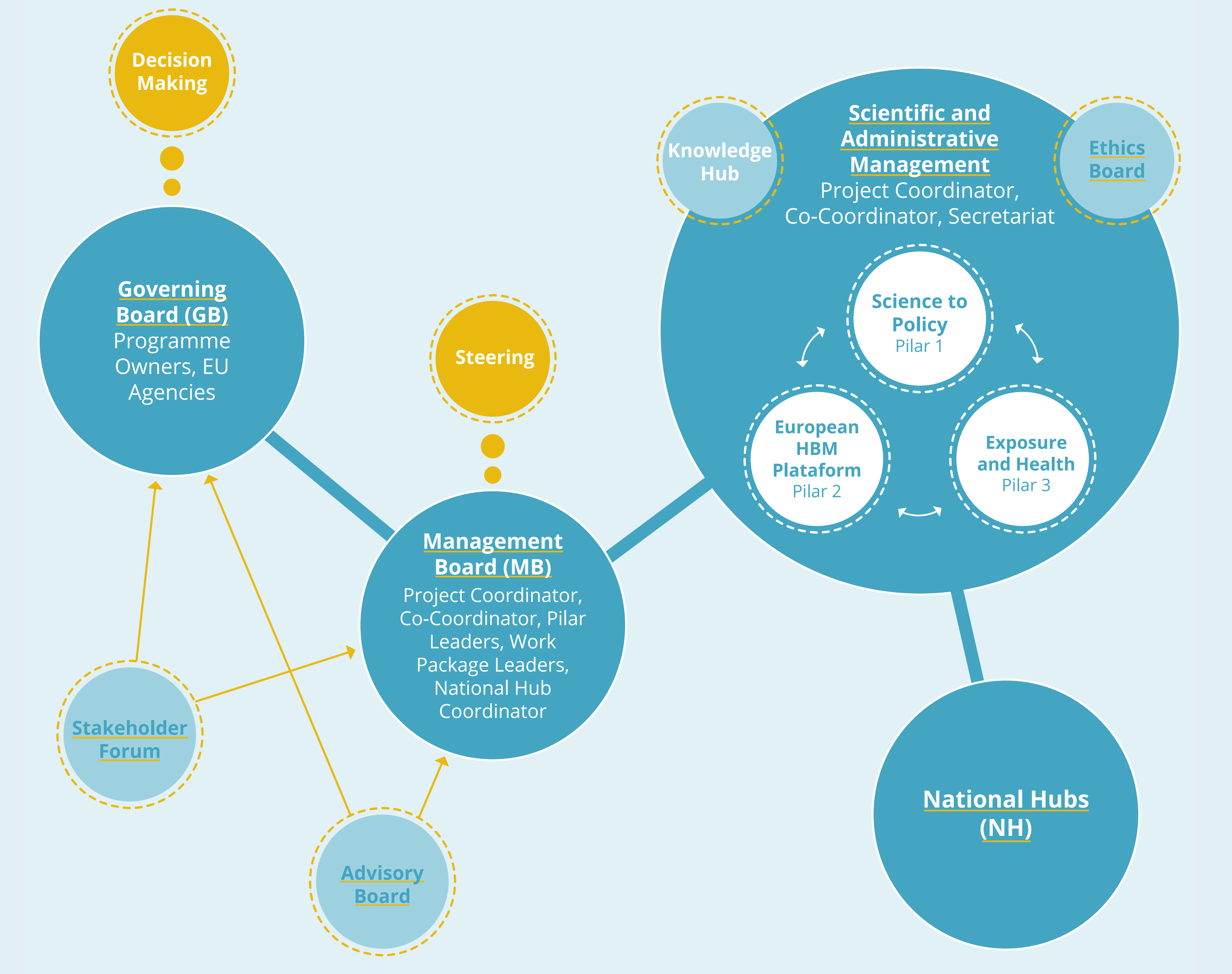
After years of intense work from national HBM programmes in Europe and the successfully finalised co-funded EU projects ESBIO, COPHES and DEMOCOPHES, the need to establish a permanent HBM on a European level became urgent.

Since 2017, the German Environment Agency is coordinating the European Human Biomonitoring Initiative which comprises 116 partner institutions from 30 members countries. Over 5 and a half years, HBM4EU established highly capable networks, which have developed a new mode of cooperation including the generous, prompt and free sharing of data. This network ensures political support through the engagement of the national Programme Owners and the EU Policy Board, and includes scientific Europe-wide excellence by involving governmental and research institutions alike. Valuable knowledge of the scientific communities and EU agencies served as foundation for the planning of work even before the beginning of the project, and have been continuously refined and expanded by ongoing feedback loops. With this new and innovative network, HBM4EU was not only able to react quickly to consulting and research needs, but also to provide an excellent basis for future partnerships and projects.

HBM4EU is a European Joint Programme, funded by the European Commission under its H2020 programme with 74M EUR. The project is located on the intersection between science and policy. It was designed to use gained scientific knowledge to answer urgent policy questions concerning prioritised substances and substance groups. The Governing Board which mainly consists of representatives of the Ministries responsible for the national programmes is the ultimate decision-making body of HBM4EU. The Management Board did the steering of the project. Both boards are in close exchange with the Stakeholder Forum and the Advisory Board, which act as consulting bodies for HBM4EU. The activities developed under the project are organised in work packages clustered under three pillars: 1) Science to Policy, which ensures the translation of results into policy, 2) European HBM Platform, which covers all components of HBM studies, and 3) Exposure and Health, which deals with the research of innovative methods to determine the relation between exposure and health. The respective expertise of each country is bundled in 'National Hubs', which function as conduits to both sides between HBM4EU and the member countries to ensure that national requirements are fed.

The project's large scale was quite a challenge for setting up an efficient and transparent cooperation, but HBM4EU produced data that can serve as a baseline to evaluate the success of the measures taken to operationalise the Chemicals Strategy for Sustainability and the Zero Pollution Agenda in the frame of the European Green Deal. The results of HBM4EU clearly show that the levels of some substances in the human body of the European population are still so high that adverse health effects cannot be excluded according to current knowledge and that there is an urgent need to address mixtures effects in risk assessment. Accordingly, proposals and evidence were supplied by HBM4EU. The results show clearly that we need to put more effort into information for the general public and multipliers, as such for the consumer behaviour which results in a permanent exposure of human bodies to plasticizers. Not only regulations for the environment are necessary, but also a clear plastic strategy that focuses on human data and effectively prevents the pollution of the human body. This serves just as an example and more conclusions like this can be drawn based on HBM4EU findings.

We as the coordination team at the German Environment Agency would like to express our heartfelt gratitude to the entire consortium of the HBM4EU project and all partners for putting endless hours in this fascinating and challenging project. The intensive and fruitful collaboration between all partners and national efforts dedicated to HBM4EU during our journey were the basis which made this project a success and made the establishment of our network possible. In addition, it was a great pleasure and honour for us to act as coordinators in this process.



HBM4EU governance structure

“The role of HBM in a new European Chemicals Strategy for Sustainability“

— Thomas Jakl
Deputy Director-General of the Ministry of Environment of Austria, which is responsible for chemicals policy

Citizens have the right to know what they are exposed to, what chemicals are in their bodies and how their health is affected. Understanding and responding to citizens’ concerns, raising public awareness and making science accessible were core parts of the HBM4EU initiative, which I am regarding as a true masterpiece among all the projects performed under the Horizon 2020 Programme.

This project bridged science and policy while at the same time equipping the European Union’s chemicals policy with both an effective tool of quality control as well as an intelligent “early warning system“. HBM4EU tells us if the risk management measures we set in place are doing their job and effectively reduce the chemical burden. It tells us to adjust our instruments to embrace new substances and recently detected toxicological effects, in particular to ensure a high level of protection of vulnerable groups such as children.

On its way towards “zero pollution“ Europe is relying on a robust and sustained comprehensive human biomonitoring programme to assess the risk of chemicals in the bodies of European citizens and to assess the associated health impacts. Human Biomonitoring already today is the guardian angel for chemicals policy. And chemicals policy itself stands in the very centre of the Union’s flagship initiative: Within the framework of the Green Deal we all together have to join hands to accomplish transition towards a circular economy. And it is beyond doubt that this giant undertaking desperately needs a wise and well equipped guardian angel.

“In order to protect citizens from chemical risk, it is crucial to comprehensively understand the compounds present in our living environment and their effects. HBM4EU has been instrumental in advancing the field of human biomonitoring and informing environmental protection policies in the EU. Since its inception it has been working to build a strong knowledge base and has contributed to important EU initiatives such as the Chemical Strategy for Sustainability and the Zero Pollution Action Plan. HBM4EU has also served in several consultations in the EU on the restriction of use of substances, by providing evidence on the levels of exposure to compounds such as pesticides, mercury, chromium VI and many others. It is for this reason that HBM4EU is a major tool to share harmonised information at the European level, limit chemical exposure and prevent illnesses stemming from it. We hope to see this programme’s achievements used to expand knowledge and further protect people and the environment in the upcoming Partnership for the Assessme.”

— Carmen Laplaza Santos
Head of Unit ‘Health Innovations’, People Directorate of the DG Research and Innovation, European Commission

“The conclusions of the HBM4EU project are very timely. This year, the European Commission is busy defining policy options for revising key legislation such as REACH. We need to have a vision of which chemicals are present in the bodies of European people and in which quantities. This is key to improve our understanding of their impact, and hence an important element in our policy making. Therefore the Commission will also continue to foster research and (bio)-monitoring to better understand and prevent chemicals-related risks and drive innovation in chemical risk assessment and regulatory science through our framework programme for research and innovation.”

— Cristina de Avila
Head of Unit Sustainable Chemicals DG Environment, European Commission

“Programmes like HBM4EU are crucial to detect what toxic chemicals accumulate in the human body. But they also show the presence of certain toxic chemicals which should not be in the human body in the first place. The message must be: Exposure to toxic chemicals needs to be stopped, stronger regulation is needed. We know that women are affected differently by chemicals. Therefore, more gender disaggregated data is needed and had to be taken into account in decision making and risk assessments. We will use HBM4EU data to call for action on the political agenda.”

— Johanna Hausmann
Senior Policy Advisor, Chemicals and Health, Consultant for WECF

“HBM4EU is a sorely needed public health tool for providing real-life data to policy makers on the widespread daily exposure of Europeans to harmful chemicals such as pesticides, phthalates, Bisphenol A and PFAS and the impact these may have on our health. HEAL is pleased that the project has successfully delivered the first comparable data to answer policy questions, which must be used to trigger new legislative measures to reduce people's exposure and protect our health, especially those most vulnerable.”

— Dr Angeliki Lyssimachou
Senior Science Policy Officer, Health and Environment Alliance

“HBM4EU is a good example of transparent and open collaboration between authorities, academia, civil society and industry. We were very pleased to actively support and contribute to the HBM4EU program. We use human biomonitoring data as an appropriate tool for specific and key evaluations because they offer complementary and distinct advantages over other exposure monitoring methods currently in place or under development. As demonstrated during all the work, while the work generate very useful information for experts, it is important to remain very careful about how to communicate and use the data because taken out of context and without the necessary scientific background, the generated information can be misused.”

—Dr Michel Cassart
Sustainability Director, Plastics Europe

“Metals play a crucial role in society. They enable existing and emerging technologies and represent a strategic and recyclable resource. Managing the potential risks associated with their manufacturing and uses is a key priority. This requires in-depth knowledge on exposure and understanding the possible impacts. HBM provides very useful information to achieve this and identify where to further reduce exposure, if so needed.”

— Violaine Verougstraete
Chemicals Management Director, Eurometaux

“The EEB welcomes the important HBM4EU results and we hope that this project takes us one step closer to the establishment of a permanent biomonitoring program in the EU. HBM4EU data is relevant because it can support regulatory action to reduce exposure to highly hazardous chemicals, such as those included in the EU Restriction Roadmap, PFAS and bisphenols. This biomonitoring project is a showcase for the benefits of prioritising, supporting and evaluating policy measures when it comes to reducing the exposure to hazardous chemicals and their mixtures.”

— Tatiana Santos
Policy Manager Chemicals & Nanotechnology, European Environmental Bureau

“Being part of the HBM4EU's journey was very exciting and educational for me. Now I am curious, how this area will develop further and to what extend it can support SME to navigate in a highly complex regulatory framework like the EU's chemicals legislation.”

— Marko Susnik
Senior Advisor Chemical Policy, Austrian Economic Chamber and Advisor to the Secretary General on Chemicals Policy, SMEunited

Bridging science and policy to better protect human health

Protecting the health of European citizens is a priority of the European Union. In this context, the science-policy interface of the 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.

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 citizens' health across Europe. Hence, HBM4EU designed its research programme to answer concrete policy questions from EU and national policy makers. After 5 years of top-notch research, we have answered key policy questions, such as whether chemical bans successfully reduced exposure and how exposure to substitutes has evolved over time, whether people in certain regions are at risk, and how the chemical body burden varies with sex, age, and socio-economic status.

HBM4EU results on human exposure to **chemicals in products**, such a phthalates and bisphenols, and potential health impacts, support regulatory action to make products safer. Health-based human biomonitoring guidance values provide **benchmark values** against which to compare exposure in the general population, as well as in the occupational context. Evidence of exposure to multiple chemicals at the same time supports efforts to consistently address **mixtures** 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 and workers to chemicals and their effects on human health and provided new tools to facilitate the use of these results. For instance, to allow interpretation of HBM data in a health risk context, HBM4EU's scientists derived HBM Guidance Values for the general public and for workers for a number of substances. 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.

Another tool is the set of indicators, developed to assess time and spatial trends in the exposure of European citizens to chemicals and to get a picture of the population at risk. HBM4EU first developed an approach to producing European HBM indicators and proposed two types of indicators, indicators of internal exposure derived directly from biomarker concentrations and indicators of health risk, comparing exposure concentrations to HBM guidance values. These indicators have been produced for bisphenol 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. These indicators can be used to assess the effectiveness of current EU chemicals regulations and to identify the need for additional action to protect citizens.

Highly exposed groups like workers present a concern, as **occupational exposure** to specific chemicals may be several times higher than environment exposures experienced by the general population. Harmonized occupation studies on exposure to chromium VI, to diisocyanates and to hazardous chemicals in e-waste handling have yielded results that support improved protection of workers.

To provide **coherent datasets** that can be used in decision making at European level, significant efforts were devoted to harmonising methodologies and standardising data collection under HBM4EU. The **HBM4EU Aligned studies** have generated new human biomonitoring 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 citizens. The data is available at the **European Human Biomonitoring Dashboard,** which also includes human biomonitoring data from previous studies collated under the HBM4EU project. Furthermore, aggregate data is included in the **Information Platform for Chemical Monitoring** (IPCHEM), facilitating the use and reuse of human biomonitoring data in regulatory processes and research.

HBM4EU results confirm 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. Moreover, 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.

All data from HBM4EU were shared with national and EU policy makers as soon as they were quality assured – to ensure that they are available to support for regulatory decision-making as soon as possible. Additionally, 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, such as the request from the Directorate-General for Health and Food for information on human exposure to copper.

Exploring the different ways human biomonitoring and health surveys might be combined is another opportunity explored by HBM4EU, as it would produce an extensive database for research to support policy decisions. Combined surveys are cost-effective, reducing the resources required to collect information and recruit participants, while at the same time collecting more information from each study participant. Guidelines for how to combine cross-sectional health surveys and human biomonitoring studies at general population level are now available.

HBM4EU partners are actively identifying windows of opportunities in regulatory processes on chemicals where they might feed in evidence. HBM4EU has fed results and data into chemical-specific regulatory processes led by the **European Commission**, the **European Chemicals Agency**, the **European Food Safety Authority**, and Secretariat of the **Minamata Convention on Mercury** at the United Nations Environment Programme. HBM4EU is also supporting regulatory measures addressing priority substances, such as the ongoing proposal to restrict a wide range of **per- and polyfluoroalkyl substances (PFAS)** under REACH and the recent EFSA draft opinion on **Bisphenol A**.

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** will be measured. We have also contributed to shaping the next research agenda for chemical at European level - the **European partnership for the assessment of risks from chemicals (PARC)**.

HBM4EU has realised the vision of a human biomonitoring programme in Europe to support the delivery of chemical safety for Europe's population – it is now time to make it a permanent reality.

Reconciling chemical legislation with the state of HBM science

written by Dr Robert Barouki

Scientists in the field of chemical safety often face a dilemma when they need to present the different classes of chemicals and their regulation: should they first address the different professional sectors and legislations? Or should they focus on the substance irrespective of its sources? Or even should they highlight the mechanisms of action corresponding to groups of substances? Depending on which classification is chosen, the outcome may end up being quite different. These questions can be addressed by filling the gap between regulation and exposure and toxicological sciences.

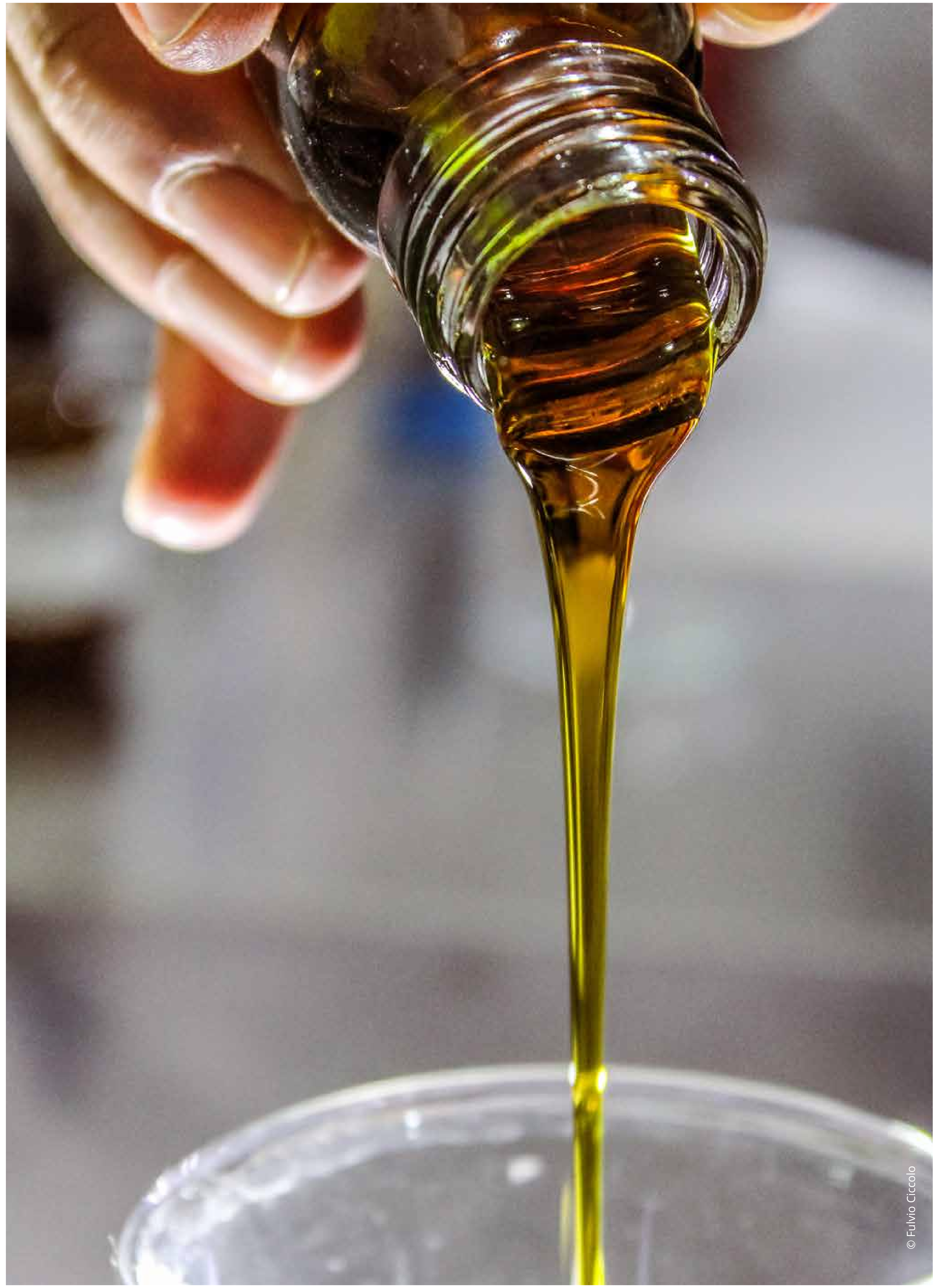
The Chemical Strategy for sustainability has highlighted the "one substance one assessment" concept. This would be a major improvement over the current situation in which the same substance can be evaluated and eventually regulated in different sectors, sometimes with different conclusions. This is the case for example if the substance has different properties and applications, e.g. as a biocide or in consumer products or in cosmetics. This has been primarily justified by the fact that legislations are sector-dependent and decisions are focused on acting on the source of contamination without taking into consideration the presence of multiple sources. Indeed, for a long time, the only available information was the amount of contaminants in different sources with little information on the impact of combinations of intakes. This has changed with the development of human biomonitoring (HBM) and kinetic modeling.

By assessing the internal dose of chemicals, HBM integrates the intake of chemicals from different sources and from different routes (ingestion, inhalation, skin). In the exposure science field, this is now referred to as the "Aggregated Exposure Pathways" or AEP. Furthermore, HBM takes into consideration the physiological steps that lead to internal dose such as the absorption, distribution, metabolism and excretion. In addition, in the case of storage of persistent chemicals in the body (persistent organic pollutants, some metals), HBM also integrates the release of the chemicals from their storage sites, e.g. adipose tissue and bone, in the bloodstream. Furthermore, it should be stressed that the internal dose of contaminants is the actual trigger for the adverse outcome pathways. When combined with computational tools such as PBPK, HBM studies provide critical information both on the actual level of contamination that can initiate a health effect, and on the contribution of the different exposure sources and pathways.

"The Chemicals Strategy for Sustainability has highlighted the *one substance one assessment* concept."

Clearly the combination of internal dose data and exposure pathway analysis is an important contribution to decision making and to the protection of citizens. With this in mind, a sector-based decision making is not sustainable and may not be protective enough. 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.

Yet, this is not enough. The Chemicals Strategy also highlights the importance of certain mechanisms of action such as endocrine disruption and immunotoxicity and of the mixture issue. Therefore the "one substance one assessment" should not be interpreted as an approach that would not take into consideration the grouping of chemicals according to their mechanisms of action or that would separate the assessment of substituents from that of parent chemicals. Au contraire, the "one substance one assessment" approach is in fact the first step towards a mechanism-inspired assessment of chemicals and towards an improved rational assessment of mixtures.



Health impacts of chemicals

The interest of assessing exposure to chemicals in human biomonitoring is ultimately to evaluate how it affects our health. HBM4EU priority substances were selected, among other criteria, according to the level of current knowledge about hazards they pose to human health. All the examined substances have been associated with some adverse health effects, including severe impacts, depending on the dose and duration of exposure. Affecting various organs and systems in the human body, this section introduces diseases linked to the HBM4EU priority substances.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease causing no non-reversible breathing difficulties. COPD is usually caused by a long-term exposure inhaled irritants such as tobacco smoke, which damage lungs and airways.

Exposure to pesticides, especially organophosphate and carbamate insecticides and some herbicides, lead and PAHs has been associated with increased risk of COPD. Cadmium, chromium, arsenic and diisocyanates are possibly associated with increased risk of COPD and/or decreased risk of lung function.

Reproductive health

Reproductive health refers to the male and female reproductive systems including fertility, menstruation, pregnancy, menopause, and several chronic health problems such as endometriosis.

Pesticides are shown to be associated with an increased risk of female infertility and miscarriage and cause increased length of the menstrual cycle. They may also be associated with delayed pubertal onset. Among males, occupational use of pesticides is shown to be associated with decreased sperm quality.

New emerging chemicals, such as replacement flame retardants, have been shown to have adverse health effects on reproductive health by in vitro studies.

Brain development

Thyroid hormone is important for brain development especially during the fetal and postnatal period. Thyroid hormone deficiency may cause retarded maturation, intellectual deficits, and neurological impairment.

One cause for thyroid dysfunction may be EDCs which disrupt thyroid hormone of mothers and foetuses. Bisphenol A has been shown to affect thyroid hormone levels in pregnant women which implies that boys may have increased risk of ADHD-related behaviours and girls internalising and externalising behaviours.

Many pesticides exert toxicological effects, including on thyroid signalling. The mother/child cohort studies have shown that organochlorine (OC) pesticides may exert significant thyroid hormone inhibitory effects. Organophosphorus pesticides (OPPs) and carbamates have been associated with thyroid dysfunction, increased hyperthorydism and brain function impairment.

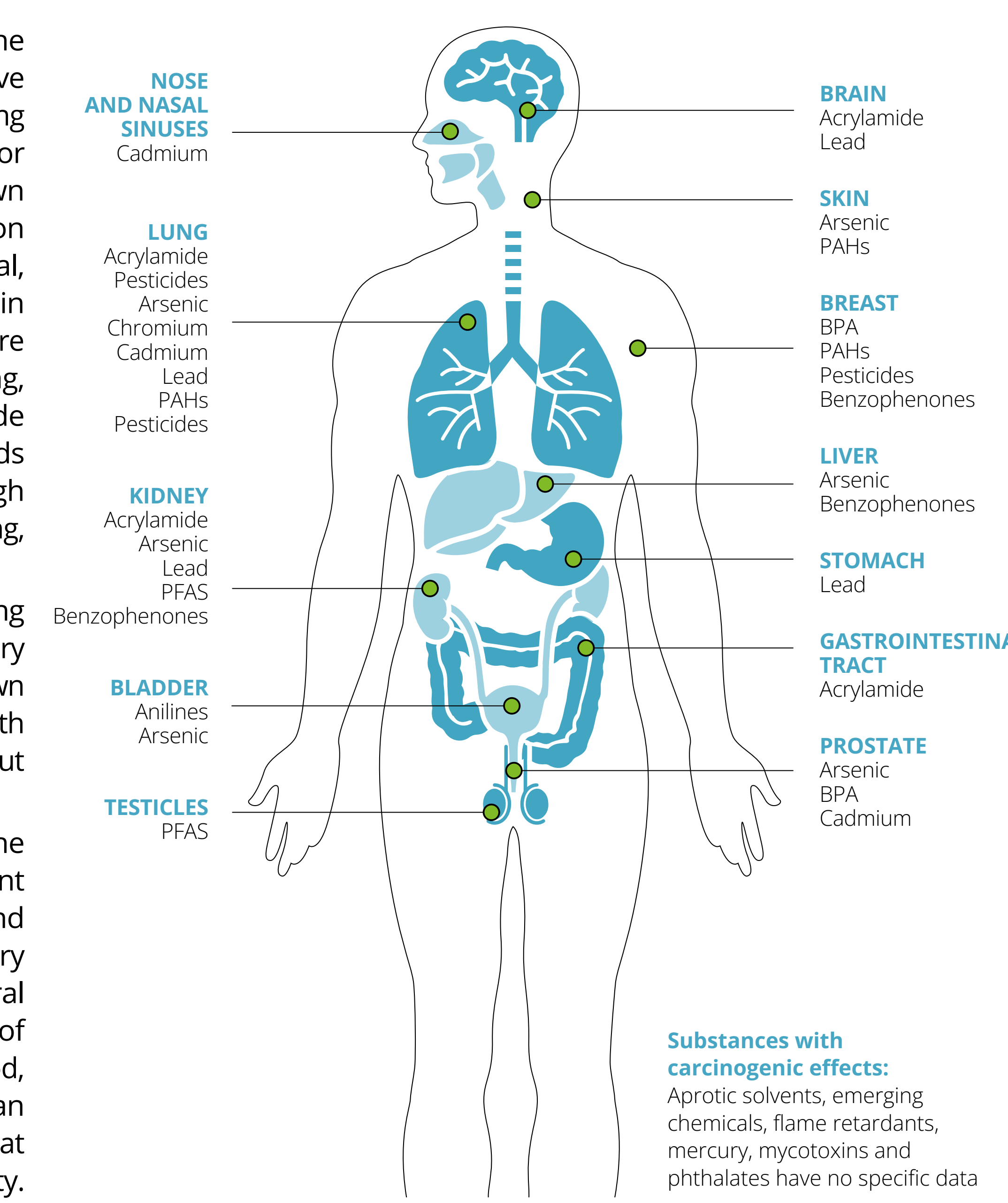
Cancer

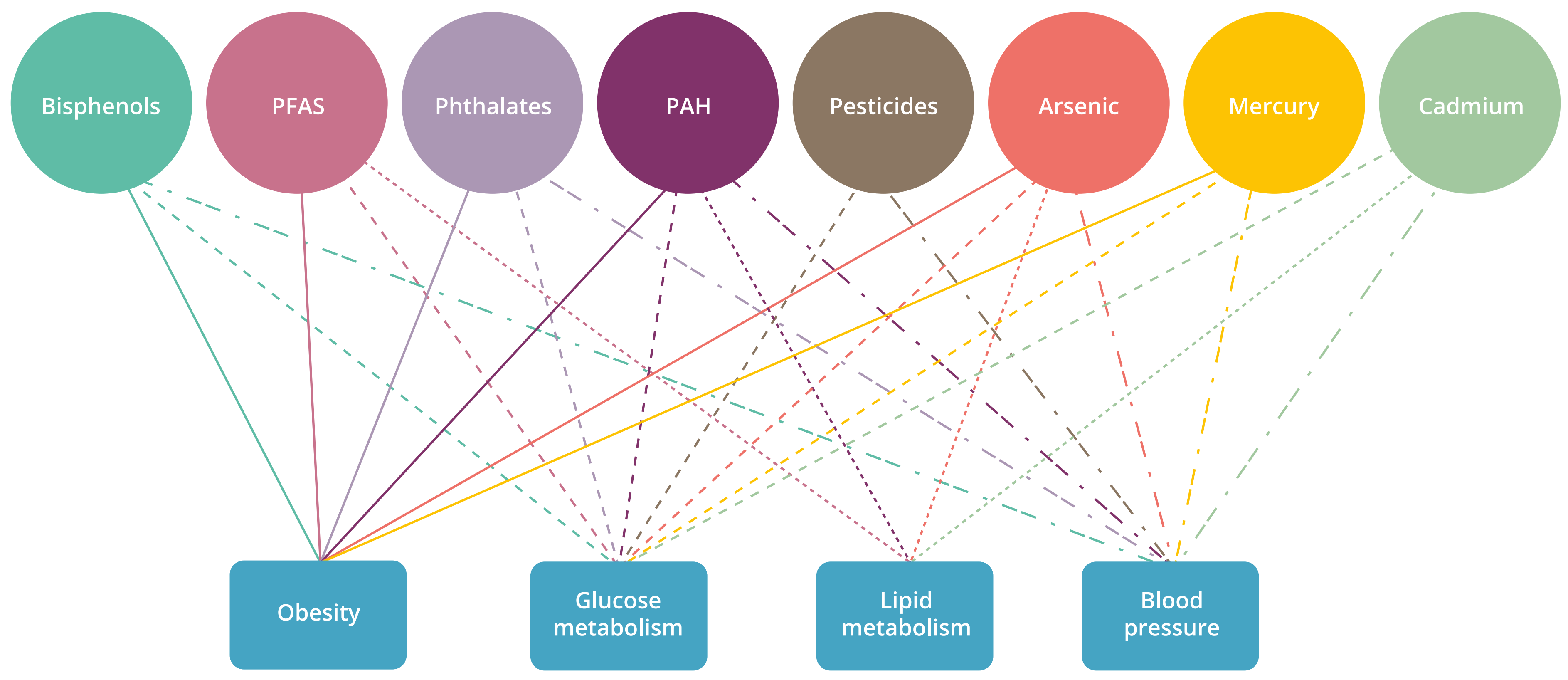
Cancer is a group of diseases involving abnormal cell growth. Majority of the cancers are due to genetic mutation and a small proportion due to inherited genetics. In Europe, cancer is the most frequent non-communicable disease and the second most common cause of death. Common contributing factors are tobacco smoking, diet and obesity, lack of physical activity and infections. WHO estimates that around 20 % of the disease burden is due to environmental (including occupational) factors, and thus preventable. About 120,000 work-related cancer cases and 80,000 related fatalities occur each year as a result of exposure to carcinogens at work in the EU. Evidence supports association between anilines, arsenic, cadmium, chromium VI, mycotoxins and PAHs and different cancers. For acrylamide, aprotic solvents, benzophenones, flame retardants, lead, mercury, PFAS, pesticides, and phthalates there are possible associations with cancers.

Several (16 out of 18) of the HBM4EU priority substances have carcinogenic properties, with varying levels of evidence from studies. For example, acrylamides are shown to have a possible association with female breast, endometrial, and ovarian cancers. The main exposure sources for acrylamide are occupational exposures, smoking, and diet in humans. Acrylamide occurs naturally in starchy foods during cooking processes at high temperatures such as frying, baking, and grilling.

In the meta-analysis, among non-smokers, higher levels of dietary exposure for acrylamide have shown to have a possible association with endometrial and ovarian cancer but not with breast cancer.

Cadmium (Cd) is one of the most toxic metals that is present in the environment naturally and due to human activities in industry and agriculture. In the general population, the main sources of cadmium are cigarette smoke, food, water and ambient air. Cd is an endocrine-disrupting chemical that demonstrates estrogen like activity.





Associations between metabolic syndromes and HBM4EU Priority Substances
(color of the line refers to the substance and line type to the component of the metabolic syndrome)

Osteoporosis

Osteoporosis is a disease affecting bone health of 200 milion people worldwide. Traditional risk factors for osteoporosis are high age, early menopause, low body weight, diet without sufficient calcium and vitamin D concentration, smoking and unhealthy drinking. Evidence exists that certain environmental substances may also increase the risk of osteoporosis.

A possible link between osteoporosis and the body burden of heavy metals, such as cadmium (Cd) and lead (Pb), and industrial chemicals such as phthalates and per- and poly-fluoroalkyl substances (PFAS) has been observed.

About 23% of osteoporosis cases could be attributed to cadmium exposure. Food is the most significant source of exposure to Cd, nevertheless other sources, contribute to the total human exposure, such as the inhalation of tobacco smoke or particulate matter from ambient air for example.

Metabolic syndrome

Metabolic syndrome (MetS) is a cluster of conditions: increased blood pressure (hypertension), diabetes/increased blood sugar, obesity, and abnormal cholesterol levels increasing the risk of several diseases including cardiovascular disease, dementia, cancer, and type 2 diabetes.

Exposure to EDCs has been identified as an additional and inadvertent risk factor for metabolic disorders. Exposure starts already in utero and continues throughout the human lifespan. Highly vulnerable groups are pregnant women, small children, certain occupational groups, and people with low socioeconomic status.

At least bisphenol A, PFAS, phthalates, PAHs, pesticides, arsenic, mercury, and cadmium have been shown to be associated with increased risk of MetS.

Endocrine disrupting chemicals

Endocrine disrupting chemicals (EDCs) are chemicals or chemical mixtures that interfere with the human endocrine system and disrupt hormone levels, or how our body reacts to different hormones.

A group of EDCs includes pesticides, plasticizers such as phthalates, bisphenol A, heavy metals such as lead, brominated flame retardants and UV filters. Exposure to EDCs happens through air, food and water, skin or in case of foetuses and breastfed children, through the mother. EDCs are present in pesticides, plastic, food storage materials, electronics and building materials, personal care products, sunscreens, and textiles.

EDCs are associated with several health problems including those linked to reproductive health, child development, immune system, cancers, metabolic syndrome, coronary disease, and neurological and learning disabilities.

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterised by hyperactivity, inattention, lack of focus, weak impulse control and exaggerated emotions. Its more common among children but also diagnosed among adults.

Current evidence indicate that several environmental chemicals and heavy metals may be associated with increased risk of ADHD. Moderately high association between ADHD and lead, phthalates and bisphenol A has been observed while more limited evidence suggest possible association also with PAHs, flame retardants, mercury, and pesticides.

Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia affecting memory. It is a progressive disease interfering with cognitive abilities, behaviour and functioning of the affected person.

Current evidence suggests the association between exposure to pesticides and increased risk of AD. For mercury, cadmium, arsenic, and lead a possible association has been observed but more studies are needed.

Current knowledge comes mainly from occupational studies where exposures are higher than among the general population.

Asthma

Asthma is one of the most common chronic diseases. Mechanisms lying behind asthma's development are complex and include host factors such as genetics and sex, and environmental factors, like exposure to allergens or smoking. Various environmental chemicals may also affect the risk of asthma development and can escalate asthma symptoms.

Exposure to PAHs and some pesticides is associated with increased risk of asthma. Diisocyanates and Cr(VI) cause asthma with specific sensitization.

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Asthma

Osteoporosis

Alzheimer's disease

Chronic obstructive pulmonary disease (COPD)

Brain development

Attention deficit hyperactivity disorder (ADHD)

Harmonizing human biomonitoring surveys across Europe

Human biomonitoring (HBM) is an important tool not only for understanding exposure to chemicals and supporting environmental and health policy development, but also for awareness raising campaigns or remediation actions. Some EU countries have HBM programmes that monitor exposure to a wide variety of chemicals. Examples are the German GerES studies the Czech-HBM (Czech Republic), ELFE (France), PROBE (Italy), BIOAMBIENT.ES (Spain) or FLEHS (Flanders, Belgium). However, most European countries lack such a national programme and collect HBM data in the frame of specific research projects. Hence, the studies are fragmented and heterogeneous. Up until now, there was not an overarching strategy within Europe, and current studies were not harmonized or aligned to meet common goals. Therefore, to generate comparable HBM data across Europe, ongoing and planned HBM studies from different European countries and regions have been aligned under the HBM4EU Aligned studies initiative.

The importance of this work is highlighted by the European Commission's announcement of the European Green Deal, the Chemicals' Strategy for Sustainability and the Zero-Pollution Action Plan for a toxic-free environment. Having reliable and comparable HBM exposure data representative of the EU population is crucial to feed into chemical risk assessment and support chemical policy making.

"The HBM4EU Aligned studies is the first large scale survey in which ongoing HBM initiatives in Europe are aligned and data and questionnaire information harmonized, laying the foundation of a sustainable European HBM platform in support of environmental and health chemicals policy" states Prof Greet Schoeters, University of Antwerp, Environment and Health, Flemish Institute for Technological Research (VITO Health).

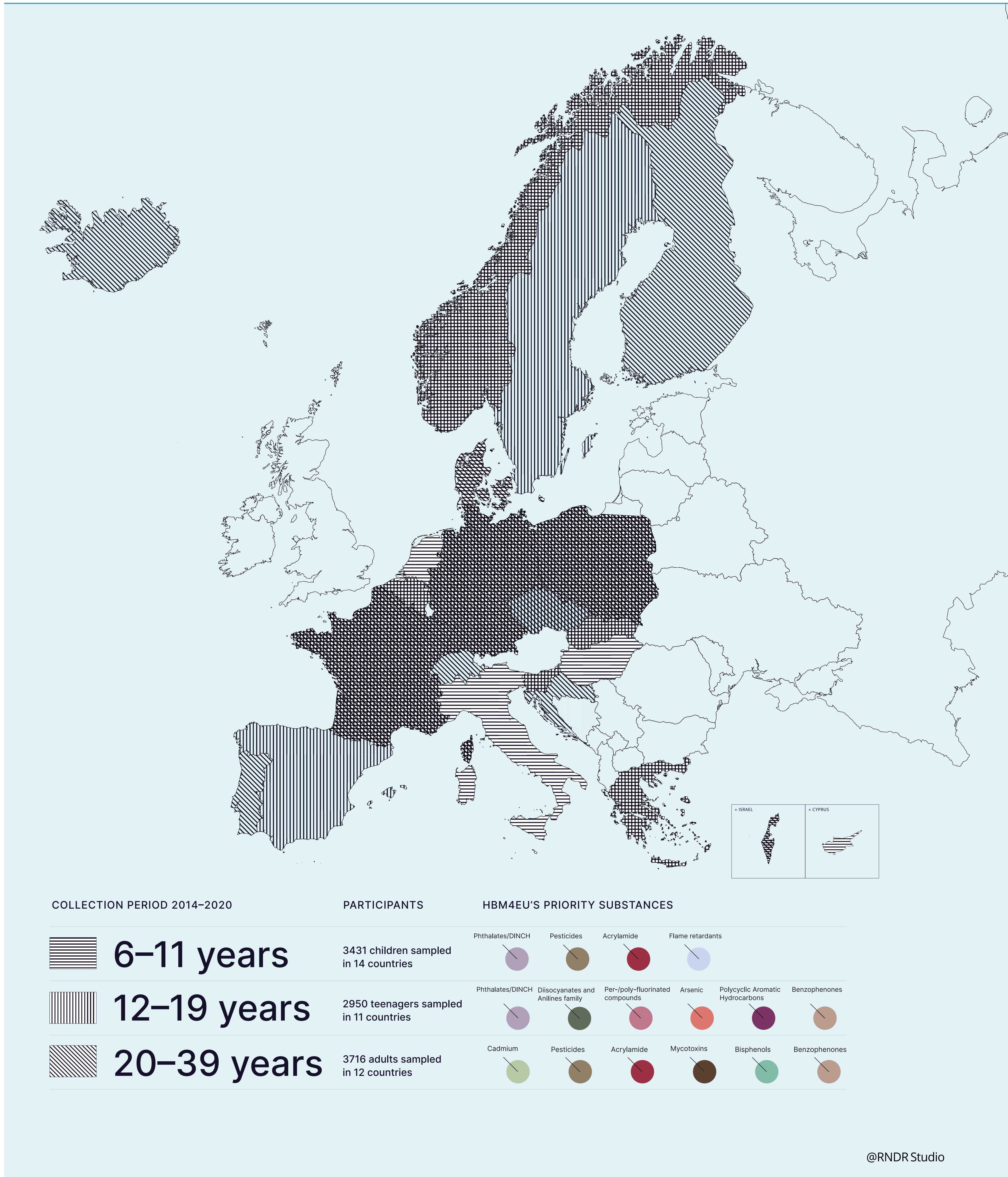
A primary goal of HBM4EU was to build up an EU-wide surveillance of the exposure of European citizens to chemicals.

"In a first step this was meant aligning and harmonising national HBM programmes as much as possible. New EU-wide biomonitoring data have also been generated in the HBM4EU Aligned studies" stresses the expert. In order to select participating studies, a theoretical sampling frame was developed defining criteria to obtain an EU-representative sample.

For the samples, three age groups were selected, a selection that facilitated comparison with other international programmes such as Health Canada. Criteria were set to include subjects of different socio-economic status, for example, or living in areas with different degree of urbanisation (e.g. rural and urban). Specific priority chemicals were nominated. For instance, pesticides were studied in children and adults, bisphenols in adults and PFAS in teenagers. "Within each age group EU-wide coverage was achieved by including a number of countries per European region - North, East, South, West - in proportion to the number of inhabitants of the regions" specifies Liese Gilles, researcher at VITO Health. "Samples were collected between 2014-2021 to reflect recent exposure levels", she adds.

"This resulted in 3431 samples collected from children 6-11 years from 14 countries, 2950 samples from teenagers aged 12-19 years from 11 countries and 3716 samples from adults 20-39 years from 12 countries. In total 37 studies from 23 countries took part in this initiative. Each participating study contributed with a maximum of 300 samples per age group, except for a few studies that participated with a reduced number of subjects" reports Dr Eva Govarts, researcher and statistician at VITO Health. According to the expert, "individual biomonitoring data from more than 43,000 analyses were performed, covering 16 chemical groups".

"The obtained exposure data show the current exposure levels in European population. This data can be used as a baseline for comparisons, for instance between European regions and between existing, as well as new international monitoring programmes. The data has been compared to existing health guidance values in order to assess whether observed exposure levels exceed safe limits. Generated exposure data are used in (mixture) risk assessment. Moreover, exposure data is being used for identifying exposure determinants and investigating possible exposure-effect associations" explains Govarts.



In March 2021, the European Human Biomonitoring Dashboard, which visualises summary statistics from 62 human biomonitoring data collections from 15 European countries was launched. "We wanted to make human biomonitoring data accessible to a broader community, allowing users to explore levels and trends in the exposure of European citizens to chemicals" highlights professor Schoeters.

The data in the dashboard also confirms earlier findings. For instance, observed concentrations of perfluorooctane sulfonic acid (PFOS) in blood are generally lower in female compared to male subjects within the same study population. This was already reported in literature, explained by the elimination of PFAS through menstruation, and for mothers also through delivery and lactation. Another example is cadmium. Observed concentrations of cadmium in blood are generally higher in smokers compared to non-smokers within the same study population. This association between smoking and higher cadmium levels was already reported as well.

"We are about to incorporate all data from the HBM4EU Aligned studies within the dashboard. Even though the project ends in June 2022, the website will remain online for the next 10 years to ensure continuity and access to the data", reports Schoeters. Additionally, HBM4EU data is openly accessible via IPCHEM, the Information Platform for Chemical Monitoring, available to risk assessors and researchers for use, thus multiplying the added value of this new evidence base.

"We are thankful to the study coordinators and data owners who managed and executed the studies within their country or region and shared their data, making them widely available for risk assessment and management. We are also developing a protocol enabling further use of the data in other projects via the VITO data platform".

The European Human Biomonitoring Dashboard includes data:

From existing HBM studies:

- **61** HBM data collections
- **15** countries
- **17** substance groups
- **152** biomarkers
- **13** unique matrices

From HBM4EU Aligned studies:

- **3431** samples collected from children 6-11 years from 14 countries,
- **2950** samples from teenagers aged 12-19 years from 11 countries
- **3716** samples from adults 20-39 years from 12 countries

The Human Biomonitoring Laboratory Network, a key asset in supporting human biomonitoring and risk assessment in Europe

Many European countries run human biomonitoring (HBM) programmes to monitor exposure levels of environmental chemicals, some of them on a regular basis. However, these programmes had previously worked independently of one another. As a result, the comparability of human biomonitoring data is limited. There is an urgent need for harmonizing the design and implementation of human biomonitoring studies, as well as sample and data analysis across national borders to improve health protection and chemical policies in Europe.

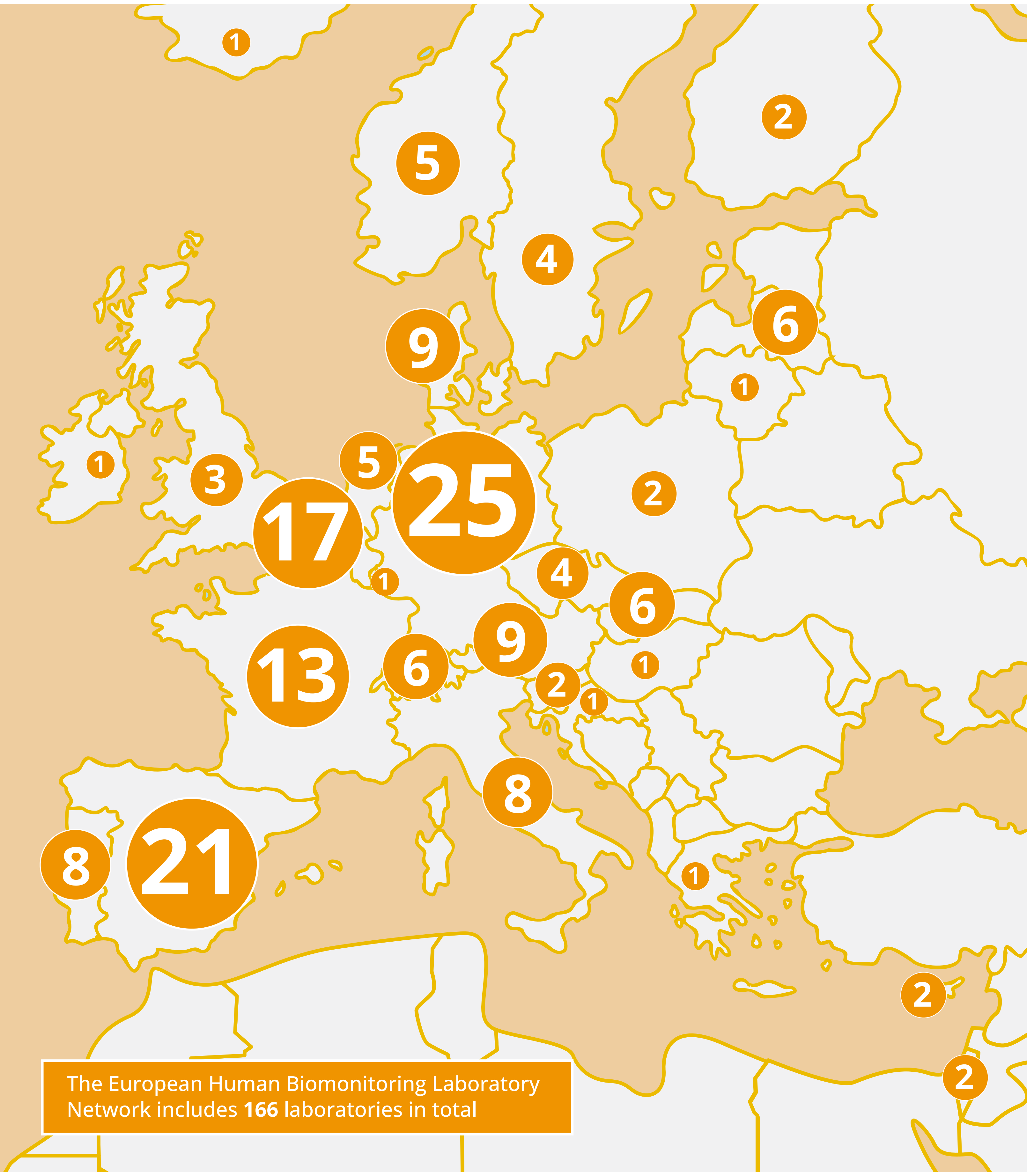
The one-of-a-kind European Human Biomonitoring Laboratory Network includes 166 laboratories, together with the Quality Assurance/Quality Control (QA/QC) programme, has been the key to achieve comparable results of high quality in HBM4EU and to connect human biomonitoring laboratories in Europe.

Professor Argelia Castaño, Director of the National Center for Environmental Health (CNSA) at the Instituto de Salud Carlos III (CNSA-ISCIII) in Spain and leader of the European Human Biomonitoring Platform, sets out the objective of the work. "We have built a European platform for human biomonitoring, with harmonized tools and laboratory networks to provide comparable information on the levels and determinants of chemical exposure in citizens. The performance of HBM studies in a harmonised way and the application of rigorous quality control measures ensure that observed differences in exposure levels to chemicals are not related to variability in analytical methods and protocols". The network was created after inventorying potential candidate laboratories with capacity to perform chemical analysis of the samples coming from the different studies in HBM4EU. "The main goal of the HBM Laboratory Network was on one hand, to ensure the quality and comparability of the analytical results in HBM4EU and on the other, to identify the analytical capacities in EU Member States to support human biomonitoring", declares Dr Marta Esteban, senior scientist at CNSA-ISCIII and a leader of this activity within HBM4EU.

The network, spanning across 28 European countries, includes laboratories with experience in the organisation of Interlaboratory Comparison Investigations (ICIs) and External Quality Assessment Schemes (EQUAS), laboratories that participated successfully in the QA/QC programme, as well as expert laboratories that have acted as reference laboratories. Dr Holger Koch, scientific head of laboratory at the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance explains how the process played out for his institute. "Our lab participated as reference laboratory for some biomarkers supporting the QA/QC programme, as well as in the HBM4EU training school. In this way, we helped other candidate laboratories to fine tune their methods, identify and solve technical difficulties, and build up capacities. The HBM4EU QA/QC programme was very labour intensive, but in the end, a great success story. Most of the participating laboratories significantly improved their results over the four rounds, and many succeeded in obtaining the HBM4EU certificate for various exposure biomarkers".

The usefulness of this network has been proven during the project since it has also supported capacity building of national laboratories in the participating countries. As Prof Castaño explains, "overall, the programme has been a complete success and has demonstrated the capacity of European laboratories to analyse contaminants in human samples with a high quality and in a comparable way. Technical difficulties were resolved, especially for certain groups of substances, such as, organophosphate flame retardants and phthalates. "An important contribution has been the development of materials, such as the Standard Operating Procedures for example, all of them available in the HBM4EU Online Library on the project website", explains Dr Susana Pedraza-Díaz at CNSA-ISCIII and responsible for the library.

More than 43,000 analyses have been performed by 34 of the 74 qualified laboratories from 26 European countries. The Trace Analytical Laboratory of the Research Centre for Toxic Compounds in the Environment at Masaryk University in Czechia, the Department of Growth and Reproduction at Rigshospitalet in Denmark and the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance at Ruhr-Universität Bochum in Germany are three examples of laboratories



Qualified laboratories in HBM4EU QA/QC

Austria	2
Belgium	7
Croatia	0
Cyprus	1
Czech Republic	3
Denmark	5
Finland	2
France	7
Germany	13
Greece	1
Hungary	1
Iceland	0
Israel	0
Ireland	1
Italy	3
Latvia	1
Lithuania	1
Luxembourg	1
Norway	1
Poland	2
Portugal	1
Slovakia	4
Slovenia	2
Spain	7
Sweden	2
Switzerland	1
The Netherlands	3
UK	2
Total	74

The European Human Biomonitoring Laboratory Network includes **166** laboratories in total

that belong to the network. They were responsible for analysing nearly 32% of the total number of samples. As Dr Holger Koch explains, “we analysed many samples for HBM4EU, from several different countries”.

Hanne Frederiksen, senior researcher at Rigshospitalet identifies some key challenges. “Sample and data transfer agreements, securing permissions from countries and handling the individual contracts required by some countries to transfer samples across borders presented the greatest challenge. Despite all the difficulties, we have generated an impressive collection of European human biomonitoring data, which will be used in many other research projects. In addition, during all these years the laboratories have worked closely together, building not only a network of competence, but also establishing great working relationships to be sustained after HBM4EU”.

By setting up the network, adds Castaño, we have identified the inequalities of analytical capacities in Europe, as well as the knowledge- and technical gaps that need to be filled in the upcoming years to support human biomonitoring studies. We have proven the value of such a network, and with that, the need to continue, extend and consolidate the network in the future as it will be an asset in support of future HBM and risk assessment studies. It will be the focal point for analytical expertise for development of new methods and be a guarantee for analytical results of high quality.

The Human Biomonitoring Laboratory Network is the project’s legacy for future human biomonitoring actions in Europe. This network will also provide the arena for the exchange of expertise among high-skilled laboratories and for supporting the less experienced ones, providing solid evidence and data in support of policy making promoting the protection of citizens’ health.

	Phthalates/DINCH									Flame retardants					
	Phthalates	DINCH	Bisphenols	PAHs	Arsenic	Acrylamide	Mycotoxins	Pesticides	UV filters	OPFRs	HFRs	PFAS	Mercury	Cadmium	Chromium
Matrix	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Urine	Serum	Serum	Hair	Urine + Blood	Urine + Serum + Blood
Number of biomarkers	15	2	3	13	6	2	1	9	2	4	6	12	1	1	1
Total number of samples analysed	5616	5960	3613	3169	900	795	1304	2188	975	1875	728	1663	1242	2647	3596
Number of laboratories that analysed the samples	9	9	8	7	2	3	4	2	1	6	3	7	1	9	9
Number of countries where the laboratories are located	8	8	8	4	2	3	4	2	1	6	2	7	1	9	8

Choosing our battles: the HBM4EU prioritisation strategy

HBM4EU has established a European Union-wide human biomonitoring programme to generate knowledge on human internal exposure to chemical pollutants and their potential health impacts in Europe, in order to support policy makers' efforts to ensure chemical safety and improve health in Europe. A prioritisation strategy was necessary to determine and meet the most important needs of both policy makers and risk assessors, as well as the needs of participating countries and a broad range of stakeholders.

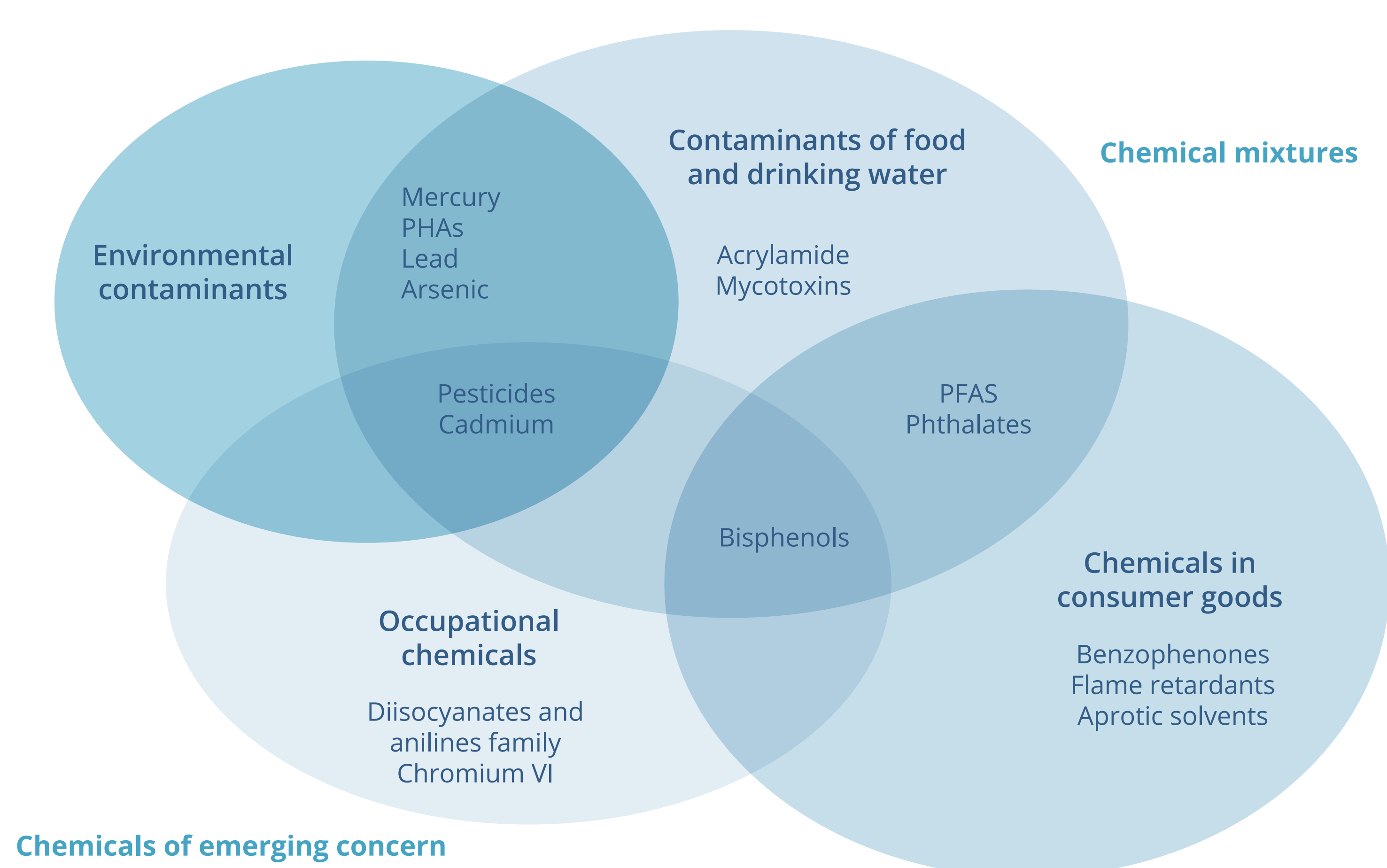
"This strategy, published at the International Journal of Hygiene and Environmental Health, consisted of three mains steps" explains Dr Joana Lobo, expert on Chemicals, Environment and Human Health at the European Environment Agency. "Mapping of knowledge gaps identified by policy makers was the first step, followed by the prioritisation of substances using a scoring system. Then a list of priority substances reflective of the scoring, as well as of public policy priorities and available resources was generated", she adds.

For the first step, relevant ministries and agencies at European and national levels, as well as members of the Stakeholder Forum, which is made of non-governmental organisations, industry and trade unions, each nominated up to 5 substances/substance groups of concern for policymakers. These nominations 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.

For the second step, a panel of 11 experts in epidemiology, toxicology, exposure sciences, and occupational and environmental health scored each of the substances/substance groups using prioritisation criteria including hazardous properties, exposure characteristics, and societal concern. The scores were used to rank the substances/substance groups. In addition, substances were categorised according to the level of current knowledge about their hazards, extent of human exposure (through the availability of HBM data), regulatory status and availability of analytical methods for biomarker measurement.

"Finally, in addition to the ranking and categorisation of the substances, the resources available for the project and the alignment with the policy priorities at European level were considered to produce a final priority list of substances/substance groups" reports Lobo.

There were two prioritisation processes finalised in HBM4EU, and a third one that was initiated and included categorisation of substances but not scoring. This process will be finalised in PARC, the follow-up partnership to HBM4EU.

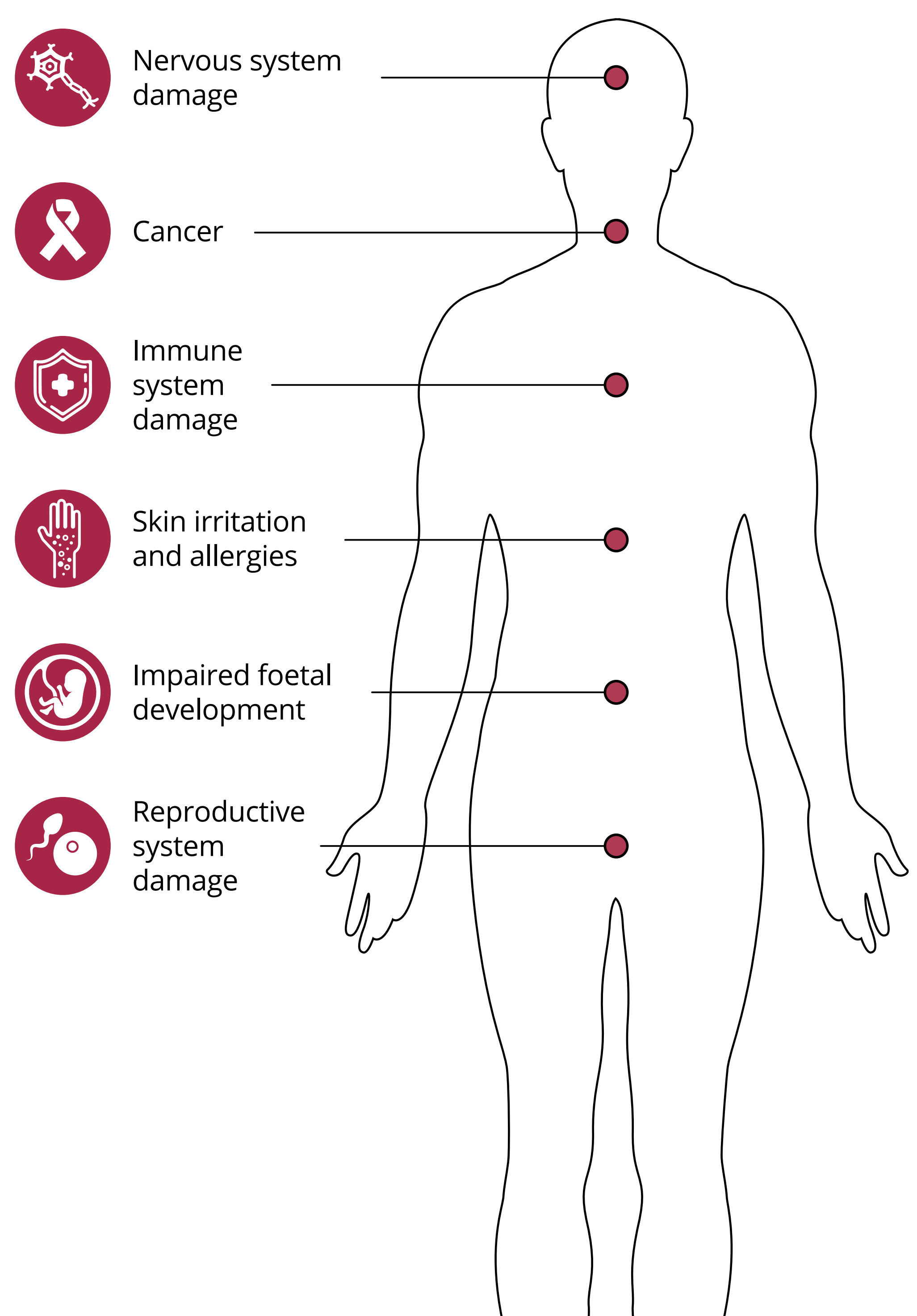


Dietary acrylamide may play a role in cancer, fetal growth and neurodevelopment: what do we know so far?

Acrylamide is a chemical employed in the industry to produce polyacrylamides that, in turn, are used for different purposes such as flocculants, dyes, paper, and textiles. In 2002, acrylamide was first detected in foods, which arose a health concern for the general population. It was found to form naturally in starchy food cooked at high temperature and low moisture including baking, frying, grilling, toasting or roasting as well as in processed foods. Acrylamide is also produced in tobacco smoking.

Acrylamide has toxic effects on the nervous system, adverse effects on foetal growth development, reproduction system and the immune system and triggers skin reactions such as irritation and allergy in humans. It causes cancer in animals, although it has not been confirmed in humans. "In HBM4EU we have performed a systematic review of the association between acrylamide dietary intake and risk of different type of cancers and we observed no association whatsoever", explains Dr Federica Laguzzi, who works at the Karolinska Institutet. However, a recent study indicates some evidence of a slight positive association between acrylamide exposure and risk of endometrial and ovarian cancer, particularly among never smokers, and of breast cancer in pre-menopausal women" says Prof. Marco Vinceti, from the Environmental, Genetic and Nutritional Epidemiology Research Center in Italy. These studies are based on self-reported dietary questionnaires that may not capture acrylamide dietary estimation well. Hence, further research is needed using human biomonitoring studies to obtain an accurate acrylamide exposure.

Aside from occupational exposures and smoking, diet is the main source of exposure in humans. During the HBM4EU project, urine samples from children and adults collected between 2014 and 2021 in four countries including Italy, Germany, France and Norway and in six ones including Portugal, Spain, France, Luxemburg, Germany and Iceland respectively, were analysed to assess current values and exposure determinants. "We concluded that 96% of the adults and 99% of the children sampled had levels exceeding the European guidance values" explains Dr Federica Laguzzi. Regarding geographical differences, the highest values of acrylamide exposure were observed in Southern countries for both children and adults. "Determinants of these differences are still unclear, although dietary factors such as fried potatoes and coffee were clearly associated with higher urinary concentration of acrylamide in adults whereas low socio-economic status and demographic factors such as living in urban areas seemed to be associated to higher urinary levels of acrylamide in children. "That might be explained by the fact that in those households, there is poor awareness of healthy food habits. Boiling or steaming is a safer method of cooking in terms of acrylamide, and healthy diet in general".



The food industry and local authorities have made efforts since the discovery of acrylamide in foods in 2002 to reduce acrylamide formation during food processing. However, only in November 2017, the EU legislation established measures to reduce levels of acrylamide in food and set safe benchmark levels for specific foods. Food establishments must identify food processing steps that can result in the formation of acrylamide in foods and take action to reduce those levels to a minimum. "In a time-trend analysis of published and new European human biomonitoring data, we observed an increase of acrylamide exposure between the year 2000 and 2018 in European non-smoking adults and children. "However, a new study analyzing adult samples collected after 2018, does not show an increasing exposure levels, rather declining". 3 years after the implementation of the mitigation tools, our results may show first slight effects of these new measurements, in particular for adults.

Foetal growth and neurological alterations due to acrylamide is another concern that has been addressed during the project. Acrylamide may cross the placenta and lead to the exposure of the unborn child. "In a systematic review of the literature, we found that high acrylamide exposure during pregnancy is associated with reduced birth weight, birth length and head circumference. If confirmed, these findings suggest that dietary intake of acrylamide should be reduced among pregnant women" states the expert. Although a toxic effect of acrylamide on the neurological system is known in animals and occupationally exposed humans, there are no studies on neurodevelopmental functional effects in the general population exposed to acrylamide, thus there is an urgent need for further research to examine whether pre- and perinatal acrylamide exposure might impair neurodevelopment in humans".

Despite a better understanding of the impact of acrylamide on cancer, fetal growth, and neurological system in humans, there are still many uncertainties that need further research. In the meantime, we strongly encourage policies aiming to reduce the levels of acrylamide exposure through targeted public health education and awareness.

Main achievements

- One peer review publication published, two submitted, two drafted
- Synthesis of the evidence on the relationship between acrylamide and cancer risk, fetal growth and neurological alteration.
- Cancer risk assessment calculation for acrylamide
- Evaluation of time trends and exposure determinants based on European studies (possibly two papers, one is drafted)

We are exposed to a mixture of different pesticides

Pesticides compose a large and diverse group of mostly man-made chemicals used as active ingredients in Plant Protection Products (PPPs) to combat target pests such as insects, fungi, and weeds in agriculture. Some are also used as biocides e.g. indoor insect control and wood preservation. The general population is mainly exposed to pesticides from residues in food, but agricultural areas and indoor use of biocides are other important sources of exposure. In addition, some individuals such as farmers and pesticide applicators may experience higher exposure levels in occupational settings. Occupational exposure to pesticides has been associated with a variety of different health effects including impaired reproduction and increased risk of neurodegenerative diseases and asthma.

HBM4EU researchers primarily focussed on whole group of pyrethroid insecticides, the specific organophosphate insecticide ‘chlorpyrifos’ and the widely used herbicide ‘glyphosate’.

The organophosphate chlorpyrifos has been one of the most widely used insecticides in agriculture worldwide for decades. However, since February 2020 chlorpyrifos is no longer approved for use in the EU because of concern for developmental neurotoxicity and genotoxicity, although some exposure will still occur from produce originating from outside of the EU. The use of pyrethroids is increasing as they have substituted organophosphates in biocide products for residential use and, to some degree, also in agriculture.

Most insecticides, including chlorpyrifos and pyrethroids, can affect the brain and nervous system. Also, chlorpyrifos and pyrethroids are suggested endocrine disruptors with the potential to interfere with thyroid hormones, according to a recent review. In a study conducted in 134 male adolescents from the Spanish Environment and Childhood (INMA)-Granada cohort, a team of Spanish and Danish scientists reported that higher urinary concentration of 3-PBA, a common metabolite of several pyrethroids, was associated with higher concentration of the thyroid hormones. “It is well-known that subtle changes in maternal thyroid hormone concentrations in pregnancy can affect foetal brain development. Thus, exposure to these insecticides during vulnerable time windows in pregnancy and childhood, when the brain is rapidly developing, may have long-term impact on neurodevelopment” explains Dr Helle Raun Andersen from the University of Southern Denmark. In another study published in June 2021 from the Danish Odense Child Cohort, the expert adds, “we found that maternal urinary concentrations of chlorpyrifos or pyrethroid metabolites in pregnancy was not associated with delayed language development at age 2-3 but an association with attention deficit hyperactivity disorder symptoms in the same age-group was previously reported from this cohort”. In a literature review conducted under HBM4EU, the authors conclude that pyrethroids are probably human developmental neurotoxicants and that adverse impacts of pyrethroid exposure on neurodevelopment are likely at current exposure levels.

Previous human biomonitoring studies in Europe showed widespread exposure with detection rates above 80% for the chlorpyrifos metabolite, TCPy, and the generic pyrethroid metabolite, 3-PBA, in urine samples including pregnant women and children. However, a limited number of European countries have biomonitoring data on these pesticides and differences in analytical methods further hamper the comparability of the results. “Thus, we don’t know well what the current exposure across Europe is, whether there are geographical differences and time trends in exposure. To gain knowledge, scientists from HBM4EU have analysed urine samples collected between 2014 and 2021. Pyrethroid and chlorpyrifos metabolites were measured in 863 samples from children from five countries and 1184 samples from adults in six countries. “As the urine samples were collected before the ban of chlorpyrifos, the results will provide a good base level for comparison with future studies on chlorpyrifos, to explain how the exposure changes when chlorpyrifos is no longer approved in the EU”, stresses the expert.

Since 2015, glyphosate, a widely used herbicide, has been classified as probably carcinogenic to humans by the International Agency for Research on Cancer, a classification that triggered a debate on potential health risks of this substance. Glyphosate is currently approved for use in the EU until 15 December 2022, and the assessment of renewed authorisation is in progress. However, knowledge on exposure levels among EU citizens is very scarce. In HBM4EU, glyphosate (and AMPA, primary degradation products of the herbicide glyphosate), was analysed in urine samples from 971 children from five countries and in adults from four countries.

According to the expert, “the results combined with recent published European studies show widespread exposure to these substances in the European population, including children. We are currently analysing the data, in a harmonised way, to assess geographical differences and exposure determinants, such as the main dietary and non-dietary sources of exposure”.

“Within HBM4EU, human biomonitoring guidance values (HBM-GVs) for two commonly used pyrethroids (deltamethrin and cyfluthrin) have just been derived, which will allow us to compare against the measured levels detected in the participant’s body and conclude which percentage of the population is at risk” explains Raun Andersen.

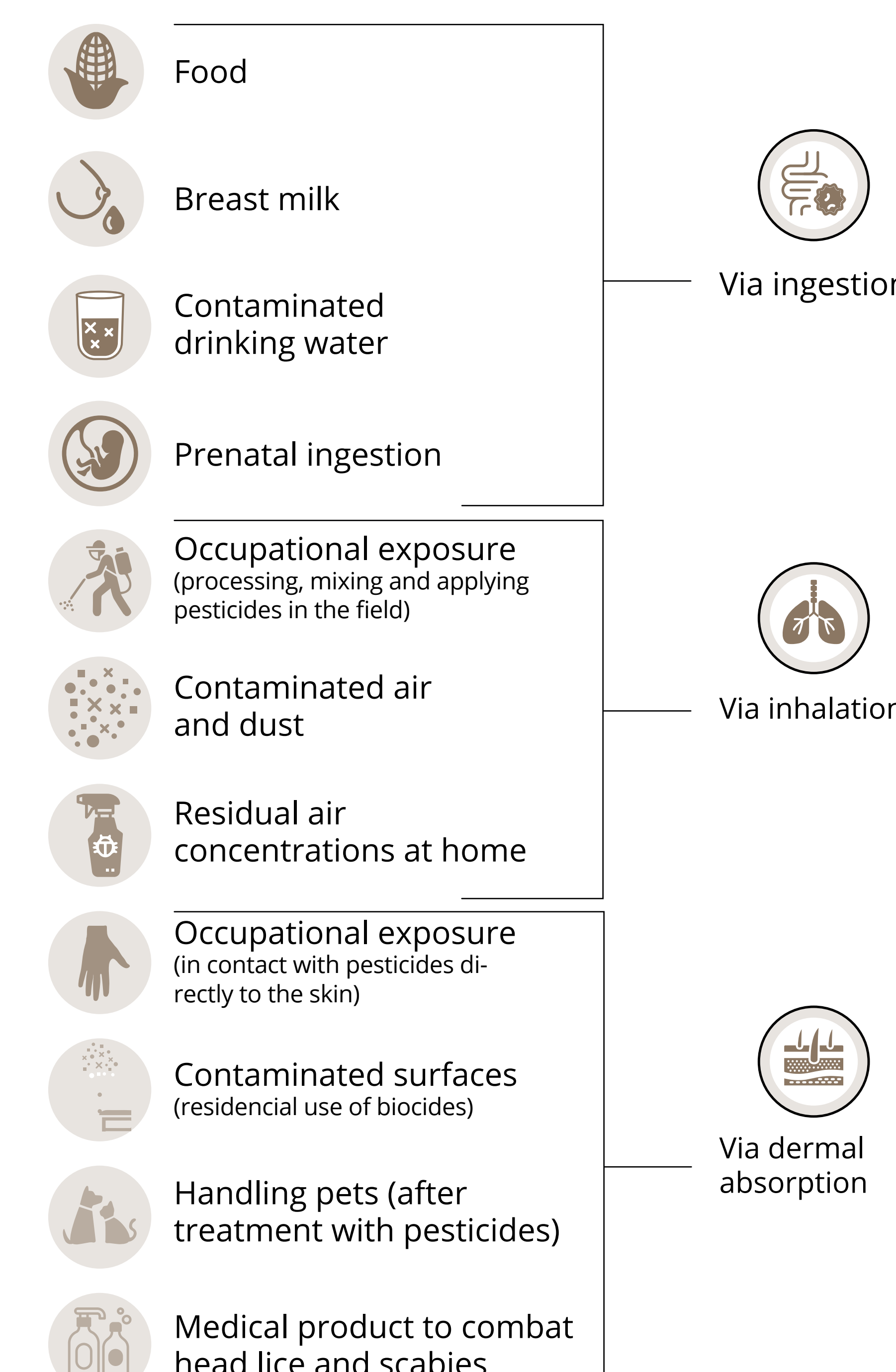
“We would like to better understand the potential health outcomes of combined exposure to multiple pesticides, as in real life we are not only exposed to one chemical. Therefore, we estimated the human exposure to mixtures of four pyrethroids using physiological-based toxicokinetic (PBTK) modelling in a study from the French ENNS cohort. The findings revealed that the population is exposed to a mixture of different pyrethroids, reflected by a high detection frequency of 3-PBA, which represents the combined exposure to pyrethroids. “This clearly illustrates the need for taking mixture effects into account in the risk assessment of pyrethroids” highlights the expert.

To further assess exposure to mixtures of pesticides, the SPECIMEn (Survey on PestiCIde Mixtures in Europe) study, has explored residential exposure to pesticides from living close to pesticide treated areas, as well as urban areas. “We have identified a total of 95 pesticide-related markers in over 2,000 urine samples from 50 parent-child pairs from hotspots and control areas in five countries using suspect screening techniques” states Dr Mirjam Luijten, Research Scientists at the National Institute for Public Health and the Environment.

In all, this new scientific knowledge can contribute to the Farm to Fork Strategy, as part of the Green Deal, that aims to reduce the use and risk of chemical pesticides by 50%, as well as the use of fertilisers and antibiotics at least 20% by 2030.

Main achievements

- Occupational exposure to pesticides associated with impaired reproduction, increased risk of neurodegenerative diseases and asthma
- Pyrethroid and chlorpyrifos metabolites measured in 863 samples from children from five countries and 1184 samples from adults in six countries
- Human biomonitoring guidance values (HBM-GVs) for two pyrethroids derived
- Human exposure to mixtures of four pyrethroids using PBTK modelling estimated
- A study on mixtures of pesticides performed, identifying a total of 95 pesticide-related markers in over 2,000 urine samples from 50 parent-child pairs
- 8 peer reviewed publications published in international journals



HBM4EU-MOM, a harmonised study in five coastal European countries, uses biomonitoring and fish consumption advice to support the control of prenatal exposure to mercury

Mercury, a substance causing great concern globally, was prioritized for research and investigation by the 'Human Biomonitoring for Europe Initiative' (HBM4EU) in 2018. For the general European population, diet - and specifically fish/seafood consumption, is the primary source of exposure. The developing human foetus is especially vulnerable to mercury exposure since mercury is a potent developmental neurotoxicant. In 2012, the "DEMOCOPHES" biomonitoring study showed that European women of reproductive age were exposed to mercury. Exposures varied across the 17 participating countries and were strongly associated with fish consumption.

However, fish is an important component of a healthy diet during pregnancy, lactation and early childhood because of the health benefits it presents to the mother and the developing child, being a lean source of protein, vitamin D, selenium and PUFA - a type of fatty acids.

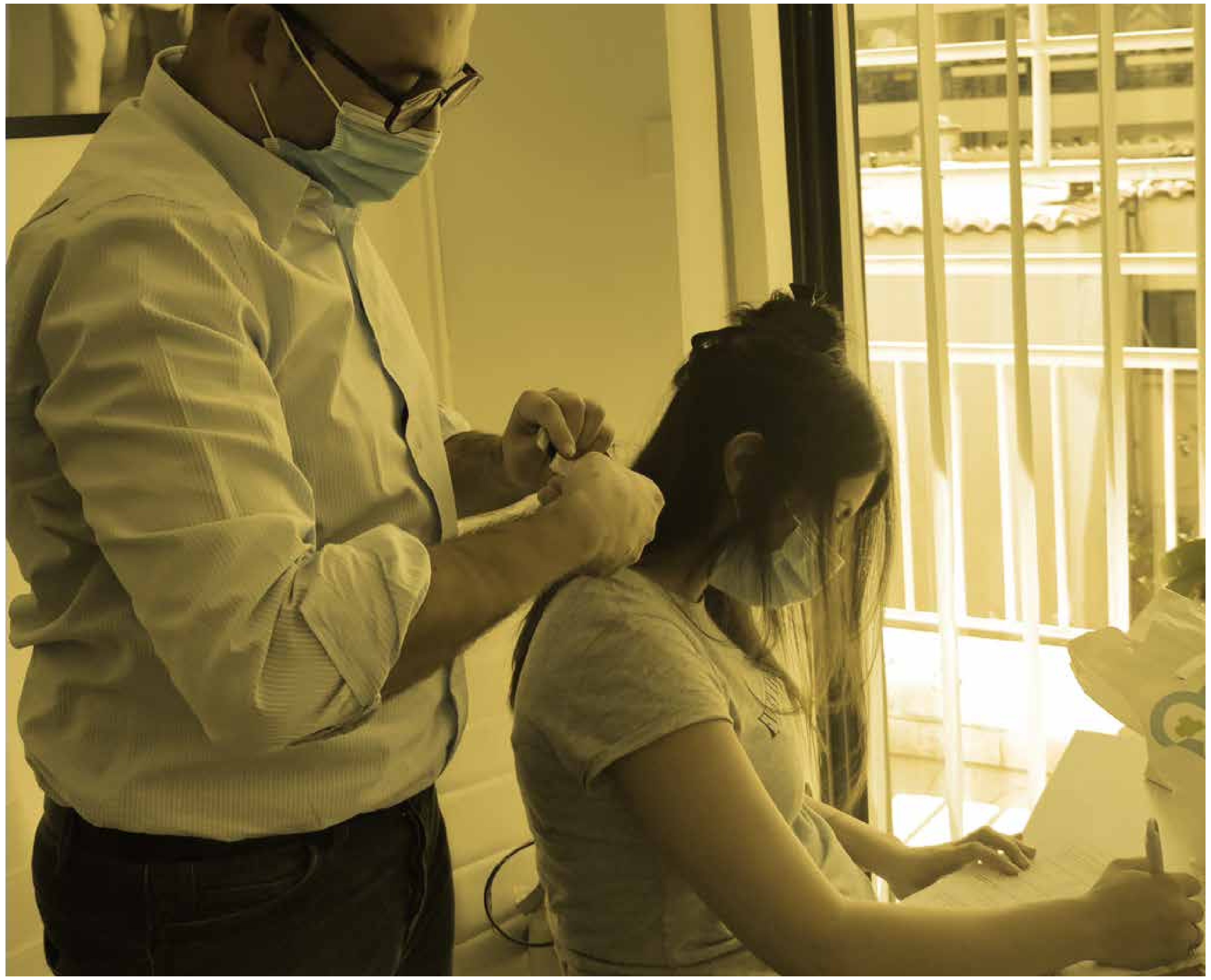
It is therefore important to balance the risks of exposure to mercury with the nutritional benefits of eating fish when pregnant. However, many European countries do not have official guidelines for fish consumption during pregnancy, and even in countries where such guidelines do exist, they are not effectively communicated to pregnant women.

"If a pregnant woman is exposed to high levels of mercury, the foetus is also exposed because mercury crosses the placenta" stressed Dr Andromachi Katsonouri of the Cyprus State General Laboratory, Ministry of Health. Katsonouri is the coordinator of the study "HBM4EU-MOM", which currently runs in five fish-consuming European countries: Cyprus, Greece, Spain, Portugal and Iceland. "Our goal was to communicate to pregnant women in coastal Southern Europe and the Arctic that fish is good as long as they choose to eat 'good', low-in-mercury fish. We also wanted to study, through biomonitoring measurements, whether following our fish consumption advice could keep the exposure of pregnant women below current guidance values", said Dr Katsonouri.

A total of 654 pregnant women participated in the study. Recruitment took place in early pregnancy, mostly during routine visits of the pregnant women to their healthcare providers. The fieldwork was quite challenging in all participating countries due to the COVID-19 pandemic and the study's tight timeframe.

Dr Sónia Namorado, the Portuguese national study leader from the National Institute of Health Doutor Ricardo Jorge, explained that "in Portugal, several pregnant women were understandably afraid to participate in the study because they wanted to minimise contacts to protect themselves and their babies. Therefore, the possibility to perform sample collection at home or at our premises was crucial and should be further explored in future projects". Dr Marta Esteban, in charge of the Spanish national study, working at the Instituto de Salud Carlos III stated "as the second sample was collected right after women gave birth, the possibility of performing sampling in the mobile laboratory was crucial to avoid the loss of those participants giving birth in a different hospital than the one we partnered with". We also used WhatsApp to keep direct contact with the participants, and that has revealed to be a very useful tool in human biomonitoring studies", she added.

Dr Catherine Gabriel, of the Aristotle University of Thessaloniki, explained that women were recruited from all over Greece and webinars of interest to pregnant women were offered to maintain the engagement of participants. Dr. Þórhallur Halldórsson of the University of Iceland, said that "nine health care clinics in the capital city of Reykjavik recruited participants, but because COVID-19 affected the samplings, adjustments had to be made to complete the fieldwork, including home visits". In Cyprus, national fish consumption advice was not available and was developed



for use in the framework of the study. Healthcare providers of pregnant women from maternity clinics all over the country were engaged, positioning the study for successful implementation and sustainable uptake of the results, according to Dr Katsonouri.

"Our preliminary results suggest that many women do not consume fish in early pregnancy according to guidelines. We observed wide geographic variability of mercury exposure, which was associated with variable fish consumption patterns, in terms of both the frequency and types of species consumed", reported Katsonouri.

"Notably, some pregnant women exceeded the current health-based guidance values".

The highest mean mercury exposures were observed in Portugal and the lowest in Cyprus, where some participants did not eat much fish.

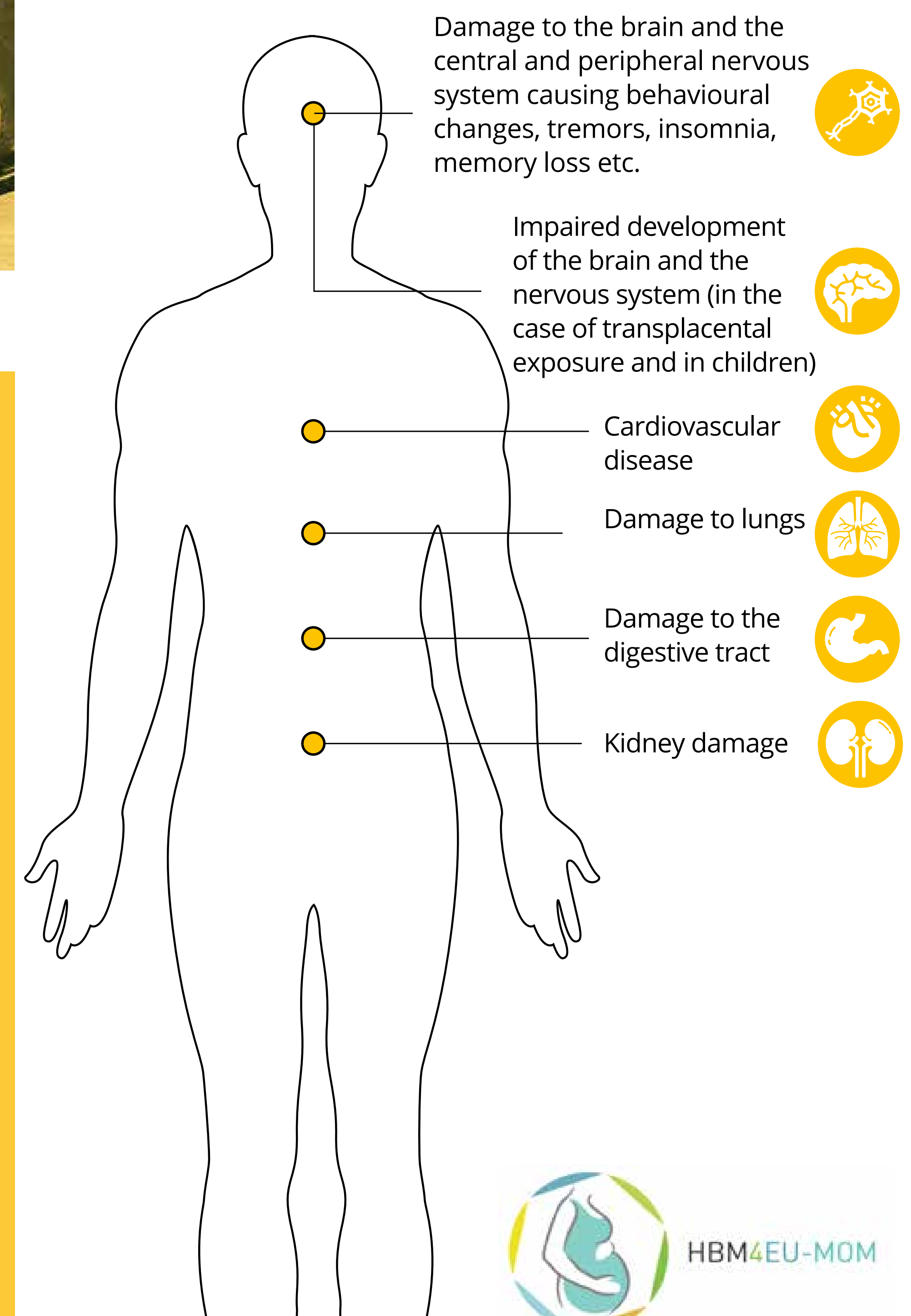
"In Portugal, most women were concerned about possible health effects due to mercury exposure and wanted guidance on how to avoid exposure" explained Namorado. In Spain, national fish consumption recommendations are available online and several communication campaigns have been implemented. Yet, those recommendations are not routinely given to pregnant women in primary care centres and hospitals, which means that a lot of work still needs to be done.

"We are analysing the data now to understand the impact of our intervention, and especially to verify whether women who follow fish consumption advice during their pregnancy remain below the current health-based guidance values", said Katsonouri and Halldórsson. Professor Denis Sarigiannis of the Aristotle University of Thessaloniki further stated that "the modelling analysis showed that the intervention was most successful in the countries with the highest mercury exposure".

"We expect that HBM4EU-MOM results will feed into European and global policies for public health protection", said Katsonouri. "A panel of multidisciplinary experts from our consortium presented HBM4EU-MOM at a United Nations side event in preparation of the Fourth Conference of the Parties (COP-4) of the Minamata Convention on Mercury in March 2022. According to the Secretariat, it was one of the most popular side events in terms of attendance".

Main HBM4EU-MOM achievements

- 654 participating pregnant women
- 5 coastal European countries in the South (Cyprus, Greece, Spain, Portugal) and the Arctic (Iceland) involved
- Analysis of current mercury exposure of pregnant women
- Provision of advice for fish consumption in pregnancy
- Evaluation of impact of provided dietary advice
- Development of biokinetic modelling of Methylmercury (MeHg) and its use to assess the impact of the intervention
- Preparation of open access publications (ongoing)
- Publishing metadata on IPCheM Portal
- Communication of personal results to participants and overall results to the public
- Increased interest and knowledge of health care providers regarding human biomonitoring



HBM4EU-MOM

Elevated cadmium exposure: are phosphorus-containing mineral fertilizers to blame?

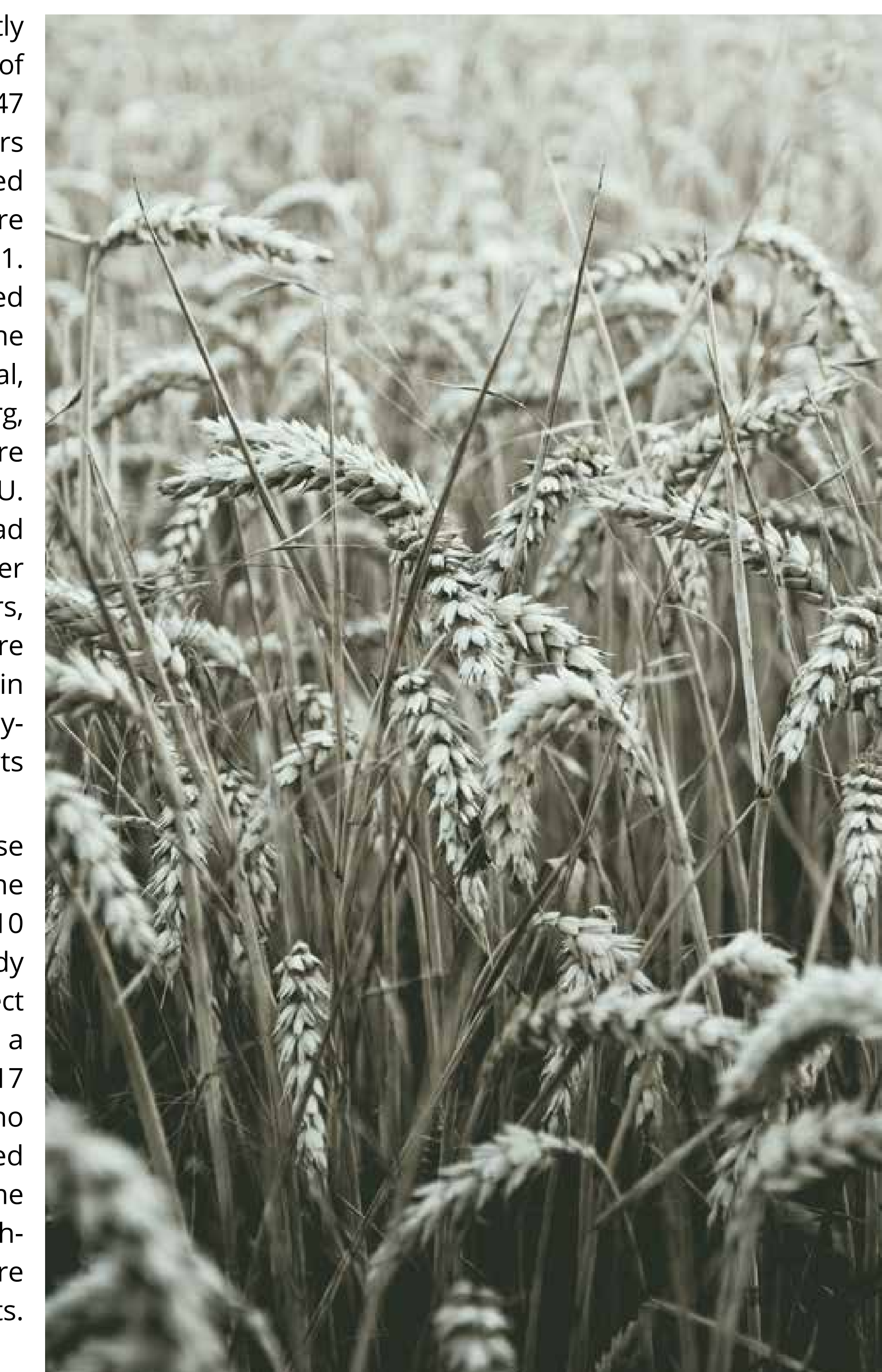
Cadmium (Cd) is a non-essential element that accumulates in the body over time, particularly in kidneys. The primary exposure route for the general population is through diet. Food items that contribute the most to exposure are cereals and cereal products, leafy green vegetables, pulses, organ meat, potatoes, cacao and shellfish. Smoking is also a source of cadmium exposure. Occupational exposure is a potentially significant source of exposure for those working in relevant industries such as manufacturing/use of pigments and the metal industry.

Cadmium affects the kidneys in particular and can cause renal failure. Association with renal toxicity has been observed even at low levels of exposure. In addition, cadmium is classified as a human carcinogen and a suspected mutagen and a reproductive toxicant. "In a recent study HBM4EU data shows that low levels of cadmium exposure contribute to the risk of osteoporosis, with 28 % of cases in women over 55 years of age being attributable to cadmium exposure

"Extensive data from previous surveys that was analyzed within HBM4EU shows that mean levels of cadmium in biological samples, both in urine or blood, are generally low in all population groups. However, there is a certain proportion of people in most of the countries who exceed the health-based guidance levels" explains Dr Janja Snoj Tratnik, who works at the Department of Environmental Sciences at the Jožef Stefan Institute, in Slovenia. "As expected, she adds, the levels

increase from younger age groups (children, teenagers) to adults. There were no distinct geographic patterns observed, but some studies showed significantly higher levels than others. As part of the HBM4EU Aligned studies, 2647 urine samples of 20 to 39 years old adults have been analysed to estimate current exposure to cadmium from 2014 to 2021. Samples have been collected from Denmark, Island, Poland, the Czech Republic, Croatia, Portugal, Germany, France and Luxembourg, and the measurements were quality assured by the HBM4EU. "Some EU sampling locations had three and even four times higher levels of cadmium than others, so the study confirmed there are no clear regional differences in exposure but rather clear study-specific differences" reports the expert.

"We have compared these current cadmium levels in urine with data collected from 2010 to 2012 from a previous study DEMOCOPHES, a European project that tested the feasibility of a human biomonitoring study in 17 European countries, there was no obvious time trend in observed exposure. Moreover, in both time periods exceedances of health-based guidance values were observed in children and adults.



Comparison with HBM-GV: cadmium in adults

Share of adults population (20-39 years; non smokers) that have urinary cadmium levels exceeding

Human Biomonitoring Guidance Value (HBM-GV) Cadmium:
Adults 21-30 years: 0.3 µg/g crt
Adults 31-40 years: 0.5 µg/g crt

CP HMINPUB parents_DYMS - Denmark	0,40%
DIET_HBM - Iceland	2,69%
POLAES - Poland	32,83%
(C)ELSPAC: YA - Czech Republic	9,58%
HBM survey in adults - Croatia	1,44%
INSEF - ExpoQuim - Portugal	1,86%
ESTEBAN - France	38,13%
ESB - Germany	31,54%
Oriscav - Lux2 - Luxembourg	4,60%

Because cadmium accumulates with age, it is important to keep exposure low at all ages. Therefore, in a research study published in December 2020, HBM4EU derived age-dependent alert values to prevent exceeding the guidance value of 1 µg/g creatinine for adults over 50 years and therefore prevent adverse kidney effects. These were set to 0.1 µg/g creatinine (crt) for children of 10 years of age or younger, 0.2 µg/g crt for 11-20 years, 0.3 µg/g crt for 21-30 years, 0.5 µg/g crt for 31-40 years, 0.8 µg/g crt for 41-50 years"According to the HBM4EU Aligned studies data for the European adult population aged 20-39 years, the age-dependant alert values for cadmium in urine were exceeded by 5 % of the study participants at most sampling sites" says Dr Milena Horvat, Head of the Department of Environmental Sciences at Jožef Stefan Institute. Exceedances in the different studies range from 1.4 % up to 42 %. The studies with largest extent of exceedance were ESTEBAN (France) and POLAES (Poland). "These findings support the recommendation by the European Food Safety Authority to reduce cadmium exposure as the estimated mean dietary exposure of adults in the EU is close or slightly exceeding the tolerable weekly intake. It also indicates that regulations are not protecting the population sufficiently" highlights the expert.

The HBM4EU worked on identifying the most reliable effect biomarkers that could be used in HBM studies and which would support improved derivation of EU regulation and policy making. HBM4EU researchers made and extensive review published in the Environmental Research in order to identify effect biomarkers linking cadmium exposure to selected adverse outcomes including cancer, immunotoxicity, oxidative stress, and omics/ epigeneticsFurthermore, a cross-sectional study has explored the relationship between cadmium levels, to a potential biomarker of effect, the brain-derived neurotrophic factor (BDNF). In this new study, led by Spanish researchers, it was found that higher urinary cadmium concentrations were associated with lower BDNF protein levels and more behavioural problems in Spanish adolescent males.

"We wanted to understand to what extent is the general population exposed to cadmium from contaminated soil through diet. Therefore, we exploited European databases to obtain cadmium concentrations in soil, percentages of agricultural areas and phosphorous fertilizer application which were than linked to the HBM levels from previous, as well as HBM4EU Aligned, studies" explains Dr Janja Snoj Tratnik. Meta-analysis of existing data, representing the period 2007-2018, showed inconsistent associations between HBM and soil cadmium concentrations across different countries, population groups or different types of matrices. "At specific study sites, positive associations between cadmium in soil and cadmium in people's body were observed, suggesting a link between cadmium in soil and exposure level through consumption of local food in those areas and/or population groups" highlights Horvat. This was further confirmed by positive associations between HBM data and percentage of agricultural and/ or cropland, and phosphorous fertilizer consumption both datasets. Furthermore, association analysis with individual food consumption data available from participants' questionnaires in the HBM4EU Aligned studies showed an important contribution of vegetarian diet to the overall exposure, with 35% higher levels in vegetarians as opposed to non-vegetarians. For comparison, "we found that smokers have 25% higher concentration of cadmiums than non-smokers".

Main achievements

- 5 peer reviewed papers published, 2 in preparation
- Age-dependant alert values derived to prevent exceeding HBM-GV at adults over 50 years old
- HBM4EU data still show exceedances of HBM-GVs for cadmium exposure, indicating that regulations are not protecting the population sufficiently
- No clear decreasing time trend observed
- Determinant exposures identified - Phosphorus fertilizers significantly contribute to cadmium exposure in the general population

— Mik Gilles
Director International Cadmium Association

"The biomonitoring data collected and processed by the HBM4EU project support the conclusion that the actual levels of cadmium exposure in the general population are not likely to cause adverse health effects. This is also the result of the EU policies that regulate cadmium, enabling its production and uses while controlling the risks. The HBM4EU project monitored body excreted levels but not actual known effect indicators like kidney Retinol Binding Protein. It is therefore important to underline that these data should not be used in isolation to propose cadmium effect health indicators."

"To which mixtures of concern is the European population exposed?"

Humans are continuously exposed to a multitude of chemicals via food, water, air, consumer products, and other media and sources. This raises concerns because exposure to multiple chemicals may increase health risks, relative to those of individual chemicals. Due to the large number of chemicals present in the environment, exposure and risk assessment of chemical mixtures is complex and extremely challenging. The HBM4EU project addressed how human biomonitoring (HBM) data can contribute to the improvement of current procedures for mixture risk assessment of chemicals.

Currently there is yet little insight into commonly co-occurring exposure mixtures and how these chemical mixtures differ between e.g., countries, population groups and time. This information may be obtained from HBM studies, by screening the data for the presence of patterns of exposure. "In HBM4EU, we explored the applicability of the so-called 'network analysis' methodology to identify such exposure patterns. Analysis of existing HBM datasets from four different countries across Europe, being Germany, Belgium, Spain and the Czech Republic, demonstrated the feasibility of identifying co-occurrence patterns of exposure with network analysis" explains Dr Mirjam Luijten from the National Institute for Public Health and the Environment in the Netherlands. "Several identified co-occurrence patterns consist of chemicals that fall under different regulatory frameworks, stressing the need to strengthen mixture risk assessment across regulatory domains and sectors", stresses the expert.

"We generated new exposure data across Europe on a broad combination of pesticides through the joint survey 'SPECIMEn' (Survey on PestiCIde Mixtures in Europe).

"We generated new exposure data across Europe on a broad combination of pesticides through the joint survey 'SPECIMEn' (Survey on PestiCIde Mixtures in Europe)."

Six partner countries participated in this survey, i.e., Czech Republic, Hungary, Latvia, Spain, the Netherlands and Switzerland. The survey has a so-called 'hotspot' design: it includes hotspots, defined as residences being located within 250 meters of agricultural application of pesticides, and control areas. In all participating countries, urine samples and questionnaire information were collected from 50 parent-child pairs in hotspots and 50 parent-child pairs in control areas in winter, the non-spraying season, and summer, the spraying season. In total, 2000 urine samples were subjected to a pioneer harmonized suspect screening method. This technique enables monitoring of hundreds of pesticide-related exposure markers (parent compounds and metabolites) in a single assay in a semi-quantitative way. "We detected 95 pesticide-related markers (parent compounds and metabolites), of which 41 were the parent pesticides in the samples. For many of these, we observed differences in detection rates when comparing hotspot areas versus control areas, samples collected in summer versus winter, and between children and adults" reports the leader of the study, adding "but not always in the expected direction". Further interpretation of the results is ongoing through more in depth statistical analysis and evaluation of questionnaire data collected within SPECIMEn as well as scrutiny of use characteristics of the pesticides detected. "Our findings will provide insight into the patterns of exposure to pesticides, which is highly relevant, given societal questions and for mixture risk assessment. Furthermore, the results will contribute to the prioritisation of certain substances in terms of further exposure and (mixture) risk assessment and may possibly generate early warning information" highlights Luijten. In order to further improve assessments of health risks due to exposure to mixtures of chemicals, a total of five different case studies was conducted in HBM4EU. Based on the lessons learned across the case studies, an advanced decision tree and workflow scheme for assessing hazards from exposure to chemical mixtures was defined. In many cases, it was possible to identify drivers of mixture risks, i.e., chemicals that contribute more strongly than others to the health risks of combined exposures. Also, most case studies had to be based on exposure assessments for single chemicals conducted separately in different study cohorts. In other words, it was not possible to directly derive which chemicals, and at what levels, occur together. This is a shortcoming that can only be overcome by developing dedicated monitoring strategies for mixture exposures. "Therefore, we recommend that cost-effective HBM strategies aimed at capturing combined exposures need to be developed by adopting multi-chemical analyses that focus on measuring identified drivers of mixture risks. This will bring focus and thereby facilitate risk management", stresses Luijten.

HBM4EU has clearly demonstrated the utility of HBM data for mixture risk assessment.

Chemical pollutants in the home

Within our home and our daily lives we are exposed to hundreds of chemicals from multiple sources, such as flame retardants in soft furnishings, phthalates in plastic food packaging, or PFAS in cosmetics. Yet most chemical safety regulations completely ignore the fact that we are being simultaneously exposed to a cocktail of hundreds of substances from a diversity of sources.

1. PFAS chemicals in waterproof clothing
2. Siloxanes, parabens, and many others in shampoo, shaving foam, deodorants
3. Oxybenzone UV filter in sunscreens
4. Phathalates, parabens, many others in makeup
5. PFAS in nonstick cookware e.g. frying pans
6. Triclosan in antibacterial handwash
7. BPA in some plastic water bottles and food can linings
8. Pesticide residues in food
9. PCBs, dioxins, PHAs found in disposal nappies
10. Phthalates, flame retardants and bisphenols in children's toys
11. Flame retardants in virtually all electronics
12. Phthalates and other substances in fragrances found in air fresheners, cleaning products, cosmetics, soaps
13. Pharmaceuticals and other contaminants in driking water
14. Tattoo inks can contain a mixture of harmful chemicals
15. Flame retardants in furniture and mattresses
16. Unknown and unwanted chemicals in recycled products
17. Bisphenols in till receipts
18. Phthalates and many other plastics additives in food packaging
19. PFAS in microwave popcorn bags, bakery bags aand compostable food packaging
20. Phthalates , flame retardants and volatile organic compounds in vynil flooring

CHEM Trust, 2022. Chemical cocktails - The neglected threat from toxic mixtures and how to fix it.

Therefore, it is recommended that HBM data, particularly data on the common occurrence of chemicals, are more widely exploited. This would support the design of toxicological mixture studies, epidemiological studies as well as mixture risk assessment and management. However, a number of challenges regarding the use of HBM data for mixture risk assessment remains. In order to assess the actual mixture exposures in the population and co-occurrence in the body, future HBM studies should aim to collect data on the full range of chemicals of interest by targeted analysis in sufficiently large study populations measured in the same individuals. To facilitate and harmonize such studies, a strategy for the measurement of multiple exposure and effect biomarkers in the same subject in HBM programmes needs to be developed, together with an inclusive HBM/exposome infrastructure in Europe. Further research should focus on broadening and refinement of a combination of approaches to identify real-life chemical mixtures of concern to which the population is exposed. This will allow prioritization of mixtures of concern and support policy decisions.

Main achievements

- Demonstration of the applicability of network analysis for the identification of exposure patterns, based on the analysis of HBM datasets from 4 countries
- Detection of 95 pesticide-related markers in the survey 'SPECIMEn', resulting from the analysis of 2,000 urine samples using a harmonized suspect screening method
- Advanced decision tree and workflow scheme for assessing hazards from exposure to chemical mixtures based on five different case studies
- A set of recommendations for future research and mixture risk governance, based on lessons learnt in HBM4EU

Fighting against occupational cancer, asthma and allergic dermatitis

Occupational exposures to specific chemicals may, in many instances, be several times higher than environmental exposures experienced by the general population. This is the case of anilines, diisocyanates and hexavalent chromium (Cr(VI)).

Although human biomonitoring provides a valuable tool for understanding human exposure to chemicals in the workplace and ensuring safety at work, a challenge in occupational studies is the low number of workers that can be recruited in national studies. As in the case of human biomonitoring studies assessing environmental exposure, the studies performed by different researchers in individual countries are usually not aligned with respect to sampling, analytical methodologies or data collection. This complicates the comparison of the findings and the use of the data in regulatory risk assessment at a European level. "Combining results from national surveys that have used harmonized study designs and methodologies can greatly improve the usefulness of the information collected from occupational studies and deliver added value at EU level" explains Tiina Santonen, Research Professor at the Finnish Institute of Occupational Health. "Within HBM4EU, we are implementing three occupational studies focusing on different priority substances", she adds.

Anilines is a large group of different compounds with aniline itself being the simplest member of the primary aromatic amines. Aniline and many of its derivatives are known or suspected human carcinogens. Several aniline derivatives can also cause skin sensitization. 4,4-methylenebis(2-chloroaniline) (MOCA) and 4,4-methylenedianiline (MDA), which are are currently authorized for use under REACH, have been studied at HBM4EU using harmonized tools. Since both MOCA and MDA are easily absorbed via the skin, biomonitoring is the best method for assessing occupational exposure to them. Both chemicals are genotoxic carcinogens to which a threshold for carcinogenic effects cannot be assigned.

In the process of REACH authorizations, the role of human biomonitoring is indeed very useful and is the recommended approach to assess exposure to these chemicals. Therefore, MOCA and MDA were included in HBM4EU quality assurance program with several laboratories showing analytical capability for these compounds. o-Toluidine is another aniline compound of interest which is included in the candidate list for authorization under REACH. It is classified as carcinogenic. Although there are published methods for the biomonitoring of o-toluidine, limited biomonitoring data is available. "Within HBM4EU, a risk assessment of o-toluidine was done based on the existing data. This risk assessment demonstrates how HBM data can be used to calculate cancer risks caused by o-toluidine for the general population and workers" states Santonen. She adds "the results suggest low risks for both the general population and workers. However, more comprehensive data on exposure is needed firm up these conclusions".

Diisocyanates are a group of chemicals that are widely used also in occupational settings, including the manufacturing of polyurethanes and as hardeners in industrial paints, glues, varnishes, and resins. Occupational exposure appears during production and handling of these materials and primarily via inhalation or dermal exposure. They are potent skin and respiratory tract sensitizers resulting in allergic dermatitis and asthma. In addition, some diisocyanates cause concern with regards to their potential carcinogenicity. The review of occupational exposure to diisocyanates conducted by HBM4EU scientists showed that the recent biomonitoring data on occupational exposure to diisocyanates is limited, especially in some specific cases like in the construction sector. "This is why an occupational study on the exposure to diisocyanates in specific sectors is planned within the project" explains the expert.

"Our work focuses on three types of diisocyanates which account for the vast majority of the total disocyanates market volume: hexamethylene diisocyanate (HDI), toluene diisocyanate (TDI), and 4,4'-methylenediphenyl diisocyanate (MDI), covering the use of HDI and MDI in the motor vehicle manufacturing and repair and the use of MDI in construction and in the use of MDI based glues. There are several biomarkers for studying exposure to diisocyanates. Most common approach to monitor exposure to diisocyanates is to measure respective diamine levels in urine: in the case of MDI, urinary MDA (4,4-methylenedianiline); in the case of TDI, urinary toluene diamine (TDA); and in the case of HDI, urinary hexamethylene diamine. Other approaches include the measurement of albumin or hemoglobin adducts in blood or, as a novel method to monitor MDI exposure, the measurement of acetyl-MDI-lysine in urine. The measurement of diisocyanate specific IgG has also been proposed as a biomarker of exposure.

"The HBM4EU project has provided a better understanding of occupational exposure to carcinogens like chromium VI or sensitisers like di-isocyanates. This is particularly useful for assessing the effectiveness of existing legislative measures to protect workers' health or for developing new ones."

— Tony Musu
Senior Researcher at the European Trade Union Institute (ETUI)

"The strengths and limitations and the usefulness of different biomarkers has been studied as part of HBM4EU diisocyanate study implemented in 5 European countries. Preliminary results suggest variable exposure levels depending on applications of diisocyanates. They also support the use of HBM as relevant method to study exposure to diisocyanates. As part of the HBM4EU diisocyanate study, we have also included the evaluation of an association between diisocyanate exposure and inflammatory or local genotoxic effects".

Specific physiologically based pharmacokinetic (PBPK) models have been developed for MDI and TDI. These models enable a reverse calculation of urinary diamine levels as external exposure levels and have been used in the risk assessment of occupational diisocyanate exposure. Risk assessment based on existing literature and biomonitoring data from the Finnish database on biological measurements shows that although in many cases exposure levels are below the limit of quantification, there are occupational tasks where measurable exposure occurs, resulting in an increased asthma risk. However, considering that it is not possible to set a safe level for asthma risk, there might be a need to increase the sensitivity of current HBM methods in order to detect lower exposure levels, which might still pose some risk for developing asthma.

"We are delighted to see that the EU has plans to set an EU-wide occupational exposure limit value for diisocyanates in order to prevent occupational asthma. However, because diisocyanates may also be absorbed through the skin, we need to emphasize the role of biomonitoring in the control of occupational exposure to diisocyanates, and so it is of paramount importance to provide recommendations concerning the role of biomonitoring as part of exposure and health surveillance in the workplace".

Hexavalent chromium (Cr(VI)) is a carcinogen to which people are mainly exposed in the workplace. Anthropogenic activities such as welding, electroplating and surfaces treatment are by far the largest exposure sources of Cr(VI), and the main exposure routes are the inhalation of dust, mist or fumes and dermal contact. Although Cr(VI) compounds are subject to authorisation under the REACH Regulation, these compounds are still widely used in different applications, especially in surface treatment of different metallic objects. In addition, workers may be exposed to Cr(VI) formed during hot processes, like welding.

A pan-European human biomonitoring study on occupational Cr(VI) exposure was performed, involving nine European countries and 399 workers in different industrial sectors with exposures to Cr(VI). "We can conclude that chrome platers show the highest urinary chromium levels, which are in some cases more than 10 times higher than the levels measured in the control population. While in the control population urinary chromium levels usually remain below 1 µg/g creatinine, in surface treatment workers the levels vary from these background levels up to 10 µg/g creatinine at post-shift. Interestingly, in some cases, chromium levels in samples taken from workers prior to starting their shifts were higher than in the general population. Although workers performing welding also show elevated levels, these seem to be lower than the levels seen in workers performing chrome plating" explains Dr Beatrice Bocca, researcher in the Unit of Human Exposure to Environmental Contaminants, Department of Environment and Health at the Istituto Superiore di Sanità.

"We have evaluated the capability of new and more specific HBM parameters for the assessment of Cr(VI) exposure. These include Cr(VI) levels in red blood cells (RBC) and exhaled breath condensate (EBC). Our findings on RBC and EBC samples show the same trend as seen in urinary chromium, whereby chrome platers show higher exposure than welders. Welders do also show elevated levels compared to the controls", stresses the expert.

"Analysis of air samples and wipe samples collected from the hands of workers will give us information on other exposure routes. Both air and dermal exposures were positively associated with urinary chromium levels, these measurements can be also used to give recommendations for how to implement risk management measures to minimise exposure to Cr(VI) in workplaces".

Workers involved in the processing of electronic waste (e-waste) are potentially exposed to chromium as well. The e-waste stream is complex because it contains many composite materials, such as circuit boards, cathode ray tubes, flat screen monitors, batteries, connectors and transformers, plastic casings and cables. These waste materials contain a broad range of hazardous chemicals. HBM4EU scientists have published a study protocol on workers' exposure and compare it to the exposure of subjects employed in the same company but with no known exposure to industrial recycling of e-waste. "We want to discuss exposure-mitigating interventions to further reduce exposures and at the same time we also want to stimulate improved work practices and contribute to raising awareness of potential hazards" explains Dr Paul Scheepers, researcher at the Radboud Institute for Health Sciences, Radboudumc.

"This HBM4EU study protocol, that can be adapted to future European-wide occupational studies, can support the development of sustainable practices in e-waste management by providing suitable methods for exposure assessment that demonstrate the need for development of sound practices in professional processing of e-waste. This may prevent e-waste from being dumped in and outside of European countries and would support a more sustainable processing of this waste stream, in line with the Basel Convention on the Control of Transboundary Movement of Hazardous Wastes and their Disposal".

In a partnership with the recycling sector in Europe, HBM4EU can help ensure sustainable processing of e-waste. This may result in an increased in the share of processing e-waste produced in Europe, using Europe's own processing capabilities, instead of exporting e-waste. By conducting an HBM study, we hope to contribute to stimulating good work practices that will lead to further improved protection of the workers' health from the risk of exposure to toxic chemicals, including that of combined exposures.

Main achievements

- One exploratory study about occupational exposures in e-waste processing
- The multi-national occupational chromate study that supports the implementation of the current regulatory actions as well as national enforcement programmes and may contribute to the update of occupational limit values (OELs) for Cr (VI) thus supporting policy actions to reduce the exposure to Cr(VI)
- Diisocyanate data generated within HBM4EU is expected to support the OEL setting and the practical implementation of diisocyanate OELs and management of exposure to diisocyanates in the EU.

Despite decreasing exposure, phthalates are still a health concern in Europe

Phthalates and the non-phthalate substitute DINCH are a group of manufactured plasticizers. Phthalates are primarily used to soften polyvinyl chloride (PVC) plastic in a wide range of consumer goods. Since phthalates are not chemically bound to the (plastic) material, they can leach, migrate or evaporate into the air and the atmosphere, foodstuff or other materials and thus are ubiquitous in the environment. They can enter in our body by ingestion, inhalation and dermal contact.

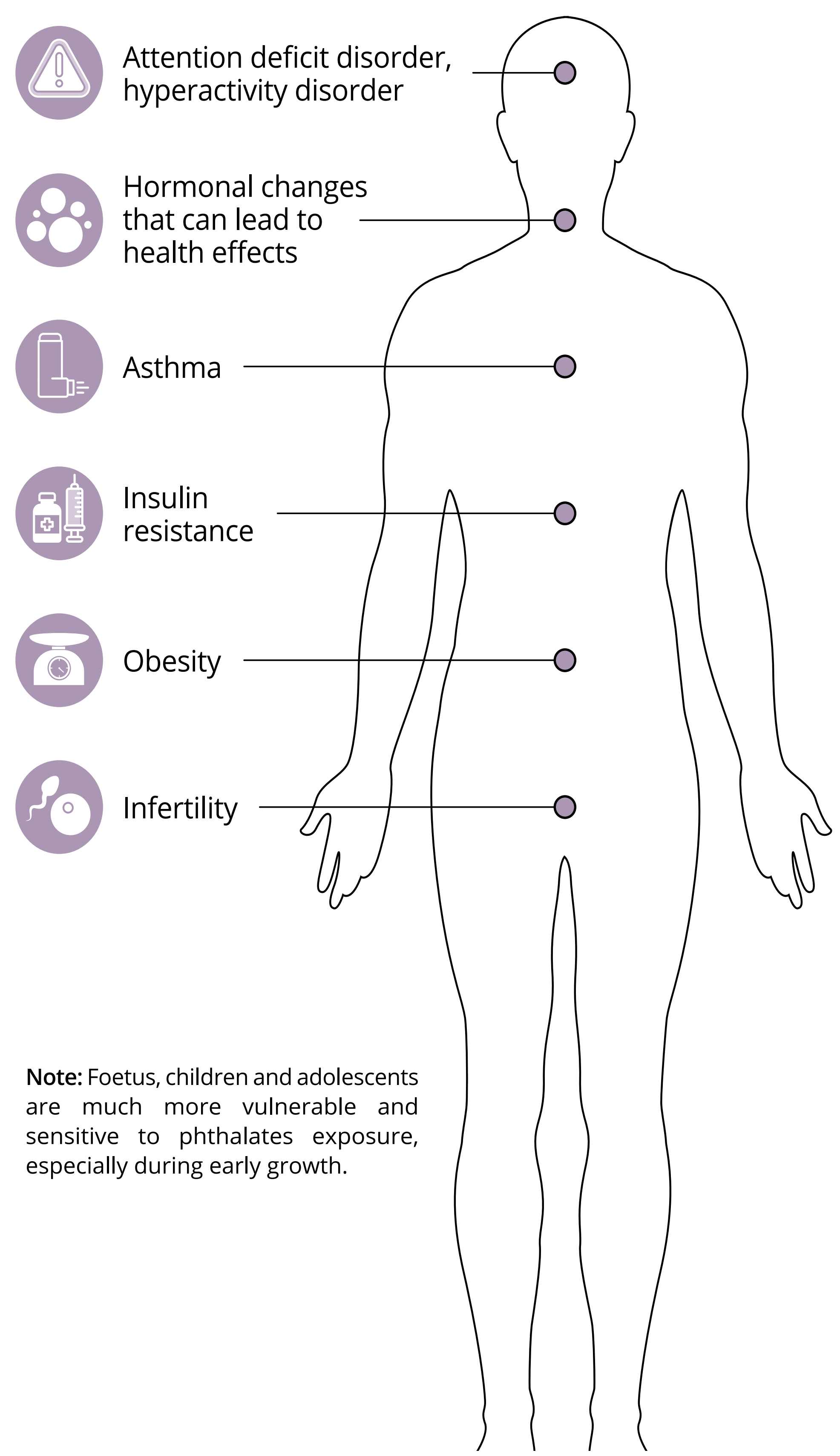
Certain phthalates are toxic and can contribute to a number of chronic diseases. For example, exposure to some phthalates such as BBzP, DEHP, DiBP, DiNP and DnBP1 is associated with fertility issues and developmental effects causing harm to the unborn child. Some phthalates are known to affect the hormonal system as they are endocrine disruptors. In addition, recent studies conducted under HBM4EU reported a possible link between phthalate exposure and asthma, osteoporosis, metabolic syndrome and attention deficit hyperactivity disorder. However, Hanna Tolonen, from the Finnish Institute for Health and Welfare, stated that "more research is needed to confirm these observations". DINCH, which was put on the market in 2002 as a substitute for some of the most toxic phthalates, is thought not to have similar effects on the reproductive system and is not an endocrine disruptor, but effects on the kidneys have been observed in rat studies at high doses.

Several human-biomonitoring (HBM) studies conducted in Europe, Asia and the US have shown that the wide use of phthalates leads to a ubiquitous exposure. However, there is a lack of recent studies on the exposure of children and teenagers for many European countries.

Within HBM4EU we have aligned and harmonized existing HBM data across the EU and generated new ones that now can be compared. For 10 phthalates and DINCH2, 2880 urine samples from children (6-11 years) from 12 countries and teenagers (12-18 years) from 11 countries, covering all European regions were studied.

"The results clearly show that children and teenagers throughout the EU are exposed to these substances. Phthalates and DINCH metabolites were detected in nearly all samples" said Dr Marike Kolossa-Gehring, coordinator of HBM4EU and Head of Section Toxicology, Health-related Environmental Monitoring at the German Environment Agency. "In particular, higher levels for most phthalates and DINCH are found in children compared to teenagers. Neither differences between the sexes nor the household's education were obvious" adds Kolossa-Gehring. Existing HBM studies since 2005 including all European regions and participants from 3 to 60 years old were analysed and HBM4EU researchers found that indeed age plays a role. Children are most exposed to phthalates than teenagers, and in turn, teenagers have higher levels than adults. Reasons for this are the higher intake of food compared to the body weight for the younger age groups, different behaviour of the younger age groups like crawling on the floor and thereby taking up dust and also putting toys (and other articles) in the mouth, whereas teenagers and adults might exhibit different exposure profiles compared to children due to the use of (specific) personal care products. The main sources of exposure for phthalates and DINCH is diet, through food contact materials. However, depending on the physicochemical properties of the phthalates, other exposure pathways might get of importance, such as indoor dust through ingestion or inhalation of phthalates in gaseous and particles phase. Based on the aligned studies the main common exposure determinants among children and teenagers were: urbanization and education, fast food, plastic food packaging, PVC floor, drinks in plastic bottle, cosmetics and hygiene products (fragrances, eyes make-up, body lotion). For children important exposure determinants found were: physical activities (DEHP) and handheld electronical device usage > 4 hours per weekdays also frequent plastic containers usage for food heating in microwaves (DINCH). Whereas for teenagers exposure determinants were the frequent use of local food (DINCH) and waste incineration nearby home, and also home construction year (2001 – 2006) (DEHP).

The study also found differences in exposure between European regions for most phthalates and DINCH. French, Italian and Slovenian children, on average, have the highest levels, while children living in Denmark, Hungary, and Belgium have the lowest concentrations. France, Slovakia, and Norway are the countries where teenagers are most exposed whereas Belgium, Poland, and Sweden are the least exposed.



Note: Foetus, children and adolescents are much more vulnerable and sensitive to phthalates exposure, especially during early growth.

Phthalates investigated

BBzP (Butyl benzyl phthalate; CAS-No.: 85-68-7);
DCHP (Dicyclohexyl phthalate; CAS-No.: 84-61-7);
DEHP (Di(2-ethylhexyl) phthalate; CAS-No.: 117-81-7);
DEP (Diethyl phthalate; CAS-No.: 84-66-2);
DiBP (Di-isobutyl phthalate; CAS-No.: 84-69-5);
DiDP (Di-isodecyl phthalate (all C10 phthalates including DPHP); CAS-No.: 26761-40-0; 68515-49-1);
DiNP (Di-isononyl phthalate; CAS-No.: 28553-12-0);
DnBP (Di-n-butyl phthalate; CAS-No.: 84-74-2);
DnOP (Di-n-octyl phthalate; CAS-No.: 117-84-0);
DnPeP (Di-n-pentyl phthalate; CAS-No.: 131-18-0);
DINCH (Di-isononyl cyclohexane-1,2- dicarboxylate; CAS-No.: 166412-78-8).

[1] Full names and CAS-No. are given below this article
[2] All substances investigated are listed at the end of this article

HBM4EU aligned studies revealed geographical differences. Samples from the most exposed country had 9 times higher concentrations of phthalates than those from the lowest exposed country.

“As phthalates are endocrine disruptors, and children and teens are more vulnerable to the toxic effects of hormone-disrupting chemicals, it is important to find ways to limit their exposure”.

In this regard, phthalates have been the subject of great societal concern for decades – which was also corroborated during HBM4EU citizen focus groups and are included in the ‘Substitute it Now List’ – and policy actions to reduce the citizens’ exposure have been implemented.

Several phthalates are classified under REACH as Substance of Very High Concern and are widely regulated such as that there are far-reaching bans, i.e. authorisation is required before usage, for example for BBzP, DEHP, DiBP, and DnBP since 2015. In addition, several phthalates are restricted in children’s toys that can be place into the mouth (DiDP, DiNP, DnOP) since 2005 or in plastic consumer products (DEHP, BBzP, DiBP, DnBP) since 2020. However, exceptions for not avoidable applications in certain industries like for DEHP and the fact that products from outside the EU can contain phthalates restricted within the EU makes the monitoring of the exposure to such phthalates still relevant– and policy actions to reduce the citizens’ exposure have been implemented. Several phthalates are classified under REACH as Substance of Very High Concern and are widely regulated such as that there are far-reaching bans, i.e., authorisation is required before usage, for example for BBzP, DEHP, DiBP, and DnBP since 2015. In addition, several phthalates are restricted in children’s toys (DiDP, DiNP, DnOP) since 2005 and in plastic consumer products (DEHP, BBzP, DiBP, DnBP) since 2020. However, exceptions for unavoidable applications in certain industries like for DEHP and the fact that products from outside the EU can contain phthalates restricted within the EU makes the monitoring of the exposure to such phthalates still relevant.

“This regulation is proving successful: HBM4EU research shows that human exposure to certain phthalates has decreased over time” states the expert. She adds “an analysis of the highly regulated phthalates from Danish and German time trend studies show decreasing exposure by 9-17 % per year since the 2000s in DEHP, BBzP, DnBP, and DiBP. For the less regulated DINP and DIDP/DPHP however, stable concentrations were observed. Time trends since 2006 for non-regulated phthalates (DEP, DMP) show decreases by about 17 % per year. This decrease in the exposure of also the non-regulated phthalates is presumably due to a decreased production/application of these substances in response to the proposed future regulations for these substances expected by the producers. The results also show that political action might be needed due to the strong increases of the substitutes DINCH and DEHTP. The new substitutes are less intensively investigated toxicologically and concerning the exposure of the population- this is needed to prevent regrettable substitution.

In a study by German and French researchers published in 2021 in the International Journal of Hygiene and Environmental Health, human biomonitoring guidance values (HBM-GVs) have been derived for five phthalates and DINCH for the general population (adults and children) and the working population. At concentrations of the substances or its specific metabolite(s) below the HBM-GVs, no risk of health impairment are expected according to current knowledge, and consequently require no need for action. When comparing the exposure towards single phthalates with the corresponding HBM-GV, despite decreasing levels over time, some European children and adolescents were still observed to exceed these values. The percentage of participants exceeding these values was highest for DnBP and DiBPin children with values of up to 27.4% (for DnBP) and 12.2% (for DiBP).

¨Even when single substances are assessed, HBM-GVs are exceeded for some phthalates. This is of particular concern since phthalates are known endocrine disruptors and have been shown to act in an additive manner in animal studies. In real life, humans are simultaneously exposed to multiple phthalates. When considering cumulative exposure to phthalates at the concentrations found in the HBM4EU aligned studies, risks for adverse health effects might be considerably increased. Currently, a mixture risk assessment is being conducted by HBM4EU researchers”, said the expert. ¨Further political measures are needed in order to yield decreases in the exposure particularly towards DiBP and DnBP. The exposure towards substitutes such as DINCH should be monitored due to the observed increase in exposure levels“ concluded Dr Kolossa-Gehring.

Occupational exposure was also assessed under HBM4EU. It found that recent occupational HBM studies comprising both old and new phthalates are lacking. Currently, samples from at least 200 workers from 10 countries are being analysed with the aim to investigate exposure of workers processing e-waste, based on a study protocol. “We hope to stimulate improved work practices and contribute to raising awareness of potential hazards¨.

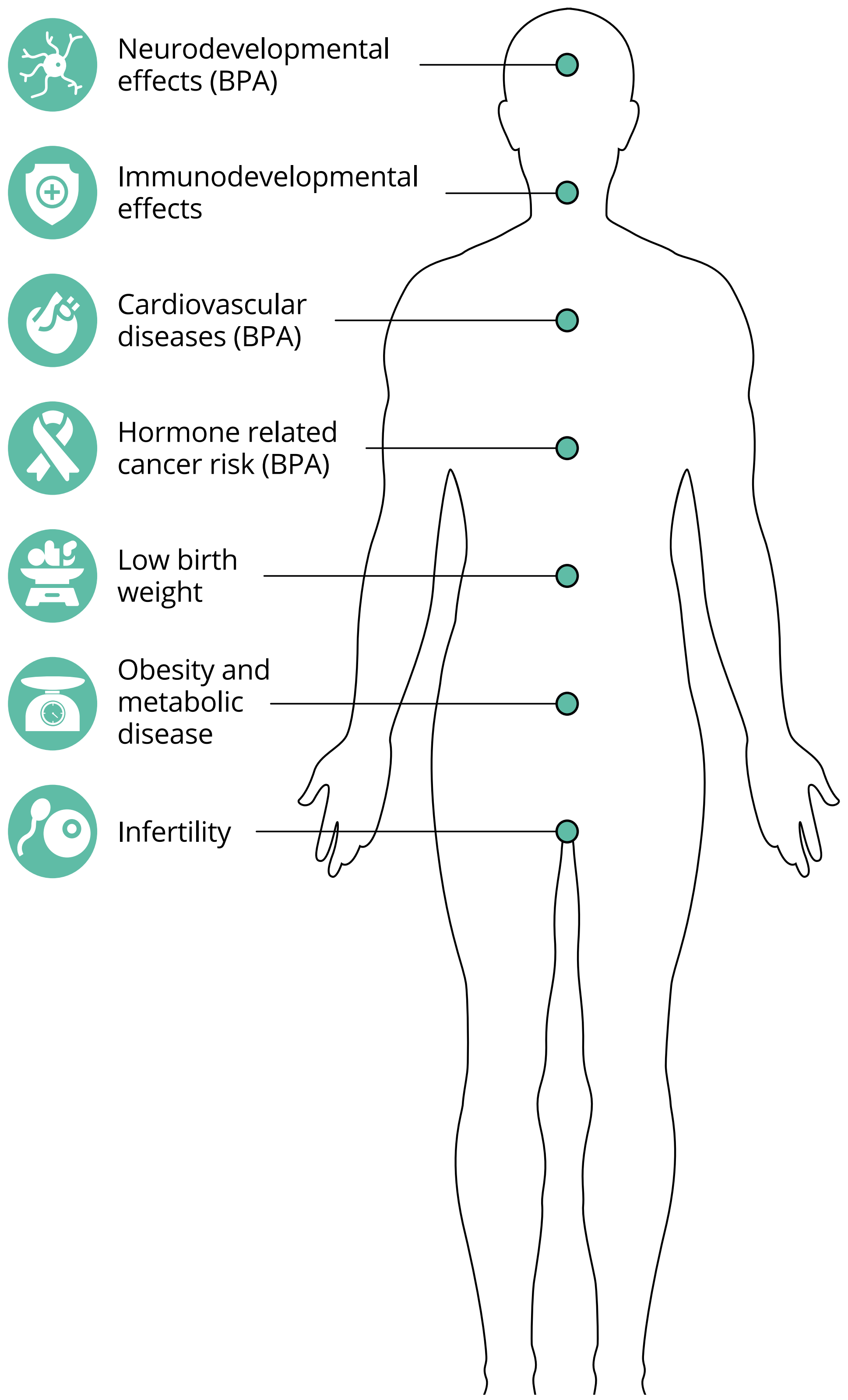
Main achievements

- Results from the HBM4EU aligned studies 2014 to 2021: Current exposure to phthalates and DINCH in European children and adolescents.
- A Harmonised Approach in the HBM4EU Initiative based on Existing Data: Phthalate Exposure of Children, Adolescents and Adults Since 2005 in Europe.
- Aggregated data from either existing or aligned studies are published on the HBM4EU Dashboard).
- Time trend analysis on phthalates and the substitutes DINCH and DEHTP provided- Urinary excretion of from Danish and German young adults between 2000 and 2017.
- HBM-GVGenPop and HBM-GVWorker derived for BBzP, DnBP, DiBP, DEHP and DPHP and DINCH
- First European HBM indicators for phthalates and DINCH have been derived.

Exposure and health impacts of bisphenols call for additional regulatory action

Bisphenols are a group of man-made chemicals that are used in the manufacturing of polycarbonate plastics and epoxy resins to produce a wide range of consumer goods including food containers, such as reusable beverage bottles and reusable plastic tableware, food and beverage can liners, thermal paper, DVDs and CDs, medical devices, toys and automotive parts, and some dental sealants.

Under certain conditions, bisphenols can degrade and migrate from the plastic to whatever they are in contact with, potentially causing adverse health effects. They are among the best characterized endocrine disruptors, particularly since they mimic or antagonize estrogen effects in the body. Amongst the numerous health risks identified to date, the major ones are reproductive and developmental malfunctions, obesity, cardiovascular diseases and carcinogenicity, cognitive and behavioural developmental alterations and immunotoxicity. The main route of human exposure is through diet, since bisphenols can migrate into food or drinks from food containers, packaging or feeding bottles, with canned foodstuffs playing a key role according to a study done under HBM4EU. Are we all equally contaminated with bisphenols? Previous surveys have shown that exposure to bisphenols is essentially ubiquitous, with a tendency for higher levels in samples of mothers and children. However, not all European countries have biomonitoring data on bisphenols, so a definitive picture of bisphenol exposure for the whole of Europe is not currently available. The HBM4EU project addressed this issue by assessing exposure in countries representing the different European regions. Urine samples from adults collected between 2014 and 2021 from eleven European studies including Denmark, Iceland, Poland, the Czech Republic, Croatia, Portugal, Germany, France, Switzerland and Luxembourg were analysed to assess the current level of exposure to bisphenol A (BPA), which is the most widely used chemical in the group, Additionally the samples were analysed for bisphenol S (BPS) and bisphenol F (BPF), two BPA alternatives. That allowed to expand the current knowledge on human biomonitoring data of BPA previously collected in mothers and children during a DEMOCOPHES (DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale) which ran from 2010 to 2012."Our results showed that median levels of urinary BPA are still pronounced in all European regions, despite the fact that the EU has implemented measures to ensure human health protection with some Member States taking additional actions. Nevertheless, median levels of urinary BPA substitutes are increasing in



all European regions, which is triggering a growing concern for exposure to BPS and BPF in Europe. More drastic actions are needed if we want to significantly decrease contamination by BPA", explained Dr Robert Barouki, professor of biochemistry at the University of Paris School of Medicine and Head of INSERM Research Unit. In other words, human exposure to BPA is widespread and of particular concern because of its known endocrine-disrupting properties.

"Previous surveys have shown that exposure to bisphenols is essentially ubiquitous, with a tendency for higher levels in samples of mothers and children."

Should we be concerned by current levels of exposure?
Other studies that have been carried by HBM4EU partners are related to the potential health outcomes of bisphenols. "Citizens would like to know whether they have bisphenols in their body but also, if this is a problem or not" explained Barouki. A recent study based on toxicological data, developed human biomonitoring guidance values (HBM-GVs) for total BPA in urine of 230 µg/L and 135 µg/L for adults and children, respectively. These HBM-GVs are based on a tolerable daily intake (TDI) of 4 micrograms per kilogram of body weight per day, set in 2015 by the European Food Safety Agency (EFSA) in 2015, which is currently reassessing the potential risk of BPA in foodstuffs. EFSA has proposed lowering the TDI to 0.04 ng/kg body weight per day based on a re-evaluation of the substance. "With scientific knowledge increasing continuously, guidance values should be regularly updated. If this new TDI value is confirmed, all exposure values from our samples will be above, which indicates that we are all at risk". An increasing number of studies show adverse effects even at current low exposure levels. For example, the recent case study led by the University of Granada (Spain), aiming to synergize the toxicological and epidemiological knowledge. This working group constructed first an adverse outcome pathway (AOP) network for neurodevelopment, identifying brain-derived neurotrophic factor (BDNF) as a central key event between BPA exposure and behavioral/cognitive alterations, and then evaluated this relationship among children from the INMA-Granada birth cohort. Researchers found that childhood BPA exposure was linked to alterations in BDNF -a promising neurological effect biomarker- and that these alterations mediated the effect of BPA on children's behavioral problems.

Are substitutes safer?
HBM4EU researchers also concluded that in five studies out of eleven, concentrations of BPF are higher than BPA, which indicates a growing concern for exposure to substitutes in Europe. 'Because these "BPA substitute' bisphenols will potentially become more widely used as BPA is becoming increasingly restricted, there is a greater need to fully understand the potential human exposure and health impacts of these substances" stated Barouki. Scientists have observed that between 2010 and 2012, only in one sampling location, the 95th percentil value (P95), representing the 5% most exposed participants, exceeded the guidance value of 1 µg/L for BPS. Between 2014 and 2021, in eight sampling locations out of ten, P95 value exceeded the guidance value of 1 µg/L for BPS, Southern Europe being the most affected region. Furthermore, "with the recent revision of the BPA TDI, our data highlights the urgency to revise the guidance values for BPA substituents". For example, using computational tools, it was possible to highlight obesity as one of the major potential health endpoints of BPS and to link BPF to an adverse outcome pathway for thyroid cancer. The findings associating BPS and obesity, as well as BPF and thyroid cancer, illustrate the use of computational tools in predictive toxicology and highlight the relevance of this approach to decision makers assessing substituents to toxic chemicals.

Contributing to science-based policy making
HBM4EU explicitly aims to support European regulatory processes on chemicals. By providing data on current exposure and on the actual impacts of regulatory

measures, HBM4EU supports decision making, for example, by inciting authorities to take additional measures. Furthermore, the new TDI proposed by EFSA was promptly translated in a new HBM-GV by HBM4EU partners clearly indicating that the internal dose of all European individuals tested is way above the guidance value. Furthermore, HBM4EU data on BPA substituents is a call for urgent revision of these compound TDIs.

Protecting workers

Another finding is on exposure at work. Data gathered under HBM4EU indicate that the risk from occupational exposure should not be disregarded. A potential risk for workers was identified, especially in industrial scenarios with BPA exposure levels 10-20-fold higher than background exposures, and that protective measures need to be taken regarding BPS exposure. The EU banned the use of BPA in thermal paper in 2016, with entry into force in 2020, to particularly protect cashiers who are in constant contact with the material. Again, HBM4EU calls for caution in using BPA substituents.

The BPA saga

Societal concern towards endocrine disrupting chemicals are highly connected to bisphenols and to the campaigns to regulate BPA in particular. The controversies, the ups and downs of bisphenol management may have triggered scepticism and misunderstandings in the population, but in HBM4EU we believe that robust exposure, health sciences and outreach to citizens is the right approach to fill the gap between science and decision. Indeed, to understand the link between exposure levels and health outcomes can positively contribute to better policy and empower citizens towards action and advocacy.

Main achievements

- $HBM\text{-}GV_{GenPop}$ derived for BPA in urine: 230 µg/L and 135 µg/L
- 8 peer review publications published
- Median levels of urinary BPA are still pronounced in all European regions
- An increasing number of studies show adverse effects even at current low exposure levels:
  - BPA childhood exposure linked to behavioural and cognitive alterations
  - Obesity link to PBS
- BPF link to an adverse outcome pathway for thyroid cancer
- HBM4EU calls for caution in using BPA substituents, as median levels of urinary BPS and BPF are increasing in all European regions

The body burden of PFASs: cause for concern

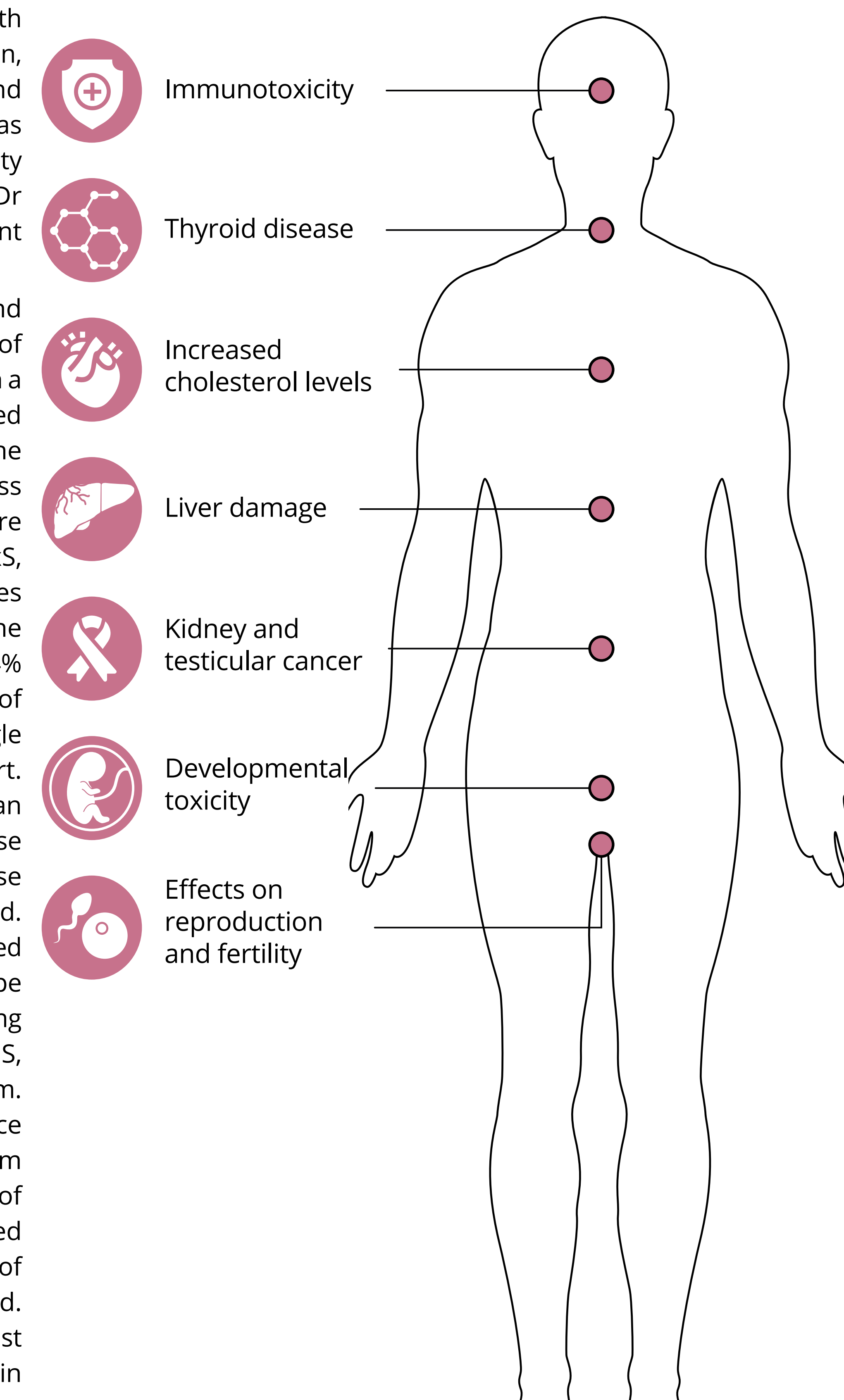
Per- and polyfluoroalkyl substances (PFASs) are a large group of man-made chemicals extensively used in a wide number of industrial and consumer applications. For more than 50 years, PFASs have been used in firefighting foams, coating additives, electronics, homeware, cleaning products and industrial processes because of their resistance to water, oil, grease and stains.

In the late 1990s and early 2000s, several long-chain perfluoroalkyl acids have been recognized as extremely persistent, bioaccumulative and toxic. According to the European Chemicals Agency, PFASs are known to persist in the environment longer than any other man-made substances. With more than 4700 different PFASs now in use, they have been detected globally in the environment, biota, food items, drinking water and in humans. This has led to regulatory actions on a variety of PFASs. However, these substances have been replaced by other PFAS compounds. These alternatives to legacy compounds, such as shorter chain PFASs and per- and polyfluoroether compounds, are also very persistent and thus very mobile in the environment, leading to ground water and foodstuff contamination.

To date, many alternatives to the regulated PFASs are used worldwide, although key data gaps remain on the potential human health effects.

Many PFASs are shown to be toxic to human health. Some have been linked to negative health effects including effects on the developing immune system, increased, reduced infant birth weights, suspected risk for cancer, and thyroid hormone disruption. "Within HBM4EU, analyses of epidemiological data from cohort studies show associations of higher maternal PFASs levels with an increased propensity for infections in the children up to age 4 and the frequency of use antibiotics until adolescent age. Furthermore, prenatal PFAS exposure could be associated with reproductive disorders in children, including delay of menarche and abnormal menstruation/length as well as decreases in semen quality and sperm count" stresses Dr Maria Uhl from the Environment Agency of Austria.

"We have sampled and analysed 1957 blood samples of teenagers from nine countries in a harmonized and quality-controlled way to better understand the exposure to PFASs across Europe". For combined exposure to PFOS, PFOA, PFNA and PFHxS, the results show that all studies have participants exceeding the EFSA health-based guidance, 24% being the highest percentage of participants exceeding in a single study" highlights the expert. Overall, 14.26 % of the European teenagers sampled exceed those levels, and so risk for adverse health effects cannot be excluded. In particular, the studies conducted in Northern and Western Europe had the most teenagers exceeding the guidance values for PFOS, PFOA, PFNA, PFHxS and their sum. EFSA's health-based guidance value corresponds to a serum level of 6.9 µg/l in women of childbearing age and is intended to protect the immune system of the unborn and breastfed child. This level is also protective against other health effects of PFASs in children and adults.



Over the time we have seen a decreasing trend for PFOA and PFOS concentrations in humans, but substitute PFASs are detected.

Food intake was found to be the most important route of exposure to PFOS and PFOA, with percentages of 97 % and 98 % of the total intake, respectively. Dietary exposure to PFOS and PFOA, PFNA and PFHxS has been thoroughly assessed by EFSA but knowledge on the exposure to short chain PFAS via diet and drinking water is scarce.

"From the HBM4EU aligned studies we can confirm that diet is found to be an important exposure determinant of PFASs". We found that higher consumption of seafood and fish increases the levels of PFNA and PFOS by 20 and 21 %, respectively and higher consumption of eggs is responsible for an increase in levels by 14 and 11 %, respectively. In addition, we found that another major source of exposure to PFOS include the consumption of offal and local food, causing a higher exposure to PFOS by 14% and 40% respectively.

Sex and education might be another determinant of exposure. PFASs concentrations are in general higher in men and there seems to be a trend that participants with higher educational level have higher exposure levels. In some studies, higher levels of PFASs were observed with increasing age.

Occupational exposure to PFASs was studied among workers in chrome-plating plants. In total 155 plasma samples of workers were analysed from five studies. "Results will be available before June 2022" said the expert. First European reference values for PFOS, PFOA, PFNA and PFHxS were derived from the data collected between 2014 and 2020.

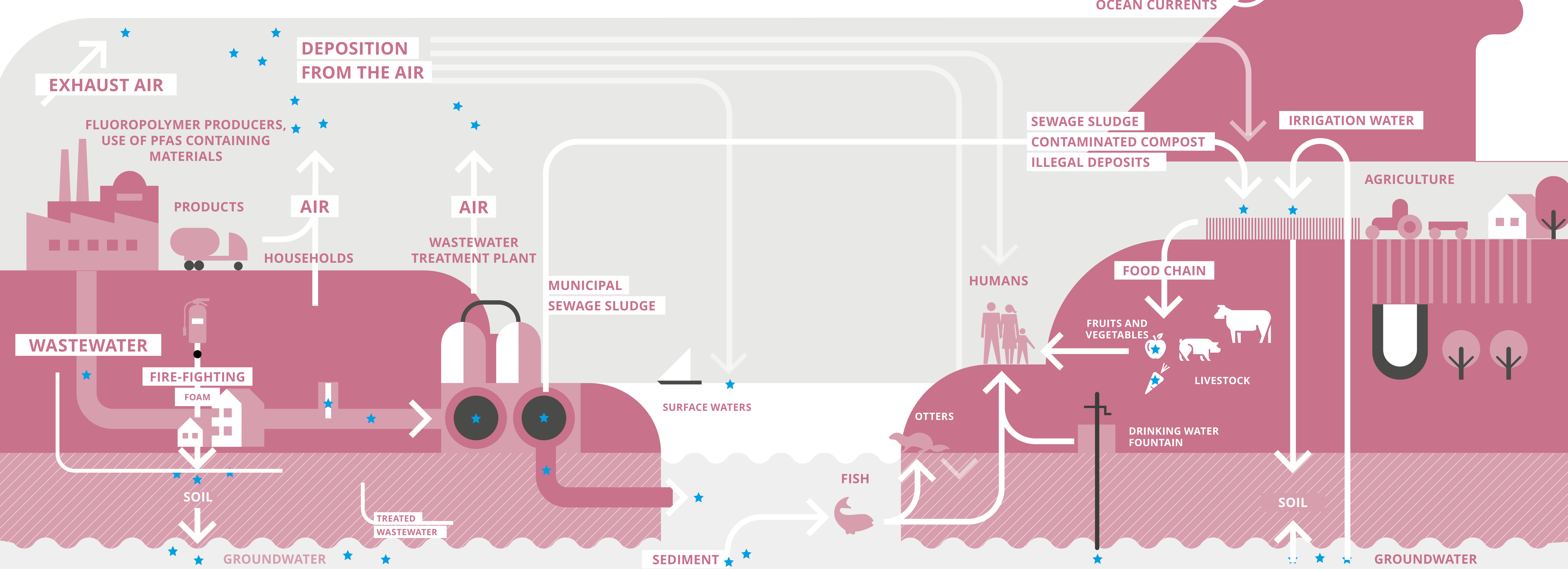
The data from cohort studies were used to investigate the link between exposure and health. Selected and non-targeted effect biomarkers were used in certain HBM studies. Physiologically based pharmacokinetic (PBPK) models for PFOS and PFOA were validated using human biomonitoring data and further developed as a tool for policy makers.

An important part of the HBM4EU programme was to strengthen the science-policy interface by answering concrete policy questions related to the HBM4EU's priority substances. In this way, key policy processes concerning PFASs were identified in a systematic way to better align policy and project timelines. A science-policy dialogue on the HBM4EU findings on PFASs was initiated and a follow-up workshop took place in March 2022. HBM4EU also contributed to the public consultation of the recent EFSA opinion. HBM4EU data will feed into regulatory processes such as the broad restriction of PFAS. The restriction is in line with a set of actions to address PFASs with a group approach, under the legislation on water, sustainable products, food, industrial emissions, and waste which was proposed within the European Chemicals' Strategy for Sustainability and in the accompanying document on PFASs. Within HBM4EU, a network on PFAS hotspots has been established and a guidance on how to perform human biomonitoring in these regions is in preparation.

Overall, the HBM4EU results demonstrate the widespread exposure to PFASs which exceeds health-based guidance values. This indicates a risk specifically for vulnerable population groups. Various health effects are related to PFASs exposure and current knowledge indicates the developing immune system is the most sensitive target of toxicity. The results point to the need for a broad restriction of this group of substances for all non-essential uses.

Main achievements

- A number of educational materials & sciences to policy workshops
- Exposure data in European teenagers
- Risk assessment of PFAS mixtures
- PBPK model established
- Summary of mechanistic data on certain endpoints
- Selected effect biomarkers
- Guidance and Network related to PFAS Hot-Spots
- >20 Peer reviewed publications (published and in preparation)



Umweltbundesamt (German Federal Environment Agency - UBA)

Understanding exposure to mycotoxins is crucial to assess the current and future risks due to climate change

Mycotoxins are fungal metabolites that can be toxic for humans and animals. They occur all over the world and are closely associated with crops contaminated with fungi, particularly cereals, although they also appear in fruits, vegetables, and animal products, including meat, dairy and eggs. Up to 25% of all food crops may have some level of contamination with mycotoxins. They are resistant to food processing and cooking practices and may be toxic even at low concentrations.

Food is the main source of exposure and ingestion is the main route of exposure to mycotoxins. In addition, inhalation and dermal routes can also contribute to exposure in certain occupational settings, mainly during tasks involving high exposure to organic dust (e.g. storage work, loading, handling, or milling contaminated grains, waste and feed). Mycotoxins have been associated with several adverse effects including hepatotoxicity, nephrotoxicity, immunotoxicity, mutagenicity and carcinogenicity. They might also cause developmental abnormalities in the embryo or fetus.

"Climate change constitutes a reason for concern, as its effects favour the spread of fungi and consequently the production of mycotoxins leading to increased risks for human health. Therefore, human biomonitoring of mycotoxins in Europe is crucial to identify the current and future patterns of exposure due to climate change and to assess the associated risks" explains Dr Paula Alvito, Investigator from the Food and Nutrition Department at the National Institute of Health Doutor Ricardo Jorge, in Portugal.

The European Union set maximum concentrations for mycotoxins in a range of foodstuffs to protect human health. Besides the regulated mycotoxins, several other non-regulated toxins are reported as modified and emerging mycotoxins. Furthermore, co-exposure to several mycotoxins is commonly found and their combined effect on human health needs to be considered as well. "Unfortunately, mycotoxins are still not recognised as a risk factor in the workplace due to lack of information and therefore there is no occupational exposure limit available" explains Prof. Susana Viegas, Assistant Professor from the Department of Occupational and Environmental Health at the National School of Public Health at NOVA University of Lisbon.

"Unfortunately, mycotoxins are still not recognised as a risk factor in the workplace due to lack of information and therefore there is no occupational exposure limit available"

Under HBM4EU, mycotoxins were studied with special focus on deoxynivalenol (DON), a mycotoxin considered as immunotoxic, reprotoxic and a probable endocrine disruptor, and fumonisin B$_1$ (FB$_1$), a possible carcinogen associated with esophageal cancer and the neural tube defects in the embryo.

A multidisciplinary team with expertise in chemistry, biology, toxicology, genotoxicity, environmental and public health set the objectives for the work on mycotoxins. "We aimed to assess the current exposure levels of the European population to DON and FB$_1$, explore regional differences, find out which are the high-risk population groups and set an HBM guidance value for these mycotoxins, and explore mechanistic evidence to link human exposure to adverse health outcomes", states Dr Maria João Silva, Investigator from the Department of Human Genetics from the National Institute of Health Doutor Ricardo Jorge.

"Previous studies revealed that the European population exposure to DON might exceed the Tolerable Daily Intake (TDI) of 1 µg/kg bw/day. In addition, there was a lack of insight into the comparability of HBM data for DON, hampering the comparison of results from existing studies produced by different research groups" according to the expert. Four European laboratories capable of providing comparable HBM data after participating successfully in the HBM4EU QA/QC programme, analysed 1270 samples of urine from adults in six European countries (France, Germany, Iceland, Luxembourg, Poland and Portugal).

Data on total exposure to DON obtained from a literature search and from the HBM4EU Aligned studies confirmed that the European population is exposed to DON and that a fraction of this population is, to some extent, exposed to levels that represent a potential health concern. Children and pregnant women are most at risk. "As cereal-based products are the main exposure sources to DON, significant efforts should be dedicated to reducing the contamination levels in the foods usually consumed by children", highlights Dr Silva. Additionally, although based only on data from the literature search, some studies reported a significant difference between workers and control groups, confirming that the occupational environment could have an important role in increasing the exposure to DON. No risk assessment was performed for FB$_1$ because the available human biomonitoring data is very limited due to its low urinary recovery and high inter-individual variability in absorption and excretion.

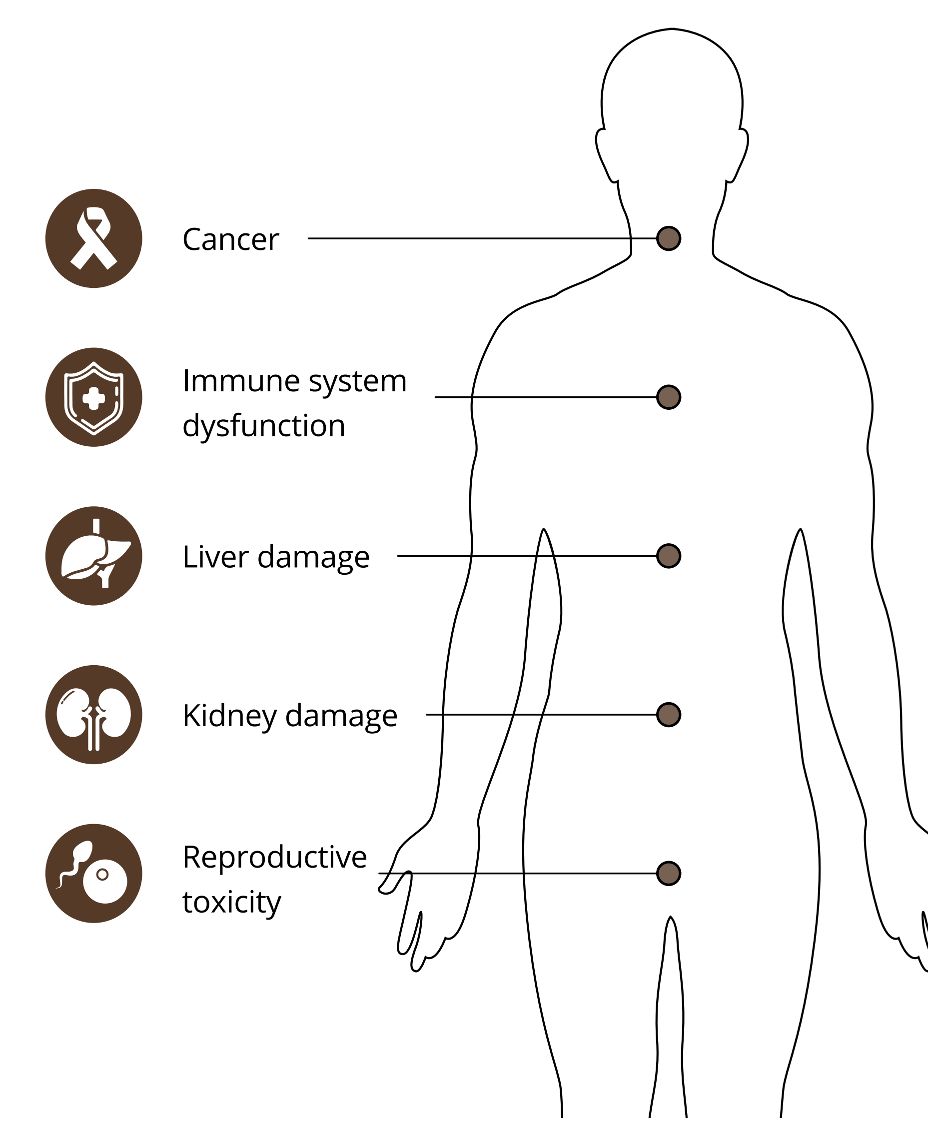
"We derived an HBM health-related guidance value (HBM-GV) for the population for DON,23 µg DON/L urine which could be of regulatory relevance for policy makers and risk assessors. It allowed for the first time, to assess the risk of DON based on exposure biomarkers and an HBM-GV. This HBM-GV was derived by expressing the tolerable daily intake value as derived by EFSA as equivalent of an 'internal' HBM value using available kinetic models and information on the metabolism of DON in humans. Unfortunately, the same was not possible for FB$_1$ due to the lack of kinetic model" stresses Silva.

"Our findings show that no relevant long-term health effects were identified for DON" reports Dr Silva. "Concerning FB$_1$, we have proposed a biological mechanism to explain how exposure to FB1 could induce neural tube malformations by inhibiting ceramide synthase, a central enzyme in sphingolipid metabolism. This reinforces the conclusion from the few human studies published previously that exposure of pregnant women to FB$_1$ may increase neural tube defects in the embryo. However, there are some uncertainties in the proposed mechanism and more studies will be needed to confirm this effect of FB$_1$ in humans".

Despite the great progress, several aspects need further research. Conducting more exposure studies covering the Eastern European countries is important to ensure a representative European exposure assessment. The impact of climate change on population exposure to mycotoxins should also be monitored regularly in order to take actions to prevent exposure and to anticipate potential health issues. Regarding the analytical methods, there is still a need for interlaboratory comparison programs for exposure biomarkers, other than DON, as well as certified reference materials, to promote comparability among research groups. Also, the use of HBM data for risk assessment still encompasses some limitations related to the use of data published in several scientific articles, non-harmonized sample collection and criteria for data below the limit of quantification of the analytical method used. There are also some gaps regarding mycotoxins' toxicokinetic data that may increase the uncertainty of risk characterization. The limitations could be overcome in the near future by developing a guidance for setting-up biomonitoring campaigns that would allow proper comparison of results from different studies with the HBM-GV. For example, since the new HBM-GV value could only be derived for 24h urine samples, the use of these samples should be encouraged. Furthermore, the inclusion of carefully selected and mechanism-based effect biomarkers in future HBM studies will allow linking exposure to health outcomes, thus contributing to predicting potential associated diseases.

Main achievements

- New and harmonized HBM data obtained from 1270 adults under the HBM4EU aligned studies for DON show European population exposure to this mycotoxin
- Exposure to DON for the population of the western European region might represent a potential health concern, particularly for children and pregnant women; some workplace environments also contribute to the exposure
- A human biomonitoring guidance value (HBM-GV) for the general population was derived for DON
- Mechanistic data from various in vitro and in vivo studies support the possibility that FB1 exposure during pregnancy may result in fetal neural tube defects
- 4 peer review publications in preparation



Broad set of alternative flame retardants challenge human biomonitoring

Flame retardant (FR) is the term given to any compound or mixture used to reduce flammability and improve product safety. Hundreds of FRs are in use, we have clear evidence that people are exposed to these chemicals, and it is essential to evaluate their potential effects on health.




The use of flame retardants has increased dramatically over the past 40 years due to changes in flammability standards and increased use of synthetic products with higher flammability risk, particularly in indoor spaces. The early use of FRs was dominated by brominated FRs, particularly the polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCD). However, due to concerns regarding their persistence, toxicity and bioaccumulative potential, these compounds have been restricted at national levels, and production has been banned under the international Stockholm Convention on Persistent Organic Pollutants. However, the need for FR compounds remains, and as a result, a broad set of alternative FRs has come into use.

Many flame-retarded products are those we come into contact with in daily life: carpeting, upholstered furniture, mobile phones, televisions, vehicle parts, car seats, building insulation. Under certain conditions, FRs can migrate from the product to whatever they are in contact with – to air, to skin, and to dust settled on surfaces.

Under certain conditions, FRs can migrate from the product to whatever they are in contact with – to air, to skin, and to dust settled on surfaces.

Concentrations of FRs in air and dust are high in indoor spaces compared with the outdoor environment, given the number of flame-retarded products and materials. As a result, much of our exposure to FRs comes from accidental ingestion of indoor dusts – particularly important for young children due to hand to mouth behaviour - and inhalation of indoor air. Several halogenated FRs, particularly the restricted PBDE and HBCD, are persistent and widespread in the environment and throughout the food web, and exposures can also occur from contaminated foods, particularly meat, dairy and sea food.

The diversity of chemical structures within the group of FRs presents a complex challenge. Under HBM4EU, 62 FR compounds – all synthetic organic flame retardants - were identified for consideration, and these differ substantially in their structures and properties, and as a result, their potential for human exposure and toxicity. Comprehensive data covering exposure, population levels and toxicity only exists for a small subset of the selected FRs. Twelve of the 62 HBM4EU priority FRs lack knowledge on human exposure, despite some indication of toxicological concern, and a review of available toxicological information revealed that 20 FRs entirely lack toxicological data from mammals. These substantial knowledge gaps present a major challenge in addressing FRs.

Moreover, the analytical methods required for the determination of FRs in both environmental and human biological samples are not standardized, and there is a wide variation in the techniques and instrumentation used. This can lead to challenges in comparability across studies; Parvaneh Hajeb, who works at Aarhus University and is one author of a critical review of analytical methods for FRs in human matrices emphasized that there is a need for a greater focus on the reliability of methods, supported by proficiency testing, particularly for the currently used halogenated FRs and organophosphate FRs. Proficiency testing under HBM4EU confirmed that a significant network of European laboratories can routinely measure PBDEs and HBCD, as well as Dechlorane Plus, a chlorinated FR for which less biomonitoring data are published. However, Darina Dvorakova, from the University of Chemistry and Technology in Prague, reporting the main outcomes from four rounds of interlaboratory comparisons, stated that the investigations revealed "critically low analytical capacity for biomonitoring of replacement brominated FRs as well as of organophosphate FR biomarkers". The low participation rate (only six laboratories in Europe) for organophosphate FR metabolites suggests that new method development and implementation across laboratories is crucially needed, especially for organophosphate FRs which are suspected to have increasing population exposure.

PBDEs and HBCDs are associated with a range of adverse health effects, including potential neurotoxic, endocrine-disrupting, and carcinogenic effects. Early evidence suggests that some of the replacement FRs have similar health concerns, yet the greater concern is that insufficient evidence exists to evaluate toxicity for many of these alternative FRs. Lola Bajard, from Masaryk University and one author of a study on the endocrine disrupting potential of replacement FRs, states that "information on potential endocrine disruptive properties is lacking for many flame retardants commonly used in consumer products." She highlights that for those FRs where the activities are known, many can inhibit the androgen receptor, emphasizing the risks of combined effects when people are exposed to mixtures of FRs. Despite this, risk assessment evaluations generally focus on individual compounds.

Contributing to science-based policy

HBM4EU explicitly aims to support European regulatory processes on chemicals. The meta-analysis of biomonitoring data on legacy FRs (PBDEs and HBCD) has demonstrated the positive impact of restrictions on chemical production in reducing population levels of FRs. Risk assessment and evaluation of hazard data highlighted the hazard posed by chlorinated organophosphate esters (tris(2-chloroethyl) phosphate - TCEP and tris(2-chloro-1-methylethyl) phosphate – TCIPP, and tris[2-chloro-1-(chloromethyl) ethyl] phosphate - TDCIPP), and HBM4EU has provided evidence on the need for restrictions on these compounds under the ECHA call for evidence on flame retardants TCEP, TCPP and TDCP in 2018. While sufficient data to generate an opinion was available for this subset of chlorinated organophosphate FRs, science-based policy cannot be broadly developed for the currently used FRs without reliable analytical capacity for biomonitoring samples, and evaluation of toxicity hazards and health risks for the FRs that are currently in use. The work of HBM4EU has highlighted the large uncertainties and data gaps that remain for the organophosphate FRs; science-based policy-making will be at a disadvantage until these gaps are filled.

Main achievements

- 6 peer review publications
- Critical review of analytical methods and capacities for biomonitoring of FRs
- Review of evidence linking flame retardants and ADHD
- Comprehensive review of toxicological information on currently used flame retardants
- New biomonitoring data on FR exposure in 1770 children
- Time pattern analysis of PBDE and HBCD levels in breast milk shows positive impact of chemical restrictions on reducing population levels

Emerging chemicals: a matter of growing societal concern

People today are exposed daily to myriads of chemicals via various routes, including the environment, food or lifestyle. The health risks that result from exposure to this cocktail of chemicals are a matter of growing societal concern.

Chemicals of emerging concern span natural and artificial chemical substances and their by-products, comprising for instance pharmaceuticals, phytosanitary products, environmental persistant organic pollutants such as flame retardants (FRs), other non persistant contaminants such as phthalates or bisphenols, UV-filters from personal care products (PPCPs) A wider definition may also include nanoparticles, microplastics and their transformation products, but also antibiotic resistant bacteria (ARB), etc. Many of them act as so-called endocrine disrupting chemicals (EDCs), that alter the normal functions of hormones.

In traditional analytical chemistry, chemical analysis methods have been developed specifically for a specific type of sample and substance group. This is called targeted analysis and has sensitivity and good identification of the specific substances. However, this traditional method can only identify the compounds we are looking for. So all compounds that are not included in the analyzes will not be identified, even if they are present at high concentrations or have a serious toxic potential. The need for a wider exposure characterization is noteworthy, particularly concerning the detection of chemicals of emerging concern, for which knowledge is limited.

"Large-scale suspect and non-targeted screening approaches open the door to the simultaneous detection of a number of chemical descriptors never achieved before." These new approaches are based on advanced instrumentation dedicated to chemical profiling (high resolution mass spectrometry), explains Dr Jean-Philippe Antignac, Head Deputy of the LABERCA research Unit. By encompassing chemicals of emerging concern, as well as unknown contaminants and their metabolites, these suspect and non-targeted approaches provide early warnings and broad support to exposure assessment. HBM4EU has developed and applied such new suspect and non-targeted screening approaches, establishing a structured European network of cutting-edge analytical laboratories, and promoting the necessary methodological harmonization. HBM4EU has secondly developed and conducted several proof-of-concept studies illustrating the usefulness of these approaches.

10

First structuration of around **10 EU laboratories** involved in suspect and non-targeted screening activities applied to human samples

3,000

Overall, more than **3,000 human samples analysed, and several hundreds of exposure markers detected** associated to emerging hazardous chemicals, **among which several dozens where structurally identified**

51

Chemicals included in **51 publicly available databases** related to CECs collected and aggregated into a single quality assured/quality controlled consolidated **database (CECScreen),** to be used as a comprehensive list of compounds to be monitored by suspect screening approaches

1

1 Global framework for QA/QC consolidated and harmonized development/application of suspect and non-targeted screening in HBM

1 first interlaboratory study, **with** a total number of **155 human urine and 60 human blood samples** from cohorts/biobanks analysed including general and occupationally exposed populations **with suspect screening** methods in 4 European laboratories from France, Germany, Belgium and Austria before the HBM4EU related harmonization work. Pesticides, plasticizers and PFAS chemicals were examples of detected markers with high detection frequencies (e.g. N,N-Diethyl-3-methylbenzamide (DEET) or 2-Hydroxybenzothiazole), showing their widespread presence in populations in various European countries

4

4 suspect screening proof-of-concept studies performed.

- Suspect screening of **serum in 10 Austrian adults, 132 compounds detected**
- Suspect screening of **urine in 61 Austrian adults, 233 compounds detected,** from which 80% of the identified compounds referred to pharmaceutical compounds and their metabolites[3]
- Suspect screening of **urine in 50 Flemish adolescents, 45 compounds detected,** chemical classes detected including personal care products, plasticizers, UV-filters, pesticides and food additives
- Suspect screening of **urine in 300 Slovenian children (6-9 years), 76 compounds detected,** from which 22 matched with the CECScreen database

1

1 harmonized large -scale study - SPECIMEn study from the general population (adult-child pairs) living either nearby (<250 m) or further away (>500 m) from agricultural fields (e.g. orchards), samples collected to time periods -winter/spring- **5 countries, 5 laboratories involved, 2000 human urine samples analysed, preliminary list of 45 exposure markers identified, several dozen if not hundreds of other exposure markers tentatively detected**

2

2 non-targeted screening proof-of-concept studies performed

- Non-targeted screening of **milk in 75 French mothers, around 300 halogenated features detected** among which 4-hydroxy-chlorothalonil, hexachlorobenzene and p,p'-DDE
- Non-targeted screening of **placenta in 25 Spanish mothers, 25 exposure markers detected,** 220 hits on endocrine disruptors and 213 hits on fluorinated compounds

2

2 proof-of-concept studies focusing on thyroid and androgen receptor-based effect-directed analysis (EDA), permitting to link a measured biological activity to given exposure markers (e.g. celestolide)

Existing or newly collected HBM data from all over Europe on substitutes of already regulated chemicals of the following substance groups: per- and polyalkylated substances, bisphenols, phthalates, DINCH and organophosporous substances

12

12 peer reviewed publications published in top rank (first quartile) peer review international journals

[3] In suspect screening results depends on the applied suspect list, i.e. if this one is including only pharmaceuticals, the detected compounds will belong to this substance class mainly. 80% of pharmaceutical does not mean that other chemicals are not present.

Evaluating the use of HBM data to support risk assessment of cosmetic ingredients

It is estimated that skin melanoma accounted for 4% of all new cancer diagnoses in EU-27 countries in 2020 (all cancers, excluding non-melanoma skin cancers) and for 1.3% of all deaths due to cancer. This made it the sixth most frequently occurring cancer, after breast, colorectal, prostate, lung, and bladder cancers, and one of the 20 most frequent causes of cancer death.

Exposure to ultraviolet radiation is the main cause of skin forms melanoma cancer. And one of the most effective ways to avoid it, and to prevent skin damage, is sunscreen. However, some of the ingredients used in those products to block out harmful UV rays, and specifically a group of chemicals called benzophenones, might have some impact on our health.

In particular, derivatives of benzophenones such as benzophenone-2 (BP-2) and oxybenzone (BP-3), a suspected endocrine disruptor, are used in sunscreens. Benzophenones are also used in food packaging and consumer products to protect the goods from UV degradation and extend shelf life. Another chemical in this group – benzophenone – is a possible carcinogen. However, more research is needed to assess the human health effects of exposure to benzophenones.

"One of the aims of HBM4EU was to determine current levels of exposure of the European population to this group of chemicals. At the outset of HBM4EU there were relatively few studies in Europe on exposure to this group of chemicals; most of the studies were conducted in Denmark and Spain, and mostly focused on BP-3 and BP-1. These studies indicated that the general population is exposed to BP-3" highlights Dr Tamar Berman, from the Ministry of Health in Israel.

New exposure data has been generated as part of the HBM4EU Aligned studies in adolescents in 6 countries including Sweden, Norway, Poland, Spain, France and Germanyand adults in 4 countries: Denmark, Luxembourg, France and Germany. "These new data, which will be published in June 2022 on the HBM4EU website, provide exposure data on a range of benzophenones: BP-1, BP-2, BP-3, BP-7".

"Although we expected to find differences in exposure between European countries or regions related to climate, no significant differences in average BP-3 levels were found between Western Europe, Southern Europe and Northern Europe" reports the expert. Based on the literature review, no significant difference was seen between males and females in European studies. Average urinary BP 3 levels were significantly lower in children and adolescents compared to adults, possibly due to the use of cosmetic products. "We also wanted to understand whether current exposure levels are safe in relation to the endocrine and carcinogenic properties of benzophenones" explains Berman.

> **"We also wanted to understand whether current exposure levels are safe in relation to the endocrine and carcinogenic properties of benzophenones"**

A risk assessment conducted using HBM exposure data from Denmark, Spain and Belgium showed that average exposure levels for BP-3 were below those associated with risk, although highly exposed individuals may potentially be at risk.

One of the main uses of BP-3 is in cosmetics. The EU Scientific Committee on Consumer Safety (SCCS), which provides opinions on health and safety risks of non-food consumer products, recently published a risk assessment on use of BP-3 in cosmetics in view of concerns related to potential endocrine disruptors properties. The SCCS teamed up with researchers from HBM4EU to evaluate the use of HBM data to support risk assessment of cosmetic ingredients, work that was published in a study in the journal Toxics. By comparing different risk assessment approaches, the researchers demonstrated the usefulness of using HBM data in risk assessment by providing data on real-life exposure. The robust and recent data collected in the HBM4EU Aligned studies has now been used to update the risk assessment, which was previously based on HBM data collected in 3 European countries between 2010 and 2013. The researchers encourage policy makers to prepare a standardized framework for incorporation of HBM data in the current risk assessment of cosmetic products.

According to Berman, "HBM4EU has provided valuable new data on population exposure to benzophenones, and demonstrated how this data can be used to inform risk assessment". She adds "it is important for Europeans to know that BP-3 is currently restricted in cosmetic products and is regularly evaluated for safety".

"Protection from harmful UV rays is critical to prevent skin damage and cancer, so we should not avoid use of sunscreens with UV filters including benzophenones. However, concerned citizens should consider mineral based sunscreens as an alternative."

Main achievements

- New data provided on population exposure to BP-1, BP-2, BP-3, BP-7
- Demonstrated the usefulness of HBM data for risk assessment
- One peer reviewed publication published

Aprotic solvents – minor concern or an underestimated risk?

Solvents are chemicals used to dissolve substances not usually soluble in water and can be grouped into non-polar, polar protic and polar aprotic solvents.

HBM4EU work has focused on aprotic solvents, which are present in a large number of products to give them consistency. HBM4EU researchers have focused in particular on four aprotic solvents classified in the EU as toxic to reproduction, which may damage the unborn child, namely NMP (1-methyl-2-pyrrolidone), NEP (1-ethylpyrrolidin-2-one), DMAC (N,N-dimethylacetamide) and DMF (N,N-dimethylformamide). Those substances, which raise particular concern for vulnerable population groups such as pregnant women and young children, are widely used both in industry and household as coating products, lubricants and greases, adhesives and sealants, anti-freeze products, personal care products and cosmetics, air care products such as scented candles, non-metal surface treatment products, inks and toners, leather treatment products, polishes and waxes, washing and cleaning products. Dermal and inhalation exposure are the most important exposure routes for aprotic solvents given their low volatility and potential to be absorbed via the skin.

Previous surveys have shown that exposure to aprotic solvents has been broadly studied in occupational settings concerning highly exposed workers. However, only a few data on general population are available. With respect to NMP and NEP, exposure from two studies conducted in Germany is used for risk assessment of aprotic solvents. These include data from the German Environmental Specimen Bank (ESB) measured from 1991 to 2014 and data from the German Environmental Survey of Children and Adolescents V (GerES V) In the first study, led by German researchers, 549 urine samples from young adults from ESB were investigated to get an overview of the exposure to NMP and NEP over time tand to evaluate associated risks. Daniel Bury from the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, informs that "metabolite concentrations were rather steady over the timeframe investigated, even for NEP which has been introduced as an NMP substitute only in the last decade". However, data from other European countries are still missing "we don't know the pattern of geographical distribution of exposure to reprotoxic aprotic solvents yet as well as the associated potential global health risks caused by these substances", indicates Normunds Kadiķis, Head of the Environmental Health Division at the Latvian Health Inspectorate. The expert adds "individual and combined NMP and NEP exposures were within acceptable ranges in the investigated timeframe".

In the second study, published in 2021 in the Environmental International journal, NMP and NEP metabolites were measured in more than 2100 urine samples of children and adolescents. Metabolites of NMP were detected in all urine samples, and the two NEP metabolites 5-hydroxy-*N*-ethylpyrrolidone (5-HNEP) and NEP in 87% of the urine samples. In addition, within HBM4EU, DMF was analysed based on samples belonging to the German ESB covering 21 years from 2000 to 2021. "We are still analysing the data and no conclusions have been drawn yet" highlights Kadiķis.

"Within HBM4EU, the health-based human biomonitoring guidance values (HBM-GV) for the general population have been derived for NMP and NEP", reports Dr Marike Kolossa-Gehring, one of the authors of the study. For children, this value is 10 mg/L in urine for both NMP and NEP, and for adolescents and adults it is 15 mg/L in urine both for NMP and NEP. With respect to DMF, a provisional HBM-GV for the general population is derived being 1 mg/g creatinine in urine.

Comparison of data obtained from the German Environmental Specimen Bank samples with HBM-GV shows that exposure of children, adolescents and adults is well below the current guidance values both for NMP and NEP, even when considering the combined exposure to both substances, as well as DMF. Nevertheless, people can be exposed to a variety of reprotoxic substances which might add to the overall toxicity of the investigated compounds. HBM4EU findings shows that the survey participants were exposed to NMP, NEP and DMF. For NMP the highest exposure was found in young children, but exposure pathways were not possible to be revealed.

HBM4EU findings shows that the survey participants were exposed to NMP, NEP and DMF. For NMP the highest exposure was found in young children, but exposure pathways were not possible to be revealed.

Exposure to NEP was highest in adolescents and participants with low socio-economic status or migration background, which means that one or both parents were not born in Germany. Association to the usage of domestic chemicals and personal care products is determined showing elevated concentration of NEP and more frequent usage of floor cleaners, oven cleaners or fabric softeners as well as body wash/shower gels or shampoos.

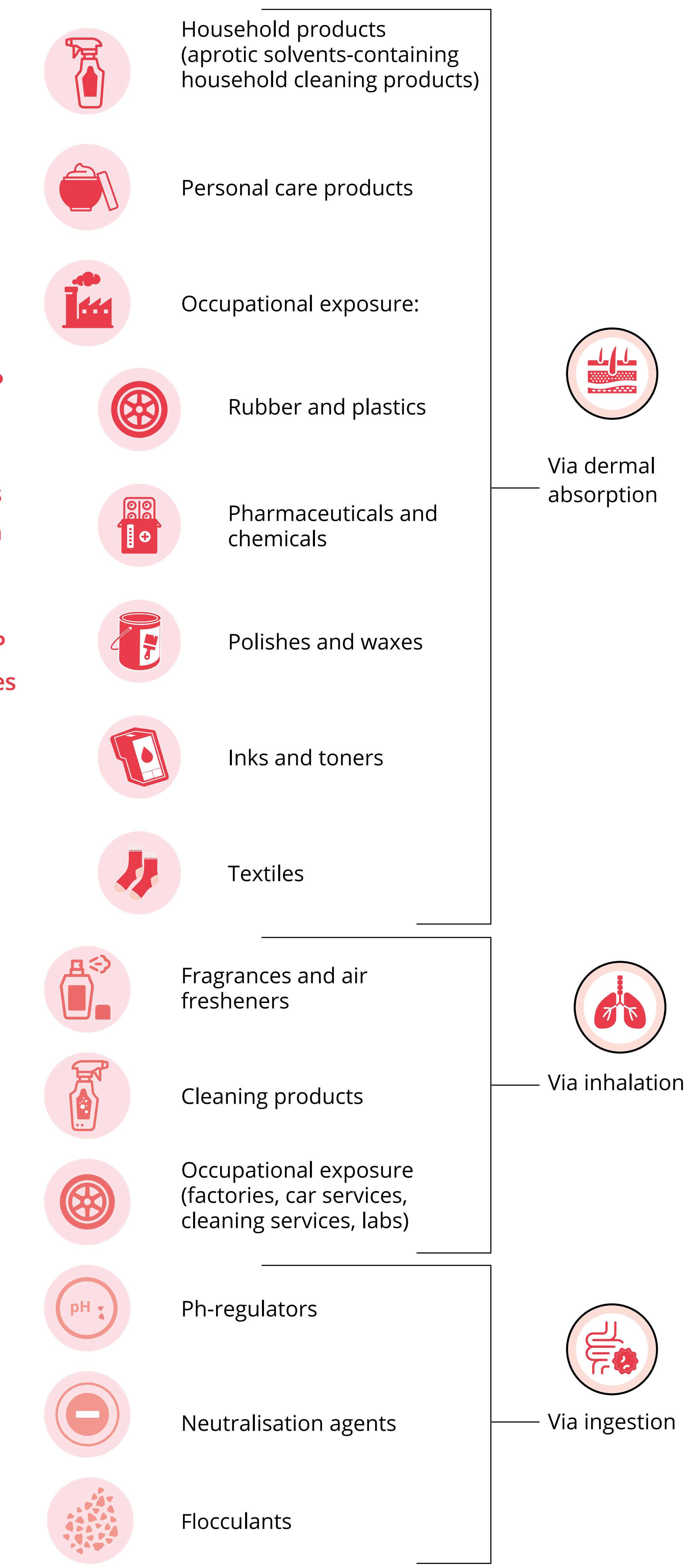
"As both NMP and NEP have been prohibited in cosmetics since 2020, my guess is that this association is not expected to be in the future" highlights Kadiķis. In the first study, the analysis of time trends of exposure to NMP and NEP, with samples from 23 years from 1991 until 2014, revealed a continuous exposure for both substances. As NEP is restricted under REACH since 2014 and NMP since 2018 with transitional period till 2020, the effectiveness of those regulatory measures cannot be assessed as of now.

For DMF, a decrease in concentration of more than 50% has been observed for the time span investigated (years 2000-2021) due to its prohibition in cosmetic products since 2010. The restriction of DMF under REACH in 2018 (with a transitional period till 2020) could lead to similar results.

The exposure data for the European general population is scarce with regards to the four aprotic solvents in question. Monitoring these substances in the European population is therefore recommended in the future. Further populations should be investigated to broaden the database on exposure to these four aprotic solvents, including susceptible subpopulations such as pregnant women. The sources of the aprotic solvents need to be further investigated and linked to environmental monitoring as well as to indoor air monitoring in dwellings.

Main achievements

- Exposure data from NMP and NEP metabolites measured in more than 2100 urine samples of children and adolescents
- The health-based human biomonitoring guidance values (HBM-GV) for the general population were derived for NMP and NEP
- Determinant of exposures to aprotic solvents identified



Scientific achievements

As a project designed to answer relevant policy questions concerning chemicals, HBM4EU had to overcome numerous limitations in terms of data availability, comparability etc. in order to provide solid scientific knowledge. An important part of the project was devoted to deal with the research of innovative methods to determine the relationship between exposure and health. For instance, the increased availability of exposure and effect biomarkers is helping HBM to become an even more valuable tool to investigate associations between internal exposures and health outcomes. From predictive models to much-needed data harmonization, the project's success is represented by not only the number of peer reviewed publications but also by its contribution to advancing human biomonitoring as a field.

Harmonised approaches

Harmonization in human biomonitoring (HBM) studies is essential to guarantee the validity of the results and must be applied in all the stages of the HBM studies. The first step is to set a common design, including the target population and substances as well as the biomarkers or the statistical plan. In the pre-analytical phase, it is necessary to define the standard operating procedures (SOPs) for recruitment, sampling, use the same materials, sampling time, etc. The analytical phase is critical and here the application of rigorous quality control measures is mandatory to ensure comparability of results among different laboratories. Finally, a harmonised data set minimises errors during the statistical analysis. In conclusion, harmonisation is necessary to ensure that observed differences in exposure levels to chemicals do not cause variability in later stage of HBM studies. HBM4EU has developed strategies, guideline documents and methods to harmonise HBM across the EU, also implementing a full quality assurance quality control (QA/QC) programme to improve comparability of HBM data and their use for policy while building the first HBM Laboratory Network.

Sampling

HBM4EU developed guidelines on how to run human biomonitoring studies for the general population and for workers. This included Standard Operating Procedures (SOPs) for recruiting participants, undertaking fieldwork, taking samples from participants and exchanging samples for analysis. Recommendations for handling bio-banked human samples, to ensure sample quality and stability have also been developed. Communication materials targeting different age groups explaining the project's study objectives to participants, requesting their consent for use of their personal data and describing the sampling process and follow up have been designed too Questionnaires for survey participants for each HBM4EU's priority substance group, exploring the different dimensions of lifestyle and behaviour that may influence chemical exposure have been developed. The HBM4EU online library includes SOPs for study design, recruitment of participants, collection and handling of biological samples, and chemical analysis and quality assurance. which can all be used by other researchers worldwide.

Adverse Outcome Pathways (AOPs)

What are the health risks associated with chemicals exposure? To address this question, toxicological research increasingly relies on non-animal-based new approach methodologies (NAMs), such as predictions based on structure or cellular assays, for financial, efficacy, and ethical reasons. Adverse Outcome Pathways (AOPs) link NAMs to hazards by describing how molecular perturbations lead to adverse effects. Within HBM4EU, AOPs were very helpful to make the most out of limited toxicological data on substitute chemicals such as flame retardants or bisphenols. AOPs also provided biological rationale for the exposure-health (or effects biomarkers) associations reported in human studies including links between bisphenols and neurodevelopmental disruptions or phthalates and reproduction toxicity. In turn, HBM4EU contributed to enhance AOPs and their use in chemical regulation by drafting new AOPs, developing the AOP-helpFinder, a web tool for comprehensive analysis of the literature to support adverse outcome pathways development and fostering communication between AOP developers and users.

From HBM to exposure (PBTK model)

Integrated exposure models for most of the HBM4EU's priority substances were developed, allowing us to assimilate the HBM data available within the HBM4EU consortium, including the Aligned studies). This way, the HBM data have been translated into intake levels of the EU population, while these intake levels have also been compared to the existing regulatory thresholds, delivering risk estimates. Additional work has been carried out to identify mixture interactions at the level of metabolism for phthalates and bisphenols, further verifying that the effect of metabolic interaction is important at exposure levels 3-4 orders of magnitude higher than the ones considered representative of the general population. Finally, beyond the priority substances, a PBPK model has been developed for copper, allowing the interpretation of biomonitored levels into differences in intake levels associated with both dietary and occupational exposure.

Method development

Analytical method development is a continuous process depending on target analytes, matrices, equipment, sensitivity demands and regulatory environment, just to name a few. HBM4EU supported participating laboratories in adapting their methods to the needs of HBM4EU. The creation of the first HBM Laboratory Network proved successful in guiding methodological advances and cumulated in the extraordinary success rates in the quality assurance exercises and the measurement campaign of HBM4EU. Specifically, we developed a new multi-method for plasticizers, including missing biomarkers for EU-regulated, reprotoxic phthalates such as DMEP, Di/nPeP, Di/nHexP and DHNUP. This method is now available for use in follow-up HBM projects to cover all EU-regulated phthalates. Additionally, we guided method developments to measure total mercury in dried blood spots (DBS) and for the analysis of Chromium (VI) in exhaled breath condensates (EBC).

Biomarkers of effect

A specific goal within HBM4EU was the implementation of biomarkers of effect to complement data provided by exposure biomarkers. Biomarkers of effect are defined as quantifiable biological changes in an organism that, depending on the magnitude, can identify or predict the development of a given disease.

In human biomonitoring studies, these biological changes also provide information on how the body responds to chemical compounds. In addition, biomarkers of effect inform on the health-disease status of the exposed subject improving the causal relationships between chemical exposures and possible harmful effects to humans.

HBM4EU has identified and prioritized novel biochemical and molecular markers, as is the case of the brain-derived neurotrophic factor (BDNF). BDNF has been related with both exposure to the plastic component bisphenol A (BPA) and behavioral problems among boys, supporting the biological plausibility of the relationships between BPA exposure and neuroconductual disorders.

Biomarkers of effect detect early changes occurring before the development of a given adverse effect, and therefore they may allow the implementation of effective preventive interventions, and the identification of susceptible individuals at higher risk from chemical exposures.

Suspect and non-targeted screening

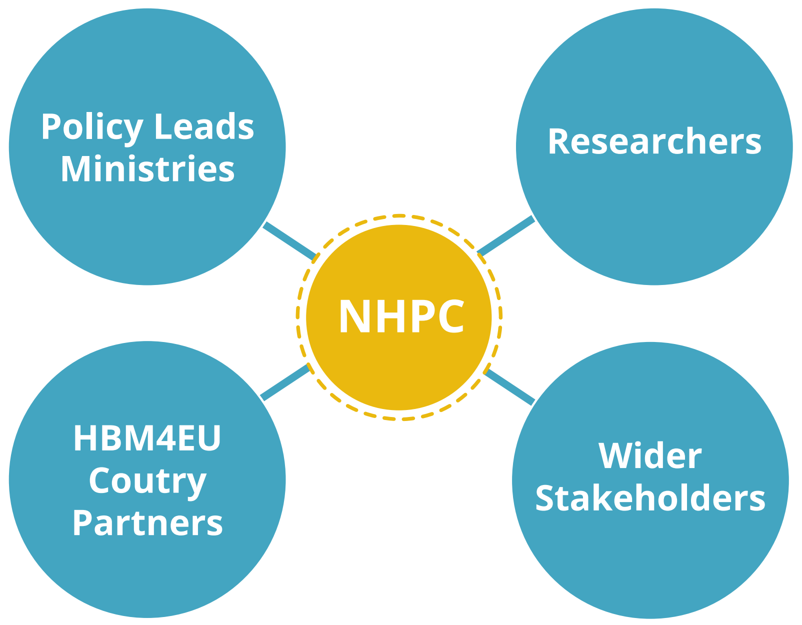
An ultimate challenge is the detection of markers not yet known to be present in a sample, including unknown chemicals. For this last category of markers of exposure, non-targeted screening (NTS) approaches can be employed, aiming to reveal chemicals of exposure and/or toxicological concern without any prior information.

To identify chemicals of emerging concern HBM4EU's researchers developed the first proof-of-concept illustrating the capabilities of non-targeted screening of halogenated markers of exposure to reveal new markers in human samples that were not initially foreseen and that are likely to be new emerging compounds. This suspect list was coupled to reference spectrometric data collected and/or newly generated for a range of chemicals to establish a new database for suspect screening of markers of chemical exposure. The wide screening of urinary pesticide-related markers (few thousands) is one particular application of these approaches that was developed in the frame of HBM4EU, more than more than 3000 samples were analysed and detected several hundreds of exposure markers. Overall, the basis of an EU network with harmonized competencies in the field of SS/NTS has been built under HBM4EU, as well as developed and conducted several proof-of-concept studies illustrating the usefulness of these approaches.

The National Hubs - the heart of HBM4EU

A hub can be defined as 'the effective centre of an activity'. One of the unique features of HBM4EU are the National Hubs not found in other European projects. At the conception of HBM4EU the NHs were not very well defined and indeed their role was unclear. However, as the first and second year progressed it was evident that the NHs are 'the effective centre of an activity' - the beating heart of HBM4EU. The role of the NHs evolved and became multifaceted. Fundamentally, they act as a two-way communication route bringing national data, needs and expertise and distributing the outputs of the project to national experts and stakeholders.

The structure and players in each hub were not prescribed, as a minimum they included the partners in HBM4EU. They could have included other research partners with an interest in the work of HBM4EU. Ministries and policy makers plus funding bodies, if included, would ensure a level of political buy-in. Wider stakeholders may have been invited - these could be industry representatives, Non-Governmental Organisations, and associations with an interest in environmental health issues related to chemical exposure. Each hub had a hard-working National Hub Contact Point (NHCP).



The NHCPs have facilitated, pushed, and battled to gather information on national studies - current, completed or planned - this was a great achievement in the first and second years. This information was the foundation for the selection of participants for the HBM4EU Aligned Studies.

There were numerous requests for information, enabled by the NHCPs, such as feeding national chemicals of concern into the 2nd and 3rd prioritisation rounds, evaluation of the HBM-Guidance values and identifying national laboratories to take part in the QA/QC activities. And many more!

How have national partners benefited from being part of the NH? This question was posed to the NHCPs.

The majority of NHCP stated that HBM4EU has had a very positive impact on national HBM efforts.

Of course, there is always room for improvements and the NHCPs commented that there is a need to create a better link between national policy makers and EU agencies. They want better communication of results and contemporaneous updates.

There is a need and willingness to keep these structures active both at a National and a European wide level. Four examples are given here of National Hubs: their activities and HBM Programmes. The advances we have made in HBM4EU should be built on and improved as we move forward into the Partnership for the Assessment of Risks from Chemicals. PARC will bring its own challenges, but the platform has been established.

The fields of PARC will allow us to bring together more players and start to integrate environmental and human health activities- the National Hubs will be even more important in the future.

- Fostered national collaboration.
- Strongly welcomed initiative has positioned HBM on the political agenda.
- NH meetings were very useful to learn from each other.
- Triggered greater dialogue - resulted in greater support.
- Comprehensive discussion and evaluation of HBM results at a national level.
- Connections and collaborations.
- Collaboration between scientists and policy makers.
- Awareness raising among citizens.

Dorothy Ubong and Ovnair Sepai
National Hub Coordinators for HBM4EU

Summary of the National Hubs activities under HBM4EU:

FRANCE:

The French National Hub includes representatives of the ministries of health, environment, research and education and scientists, as well as stakeholders. We meet four times per year to coordinate HBM activities and follow up the HBM4EU initiative, discuss contributions to the various requests from the different WPs, update partners and NH members on the decisions and main outcomes of the MB meetings and provide advice to the representatives of our ministries on HBM4EU-related issues for decision-making.

We have also organized one-day meetings with outreach to a larger number of participants. The first one held in Paris in early December 2018, was found to be extremely informative and useful by the participants. It also provided a valuable opportunity for an exchange of good practice amongst different HBM4EU National Hubs.

At the second meeting, last December 2021, we reviewed the impressive results obtained by all French partners during the five preceding years as part of the HBM4EU research effort. A specific session was devoted to the next European Partnership for the Assessment of Risk from Chemicals (PARC) and its broader Hub which will be coordinated by Santé Publique France.

Two important outcomes could be highlighted:

- HBM4EU will inspire the design and management of the next population surveys within the French human biomonitoring programme coordinated by Santé Publique France, in particular by implementing exposure and health research activities in parallel with the assessment of internal exposure.
- The French National Hub provides the arena for exchanges of knowledge, best practices and for developing joint research. As an example, discussions about analytical methods within the hub led to the implementation of an infrastructure exploring the chemical exposome. This also led to the contribution of France to the European research infrastructure for environmental exposure assessment, EIRENE ESFRI.

Robert Barouki & Elena Tarroja

SWEDEN:

The national hub in Sweden is represented by key authorities which are users of HBM-data on a policy level; the Swedish Environmental Protection Agency, the Swedish Chemicals Agency, the Public Health Agency of Sweden, the National Food Agency, the National Board of Housing, Building and Planning, the Swedish Work Environment Authority and our linked third parties within HBM4EU. The Swedish national hub has had meetings once or twice a year since the start of HBM4EU. During the meetings, the progress of the Swedish activities within HBM4EU has been discussed and relevant information on the overall progress and decisions within HBM4EU have been presented. The national hub has also contributed to the work regarding the nominations for the priority substances lists and to the policy paper on HBM data and policy development. The national hub has also been an important channel for spreading information and results from HBM4EU as well as helping with the distribution of e.g. the citizen survey to the general population. Several of the hub members are also part of the advisory board for our national HBM-program which is led by the Swedish Environmental Protection Agency. The national hub is also included in the planning of the European Partnership for the Assessment of Risk from Chemicals (PARC) on a national level. At the next national HBM conference in September 2022, we are planning to have a final presentation of HBM4EU on a national level. The presentation will focus on the main achievements of HBM4EU and what they mean in a Swedish context. The target group will be municipalities, county administrative boards and relevant national authorities as well as the academia. The sustainability and development of our national HBM-program will also be discussed.

Karin Norström and Siiri Latvala

ISRAEL:

The National Hub in Israel includes government, non-government, agencies/entities/organizations and academics related to the field of HBM. The main activity of the hub is to increase awareness about HBM and its uses in research and policy, to keep members informed about HBM4EU activities and to disseminate information about the National HBM Program in Israel. The main form of communication are periodic newsletters and hub meetings.

The hub was instrumental in encouraging researchers to share data with HBM4EU. Metadata on HBM studies from Israel on pesticides, brominated flame retardants and phthalates are now included in the IPCHEM website. By sharing material on IPCHEM and the HBM4EU dashboard with researchers, we hoped to demonstrate the advantages of making data more visible and increase motivation in the future to share HBM data.

As the National HBM program in Israel began in 2020, there was an effort to engage stakeholders during the planning process of the study. By engaging relevant stakeholders early in the process, we hoped to encourage use of the data for policy decisions. Our national hub also provided valuable insight on national nominations for substances to be the focus of HBM activities under the PARC project.

One of the unique characteristics in Israel is the high level of reliance on desalinated drinking water. For this reason, Israel has included nutritional biomarkers (including iodine) in the National HBM program. One of the challenges of the hub was engaging nutritionists and demonstrating the use of a national HBM program as a platform for collecting data on population nutritional status.

The national hub was an excellent platform for sharing HBM4EU communication materials, including factsheets and videos, with stakeholders. As public communication is an ongoing challenge, these communication materials were key to highlighting the importance of HBM to government and non-governmental organizations.

Tamar Berman

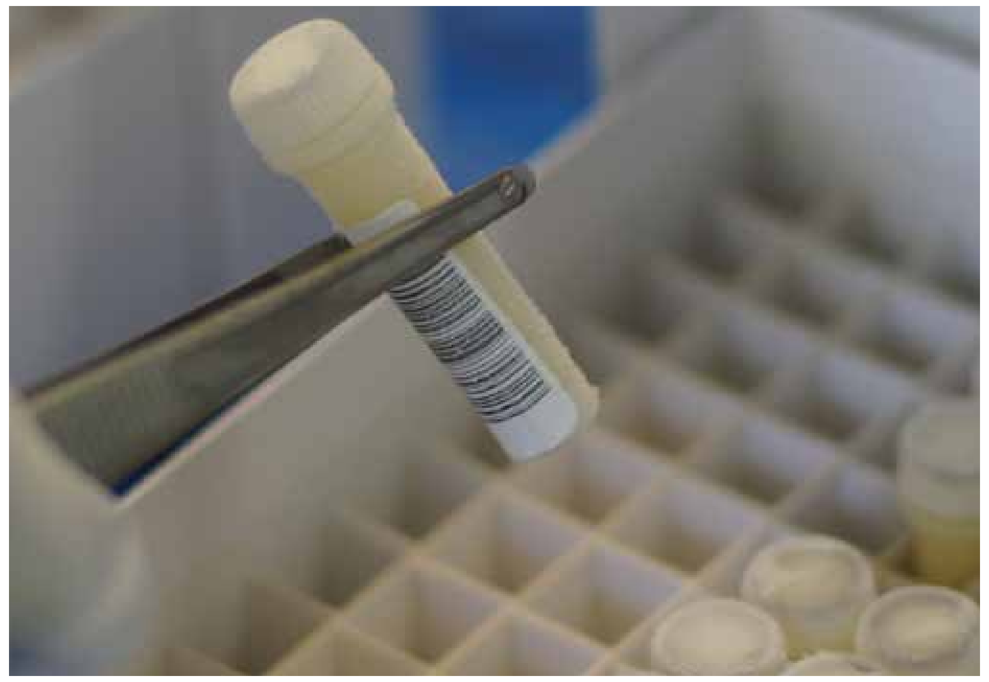
SLOVENIA:

Slovenian National Hub consists of the following institutions: EPA, Food and Veterinary Administration, Research Agency, National Public Health Institute, National Laboratory for Health, Environment and Food, the Chemicals Office of the Republic of Slovenia (CORS), Clinical Occupational Medicine Institute, National Biology Institute and Jožef Stefan Institute. There is constant communication and cooperation between ministries via intersectoral conferences and round table discussions on environmental health and chemicals.

Joint European efforts and the actual needs in Slovenia led to the first national HBM program in Slovenia, which took place from 2008 to 2015. This program was harmonized with the approaches defined at EU level and therefore, the data obtained are comparable to those of many other countries. A second national HBM program started at the end of 2018 which is expected to last until the end of 2023. The programme is to analyse the presence of chemicals for which new analytical methods are developed. New samples are still not collected as planned due to the Covid-19 pandemic.

Our participation in HBM4EU provided avenues to co-create new knowledge needed to raise awareness of the safe handling of chemicals and providing solid evidence of actual exposure to chemicals and their potential health effects. The data from HBM4EU will be used widely according to the national HBM Programme, which includes the public communication plan e.g. leaflets, videos, factsheets and presentations at different occasions to the wider public (experts, general public, policy makers).

Lijana Kononenko



Citizens are eager to learn about their chemical body burden

Chemical safety is a matter of public concern. One in four citizens is "very concerned" about exposure to chemicals in their daily life. They can choose not to purchase products containing hazardous chemicals and can drive substitution by the competent authorities. Citizens also vote and can choose to back parties that promise greater protection for their health and the environment.

The inclusion of citizen perspectives and perceptions was part of a systematic, transparent, and participatory strategy within HBM4EU. To gather in-depth understanding on citizen's perceptions of chemical exposure, trust and concerns on human biomonitoring initiatives, HBM4EU ran focus groups hosted in 11 countries including Austria, Portugal, Ireland, the UK, Cyprus, Hungary, the Netherlands, Denmark, Isreal, North Macedonia and Latvia.

The results of the focus groups revealed a general concern regarding chemical exposure on citizens' health and their daily lives. "Citizens have an interest in understanding their own chemical body burdens" reports Dr Joana Lobo Vicente, who works at the European Environment Agency. "Participants expressed their concerns 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, citizens were aware of potential exposure to chemicals in the environment and how they may enter our bodies.

Although the knowledge on human biomonitoring and chemical exposure, varied between participants and different focus groups, citizens 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 were able to make 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" says Lobo. Cocktail effect of chemical mixtures, a major challenge in the chemical safety field and thoroughly studied under HBM4EU, is also a concern for citizens. Participants agreed that mixtures may influence health, and they suggested that they should be addressed in future human biomonitoring studies.

Regarding the adverse health problems related to chemicals, participants referred to the impact of chemical exposure in both short and long term. They identified specific health outcomes like asthma, eczema, allergy, hypersensitivity, cancer, chronic obstructive pulmonary disease and diabetes. For instance, concerning the carcinogenicity of chemicals in the environment, workplace and consumer products, the outcome of the focus group discussions confirmed that this idea is firmly set as a concern in the public's mind, as illustrated by their references to chemical substances contributing to a higher incidence of 'well-known' diseases, such as cancer. Personal or family experiences were stressed as especially important aspects in raising high concern. Participants made links of cancer diagnoses with occupational exposures and hazardous chemicals in food, drinking water, and indoor and outdoor air; and specific mentions to air pollutants, pesticides, heavy metals, organic solvents, and other families of chemicals that include substances with known carcinogenicity.

Throughout the focus groups held, the citizens showed a high interest in having access to more targeted information. In other words, "they are eager to learn", reports the expert. This would lead to empowerment in citizens in general and even encourage (individual) behavioural changes. In fact, almost all participants reported that they were willing to change their existing habits at some extent if they would receive more information on the levels of exposure to chemicals, availability of healthier products, etc. However, some differences were observed between the male and female participants as well as within age groups. Younger female participants reported that they were open to new information, to read more on this topic as well as they were willing to dedicate extra time, energy, and money to change their lifestyle.

Another key aspect highlighted by the participants is related to communication. Some highlighted the unintelligibility of the information communicated by science 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. There was a need to provide information, in a context dependent manner that would help protect against misinformation and "fake news. "The need to provide information and to communicate more efficiently has been recognised by the HBM4EU. Therefore, we have actively addressed this gap by producing citizen-targeted information, such as videos on human biomonitoring and chemical exposure and factsheets and infographics on chemicals" explains Lobo. She adds "throughout all focus groups, it became visible the better citizens are informed about human biomonitoring (HBM), and HBM studies as such, their interest and willingness to articulate on this topic increased". Science was viewed as the cornerstone to preventing chemical exposure. Furthermore, focus group's participants regarded science as the cornerstone to preventing chemical exposure, allowing scientific information to better translate into policies and effective protection of human health.

As part of the outreach to citizens' activity, citizens surveys were also conducted in countries that were hosting the focus groups. Additionally, a European citizen online survey, which run from October 2020 until February 2021, was implemented and answered by 5391 citizens. It also included an extra section on indoor chemical exposure due to COVID-19. Eighty-two per cent of the total responses came from the Netherlands, Portugal, Latvia, Spain, Hungary, Denmark, Sweden and Republic of North Macedonia, followed by Norway, Germany and Cyprus with more than 100 replies.

The three issues that most concern the citizens in terms of chemical exposure are industrial emissions and pollution, followed by pesticides in food and in the environment. Respondents believe the most dangerous ways of being exposed to a chemical substance is via a psychoactive substance and environment, followed by food, drinking water, pharmaceuticals and household products.

As the survey took place with the months after the first wave of the COVID-19 pandemic, not surprisingly, slightly more than half of the responders think "that exposure from chemicals due to use of disinfection agents and use of personal protective equipment increased during the pandemic". "It would be interesting to assess if citizens are aware about possible sources of exposure to chemicals in home settings and from household cleaning agents, which presumably had increased use due to the pandemic, explains Joana Lobo".

When asked on how to reduce exposure to dangerous chemical substances, most respondents think that "improving pollution controls to industrial activities and imported products, as well as ensuring better control of existing chemicals regulation compliance as the most relevant of the proposed measures for exposure reduction". Near 60 % of the respondents considered improving our understanding of human exposure to chemicals and its consequences on health as well as informing the public on the results also necessary to reduce exposure to dangerous chemicals.

European citizens were supportive of the use of HBM as an important and reliable tool for chemical safety, that could be used not only at EU level, but also nationally coordinated. Concerning the importance that HBM studies may have, the one sentence most citizens 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.

HBM4EU also has a particular take on building trust with people who "give of their bodies in the interest of science", as we relied on people to collect human biomonitoring data. The success of the human biomonitoring surveys ultimately depends on their willingness to volunteer their time, biological samples like hair, urine and blood, and personal information, so by building trusted relationships with citizens, they are more likely to participate in sampling studies in the interest of science.

To determine the level of trust citizens have in our HBM4EU work, a questionnaire to the principal investigators was sent aiming to find out how survey participants were encouraged to take part in the HBM4EU Aligned studies. Principal investigators were invited to answer three questions: i) How does your study recruit participants?, ii) How does your study gain the trust of the participants? and iii) How do you measure the level of trust? Communicate effectively with survey participants to ensure their understanding of broader project objectives and their own role in HBM4EU research, follow up by explaining individual results to participants in a manner that is sensitive to their needs and technical understanding, including the provision of advice on reducing exposure, was key to the success of recruitment.

Ninja Reineke

Head of Science at CHEM Trust, holds a degree in chemistry and a PhD in the analysis of marine pollutants.

She previously worked for WWF on EU chemicals policy for almost 10 years before joining CHEM Trust in 2013. Her main work areas are EU regulations on endocrine disrupters and persistent chemicals. She also works at the science-policy interface to ensure the most up to date science is reflected in regulation, e.g. on combination effects and human biomonitoring studies. Since December 2018 she is the Chair of the Management Board of CHEM Trust Europe, based in Hamburg, Germany.

CHEM Trust is a charity that works at European, UK, German and International levels to prevent synthetic chemicals from causing long-term damage to wildlife or humans, by ensuring that chemicals which cause such harm are substituted with safer alternatives. CHEM Trust is also a member of the HBM4EU Stakeholder Forum.

CHEM Trust is protecting people and the environment from harmful chemicals. Which are main areas CHEM Trust is taking action on?

CHEM Trust's focus is on the identification of, and action on, endocrine disrupting chemicals. Complementary areas of work include advocating for better protection from chemicals with other harmful properties, such as persistent chemicals, and addressing hazardous chemicals in food contact materials. We also work on key chemical issues, such as mixture effects.

Bisphenols, phthalates, PFAS, brominated flame retardants, etc. are EDCs - chemicals that interfere with the hormonal system and can, for example, impact development and reproduction - that are studied under HBM4EU. How will you use that new data coming from HBM4EU?

In our view, these groups are a priority of HBM4EU, because so far only a few of the problematic substances from each group have been restricted, while the others are still widely used in daily consumer products. We shouldn't forget that they were never meant to be found in people and wildlife in the first place.

CHEM Trust regularly highlights new results and insights from research findings, using new data in our communication to the public as well as in our contributions to current policy discussions. The importance of HBM4EU data is that it shows that these chemicals are present in peoples' bodies. It demonstrates that it's an issue we are facing in real life and that it affects people and can contribute to health impacts. To lower people's exposure, there is a need for more awareness raising and regulatory action.

What do you think is the added value of the HBM4EU project? What benefits is bringing to people's life?

The HBM4EU project has significantly advanced method development, harmonization of lab procedures, capacity building and increased quality assurance as well as cooperation among all relevant institutions in the field. It also confirmed that several chemicals are present in humans simultaneously, increasing concerns due to potential combination effects. It will be important to ensure the continuation of a strong EU human biomonitoring component in the follow-up EU research project, PARC. Measuring the trends of the body burden of the general population is an important tool to assess whether legal restrictions, authorisation and other risk management measures have the desired effect, as well as to flag new concerns.

The best benefit for people would be for HBM4EU data, to be used for more precautionary decision-making and to speed up the regulation of hazardous chemicals. To avoid further contamination of our bodies in the future, we cannot wait to measure all substances in people. By then it's usually too late and you cannot get the chemicals back.

In your view, what should Brussels and its EU's regulatory system do to protect citizens against EDCs?

It currently takes decades to identify and control harmful substances, with the recent re-assessment of BPA being a case in point. The revisions of REACH and CLP must accelerate identification of substances of concern and apply more group restrictions in a precautionary manner.

The systematic underestimation of mixture effects, resulting from the combined exposures to many substances from multiple sources, must also be addressed. Human biomonitoring data can provide some insights here, even if the number of chemicals analysed will always be limited due to lack of resources or when methods are not available.

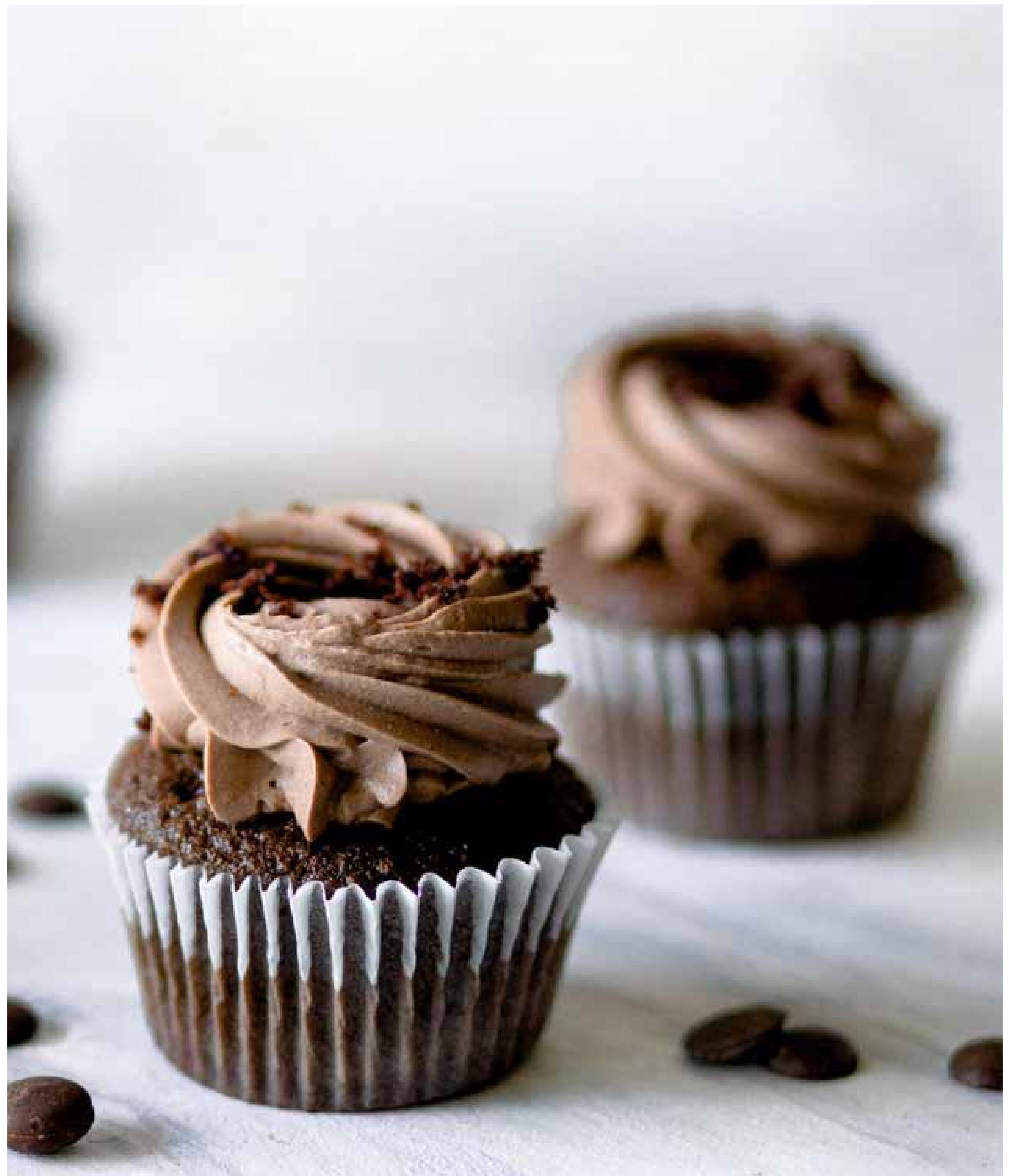
It is also important to keep in mind that while human biomonitoring data can flag relevant trends or find new substances of concern it should never become a prerequisite for action. We know that exposure starts in the womb, and we cannot wait for biomonitoring data before taking action.

How to ensure that the most up-to-date science is reflected in regulation?

We need research that can answer regulatory needs and the HBM4EU project has made some good steps in that direction. In the coming months, it will be important to draw on the main lessons learnt from HBM4EU and adapt future scientific work accordingly. In general, a stronger involvement of academic science to feed into ongoing consultation processes for new policy development would also be desirable.

Do you think that the European Commission roadmap for a Chemicals Strategy (CCS) for Sustainability is a real game changer?

The CSS has the potential to set Europe on a new path for better protection from toxic chemicals. It contains many important elements including action on the identification and control of EDCs and taking account of mixture effects, and provides a real opportunity to solve the problem of continued use of the most hazardous chemicals. The Commission has made a good start in implementing this strategy, but it is vital that the regulatory processes set out by the Strategy are not subject to delays, and that the ambitions are not weakened by some parts of industry.



Jean-Philippe Antignanc

One component of HBM4EU aims at the development and implementation of large-scale suspect (SS) and non-targeted (NTS) screening methods, in combination with effect-directed analyses (EDA), aiming at detecting markers of internal chemical exposure for HBM, environmental health studies and support to risk assessment purposes.

JP Antignac is a scientist belonging to the National Research Institute for Agriculture, Food and Environment (INRAE), head deputy of the LABERCA research Unit (Nantes, France), and member of expert working groups for the French Food Safety Agency (ANSES). His area of expertise is the characterisation of human internal exposure to organic chemical contaminants, in particular endocrine-disrupting chemicals, for risk assessment and environmental health purposes. He is involved in several projects studying the relation between this chemical exposome and human health and leads the HBM4EU WP16 on emerging chemicals. He (co)authored more than 170 publications and his current h-index is 44.

What are chemicals of emerging concern (CECs)?

Chemicals of Emerging Concern (CECs) include a very wide group of chemicals that are suspected to be responsible for adverse effects on health, but for which very limited information is available.

Despite increasing societal, scientific and policy concerns, there is no consensus about the definition of CECs nor the terminology. This “substance class” does not refer to a classification rationale, such as a common mode of action, property, intended use, or regulatory status. At HBM4EU, CECs were understood as both new chemicals that have only recently been detected, compounds that were known, but their potential health effects were not fully understood but concerns have recently increased, for example because the chemical is being used in a new way or a new route of exposure have been identified, or ‘old’ contaminants with new information arising regarding their risks.

Suspect (SS) and non-targeted screening (NTS) approaches offer new capabilities for capturing CECs in human samples. What are those techniques?

These novel holistic approaches have the promising capability to detect rapid chemical profiling, document the extent of human chemical exposure, generate new research hypotheses, and provide early warning support to policy. The suspect and non-targeted screening approaches, typically based on high-resolution mass spectrometry, generate information on the chemicals fingerprint present with a sample. These are very ambitious and promising techniques, although with certain limitations.

What is the difference between the two approaches?

“Suspects” are known compounds which are expected to be present in a sample. Suspect screening enables the detection of chemicals that are listed in chemical databases. It helps to better prioritize for further targeted developments. They are also used to characterize real-life complex mixtures and exposure trends by simultaneously generating exposure data for a wide range of markers from each individual sample.

Non-targeted screening aims to detect compounds present in a sample without the aid of a suspect list or other initial information prior to sample analysis. The ambition is then to identify potential unknown or new pollutants. This allows us to generate a new research hypothesis and contribute to an early warning system. Although highly challenging, this approach is the most promising strategy to advance our knowledge of the human chemical exposome and anticipate future health threats and related risk assessment.

What are the main challenges of using suspect and non-targeted screening approaches?

These up-and-coming methods are complex and require a highly technical methodological framework. One big challenge is capturing and simultaneously measuring a wide range of chemicals with various properties from samples. Another challenge is the resources needed for the advanced expert bioinformatics to handle and process the huge and complex datasets. Having harmonized and standardized protocols to better compare data is another challenge, while at the same time managing to keep the flexibility that this field of research requires.

One key activity under HBM4EU is the extended characterisation of internal exposure to pesticides in individuals from 5 European countries. What can you tell us about that?

HBM4EU has run a survey of human internal exposure to mixtures of pesticides across five countries: Hungary, Czech Republic, Spain, Latvia and the Netherlands. This survey, entitled SPECIMEn (Survey on PEstiCIde Mixtures in Europe), collected 2000 urine samples from adult-child pairs living either nearby (<250 m) or further away (>500 m) from agricultural fields (e.g. orchards),in two seasons. The survey was designed to assess combined exposure to multiple pesticides in hotspot and control areas using human biomonitoring.

Together with five laboratories, we developed a suspect screening method and applied it to these samples, capable of detecting multiple pesticide related markers (parent compounds and metabolites) in a single assay in a semi-quantitative way. Each participating laboratory analyzed samples originating from one country. In order to compare data amongst countries, the suspect screening approach was developed under harmonized conditions and consolidated QA/QC provisions.

Thanks to this survey, we will gain insight into the occurrence of extended exposure patterns of pesticide-biomarkers, differences across the countries participating in SPECIMEn, differences between two seasons (spraying season with active application, and non-spraying season with no active application) and/or location (living close to agricultural areas or not). The obtained results will also support mixture effect investigations and contribute to the prioritization of certain substances in terms of further exposure and risk assessment, and possibly to generating early warning information.

At this stage, all the 2000 human urine samples analyzed have been profiled, and we have identified a preliminary list of 45 exposure markers. We are still analyzing the data and we expect to detect hundreds of other exposure markers from various substances classes.

You have published a large number of peer reviewed publications during HBM4EU....

Yes, indeed, our work under HBM4EU resulted in 12 peer review publications, some of which are still undergoing the review process. These publications cover (1) the conceptual description of used approaches, (2) technical description of particular analytical aspects associated to SS/NTS/EDA (effect-directed-analysis) methodologies, and (3) a proof-of-concept demonstrating the potential of these approaches on the first outputs from human samples.

And what are some of the key findings?

We have built the basis of an EU network with harmonized competences in the field of SS/NTS, as well as developed and conducted several proof-of-concept studies illustrating the usefulness of these approaches. We have analyzed more than 3000 samples and detected several hundreds of exposure markers. This work also permitted us to identify several limitations linked to these approaches, in particular the bottleneck associated with the identification of exposure markers detected by the large-scale approaches, which impairs their implementation.

What is next?

There is so much work that still needs to be done. For instance, CECScreen database coupled with the MS reference library are strategic pieces of SS/NTS workflow and do require sustainable follow-up and resources for reinforced application and EU visibility. Aside from that, the next step would be the development of a computational framework for linking and exploiting the stored information in tandem with mass spectral libraries. Building a strong and dynamic consortium within scientific communities (e.g. within PARC) is another task. We can also extend our work conducted already during HBM4EU on the methodological harmonization and QA/QC, as this allows to increase data comparability. Finding the appropriate new resources to take maximal benefit from data generated under HBM4EU. Demonstrating the usefulness of SS/NTS for application in human biomonitoring studies on other types of biological matter than blood, plasma and urine would be worth assessing as well.

Supporting chemical safety for European citizens

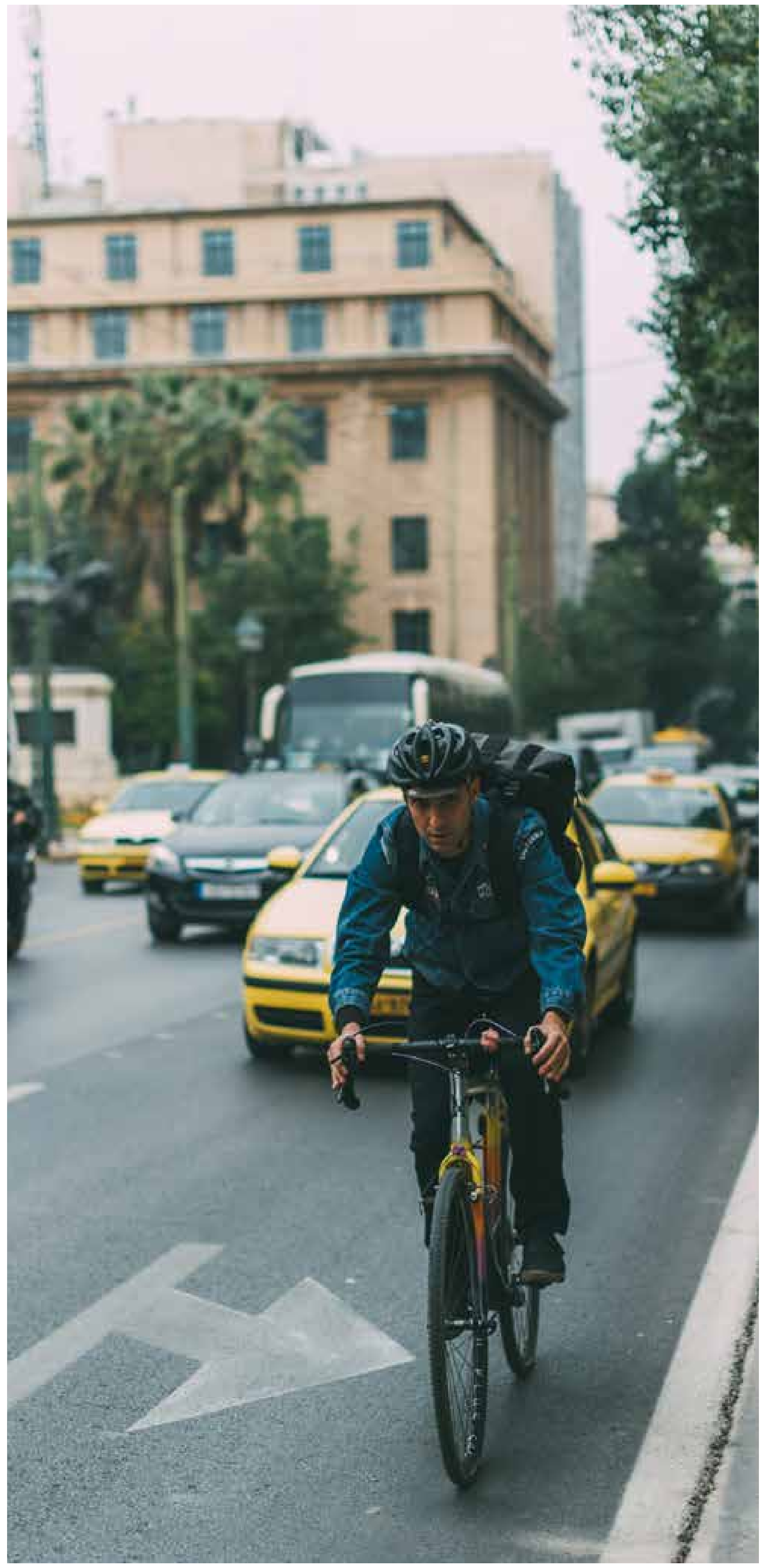
written by Hans Bruyninckx, European Environment Agency

In 2014, the European Environment Agency's **Scientific Committee** called for a European human biomonitoring programme to produce knowledge on the exposure of Europe's population to chemicals and resulting health effects - as a basis for improving chemical safety. Our colleagues from Directorate-General on Research and Innovation listened and in 2015 the call for a European Human Biomonitoring Initiative was published under Horizon 2020 - HBM4EU was born with the European Environment Agency as a partner in the consortium.

HBM4EU has created a network of scientific excellence across Europe, built on a foundation of existing human biomonitoring programmes and initiatives at national level, to make a whole greater than the parts. This **HBM Laboratory Network** has delivered coherent, robust results on chemical exposure and impacts on health in Europe to support policy making to improve chemical safety for citizens. HBM4EU has built up scientific capacities for human biomonitoring research across Europe that will continue to serve the public going forward.

With over 100,000 chemicals circulating in products on the European market, chemicals are now found in the bodies of men, women, and children across Europe. Human biomonitoring delivers a new type of **knowledge that resonates with citizens**, who contribute samples to learn how their own bodies have been polluted by society's use of chemicals. Responding to their concerns, HBM4EU has produced materials to guide citizens in how to change behaviours to minimize exposure to hazardous chemicals, in parallel to channelling evidence into regulatory processes.

The European Green Deal aims to protect the health and well-being of citizens from environment-related risks, through a just and inclusive transition. The European Environment Agency will be using HBM4EU knowledge to assess progress under several key strategies. 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. Under the Circular Economy Action Plan, implementing circularity creates new pathways through which humans can be exposed to hazardous chemicals in contaminated material flows. 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 borne by children, the elderly, persons with disabilities, and those living in poorer socio-economic conditions. Later in 2022, the European Environment Agency will deliver a first assessment on zero pollution using HBM4EU evidence to establish a baseline on population exposure to chemicals against which to measure progress.

The Chemical Strategy for Sustainability provides a genuinely progressive approach to managing chemical risks, through upstream measures to ban the most harmful chemicals and allow essential uses only. The **one substance, one assessment approach** 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 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 us 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**. Recognising the industry trend of substituting a banned chemical with another with similar properties through regrettable substitution, HBM4EU tackled chemicals in groups. **Grouping** is now advocated under the chemical strategy as a means of speeding up the risk management process, with a particular focus on per- and polyfluoroalkyl substances (PFAS). On **mixtures**, HBM4EU has delivered a wealth of data on human exposure to mixtures, as well as innovative tools. This will support a science-based derivation of the **Mixture Assessment Factor** proposed under the strategy.

Under the future Horizon Europe Partnership for the Assessment of Risks from Chemicals (PARC), the work will both continue and expand, now with the involvement of three EU agencies, the **European Environmental Agency**, the **European Chemicals Agency**, and the **European Food Safety Authority**, to cement the link to implementation of the Chemical Strategy for Sustainability. For the European Environment Agency, it is essential that PARC maintain the flow of data on priority chemicals to allow us to assess trends in population exposure over time at European level. This will feed into ongoing work at the Agency to assess progress against objectives in the Zero Pollution Action Plan and the Chemical Strategy for Sustainability, as well as 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 in Europe and establish European industry as a global pioneer.

Looking forward, Europe must establish a permanent system for human biomonitoring that is embedded in EU legislation and delivers sustained flow of evidence against which to assess chemical safety and help protect citizens. The European Environment Agency will remain engaged and stands ready to play a role as a key knowledge broker in the European policy arena.

HBM4EU has promoted the adoption of best practices in human biomonitoring activities across Europe

Training was organised to deliver an effective training programme targeted at the needs of the HBM4EU community. The aim was to build capacities and promote a coordinated approach to HBM across Europe. Many participants new to the project felt that this was a good way to learn about ongoing activities in the project. Towards the end webinars and workshops were organised also involving participants from outside HBM4EU.

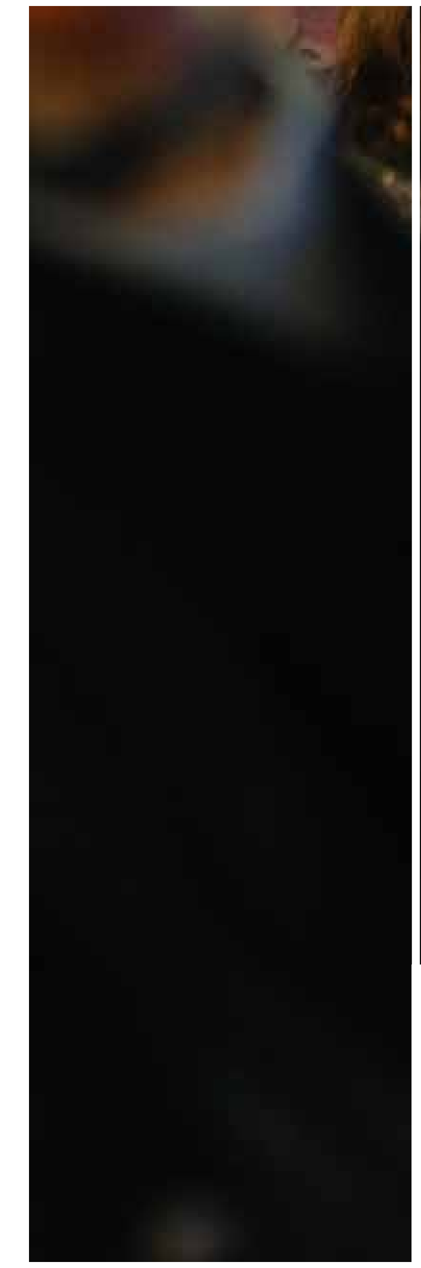
Most of the training was provided in four HBM4EU Training Schools that were held in Ljubljana (Slovenia), Nijmegen (The Netherlands) and Brno (Czech Republic). The last edition scheduled for May 2020 in Austria was converted into virtual training format because of the COVID-19 pandemic. In 2021 training was continued but not in a training school format. During the online trainings the added value of social interaction was missed, and many participants acknowledged that the training events also helped to build a HBM4EU Science Network. "We have generated added value in terms of increased scientific excellence, through an exchange of expertise, including training to promote the use of common methods and protocols. In this way, the HBM4EU promoted the adoption of best practice in HBM activities across Europe" highlights Dr Paul Scheepers, HBM4EU training coordinator and researcher at the Radboud Institute for Health Sciences, Radboudumc.

The HBM4EU training programme included both basic courses, targeted courses, workshops, and train-the-trainer sessions, as well as capacity building for PhD students. The programme was developed based on a survey of needs of HBM4EU partners, matched against available training capacities and was intended to serve the HBM4EU partners, although certain trainings were open to external participants.

Most of the content was provided from scientists working directly within HBM4EU work packages and involved experts from the HBM4EU community. Occasionally also speakers from outside of HBM4EU were invited such as for training on IPCHEM.

- 4 HBM4EU Training Schools provided, in Ljubljana – Slovenia 2018, Nijmegen - The Netherlands 2018 and Brno - Czech Republic 2019 and online training school in 2020 due to COVID-19
- 1 virtual training provided in 2021
- 2 basic and 24 advanced courses organised
- 6 poster sessions with 40 posters in total, organised to stimulate early starting researchers to present their HBM4EU related research projects
- Training materials made available for public access through the online library on the HBM4EU website

#Data management, **#HBM in occupational health**, #analytical methods, #PBKS in human biomonitoring, #risk assessment, **#HBM based indicators**, #risk communication, **#HBM guidance values**, #interpretation of and access to HBM data, #Adverse Outcome Pathways (AOPs), #mycotoxins and pesticides biomarker, #mixtures, #integrated exposure modelling, **#Information Platform for Chemical Monitoring**, #determination of phthalate in urine, **#HBM4EU aligned studies**, #occupational toxicology, #ethics.



1st Training School

Number of participants
36

Number of nationalities represented
21

Total number of person days of training[4]
125

Total number of person-trainings[4]
158

2nd Training School

Number of participants
79

Number of nationalities represented
32

Total number of person days of training[4]
177

Total number of person-trainings[4]
211

3rd Training School

Number of participants
37

Number of nationalities represented
14

Total number of person days of training[4]
74

Total number of person-trainings[4]
185

4th Training School

Number of participants
95

Number of nationalities represented
21

Total number of person days of training[4]
95

Total number of person-trainings[4]
134

5th Virtual Training

Number of participants
269

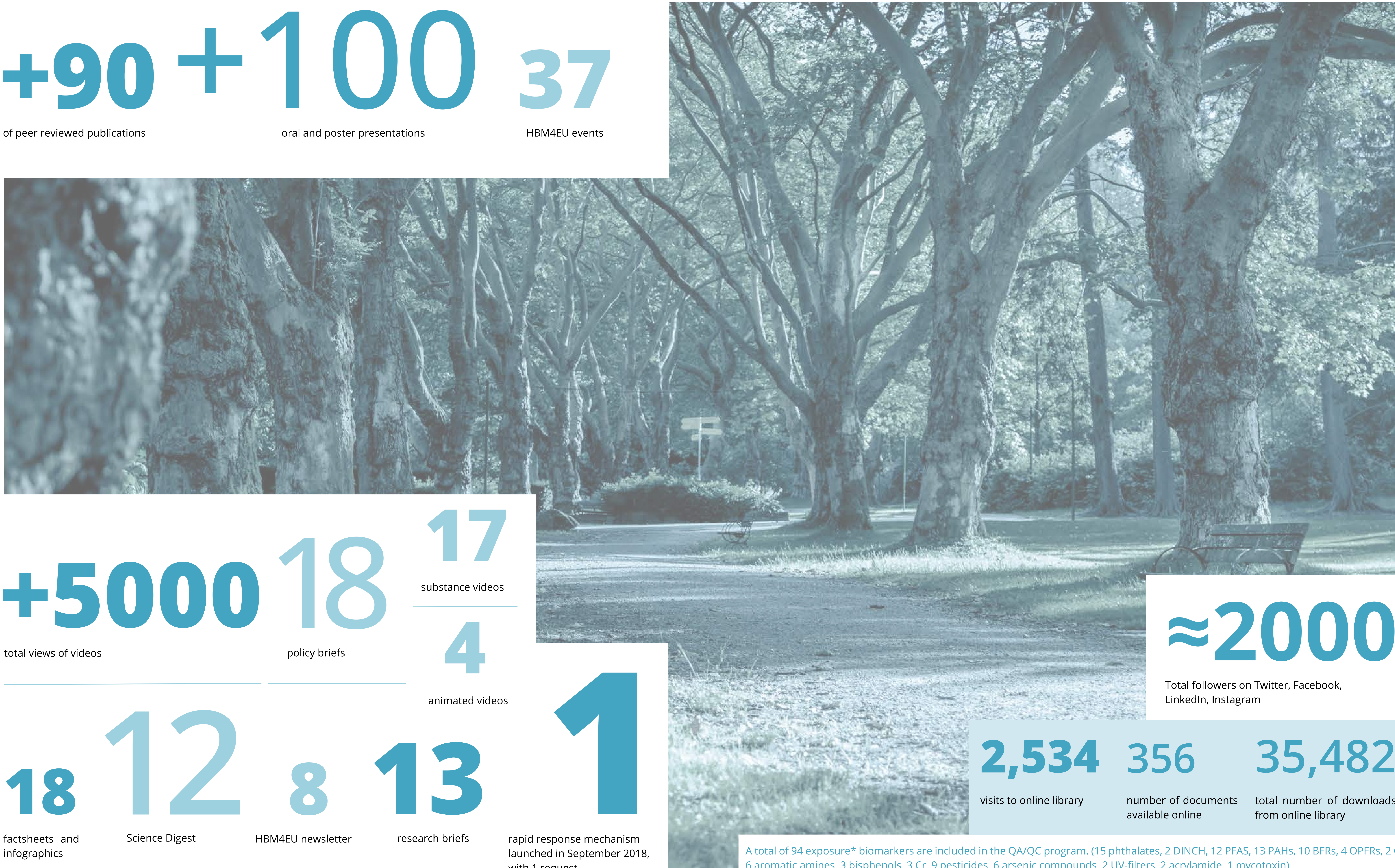
Total number of person days of training[4]
280

Total number of person-trainings[4]
339

TOTAL

Number of participants	Stakeholders representatives from outside the project consortium	Number of nationalities represented	Total number of person days of training[4]	Total number of person-trainings[4]
516	135	32	751	1027

[4] Based on signed list of attendance



+90

of peer reviewed publications

+100

oral and poster presentations

37

HBM4EU events

+5000

total views of videos

18

policy briefs

17

substance videos

4

animated videos

18

factsheets and infographics

12

Science Digest

8

HBM4EU newsletter

13

research briefs

1

rapid response mechanism launched in September 2018, with 1 request

≈2000

Total followers on Twitter, Facebook, LinkedIn, Instagram

2,534

visits to online library

356

number of documents available online

35,482

total number of downloads from online library

A total of 94 exposure* biomarkers are included in the QA/QC program. (15 phthalates, 2 DINCH, 12 PFAS, 13 PAHs, 10 BFRs, 4 OPFRs, 2 Cd, 6 aromatic amines, 3 bisphenols, 3 Cr, 9 pesticides, 6 arsenic compounds, 2 UV-filters, 2 acrylamide, 1 mycotoxin)

A new European Partnership for the Assessment of Risks from Chemicals: PARC

The European Partnership for the Assessment of Risks from Chemicals (PARC) was recently approved as part of the "Horizon Europe" framework, EU's key funding programme for Research and Innovation. Coordinated by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), this major project seeks to develop **next-generation chemical risk assessment in order to protect the health of European citizens and the environment.**

The project will be implemented by 200 partners from 28 countries, national agencies and research organizations focusing on environment and health, as well as three EU agencies – the European Environment Agency, the European Food Safety Authority and the European Chemicals Agency. Co-funded equally by the European Commission and the Member States, it is set launch in May 2022 and span over seven years.

Towards a new generation of risk assessment methods for chemicals

Over the last century, many initiatives, policies and sectoral regulations have been implemented to regulate chemicals, to minimise their negative impacts and to improve health prevention and environmental protection. The achievement of the global Sustainable Development Goals (SDGs) requires the development of sustainable chemistry, safe for humans and the environment. For this reason, PARC will establish an EU-wide Research and Innovation (R&I) Risk Assessment Hub of excellence composed of chemical risk assessment and risk management bodies to support chemical risk assessment and risk management authorities at the national and EU level.

PARC aims to advance research, share knowledge and improve skills in chemical risk assessment. It will thus contribute to supporting the European Union's "Chemicals Strategy for Sustainability - Towards a Toxic-Free Environment", paving the way for the EU's zero pollution ambition which is a key commitment of the European Green Deal.

"PARC represents a project of unprecedented scale, since it brings together about 200 French and European players, involving national and European health and safety agencies as well as research organisations. This partnership provides an excellent opportunity to boost research and innovation in support of chemical risk assessment, aiming in particular to: better anticipate emerging risks, better account for combined risks, and underpin the concrete implementation of new orientations in European public policies to safeguard health and the environment in response to important issues for health, the ecology and citizens' expectations" highlights Pascal Sanders, PARC coordinator at ANSES.

The partnership will build on work undertaken as part of the HBM4EU and will broaden the scope of its interests, specifically to the assessment of environmental risks.

> **"It is important to promote a transparent dialogue between scientific and regulatory bodies"**

Parc's objectives and main expected outcomes

The Partnership is set up to consolidate and strengthen European public R&I capacities in chemical risk assessment to protect human health and the environment. Its main objectives are to develop the scientific expertise needed to meet current and future challenges in chemical risk assessment; provide new data, methods and innovative tools for chemical risk assessment; and strengthen the networks of actors specialised in the different scientific fields contributing to chemical risk assessment.

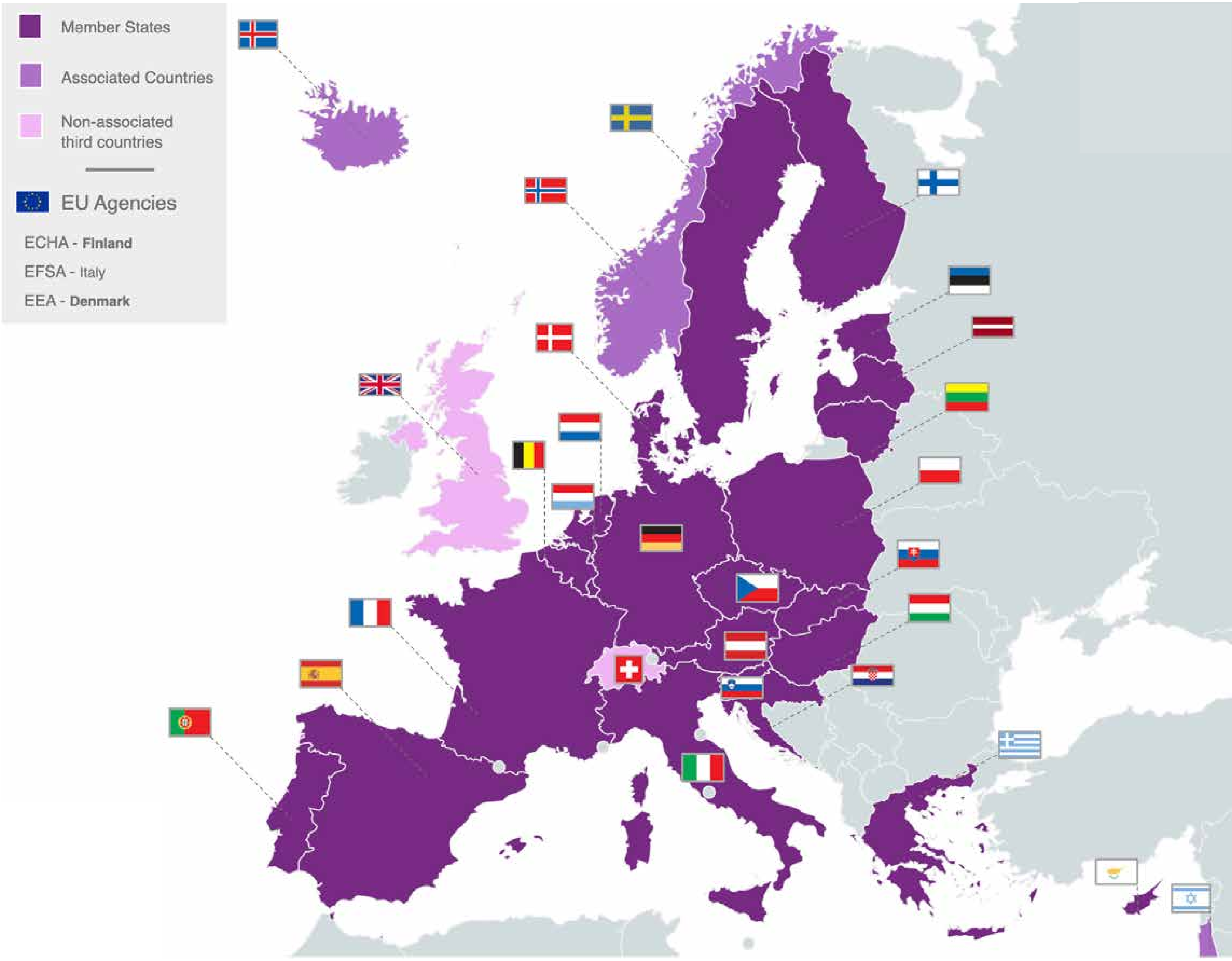
"PARC brings together chemical risk assessors and managers together with scientists and stakeholders to accelerate method development and the production of necessary data and knowledge, responding to the needs of end-users". The partnership will actively look for and implement synergies as well as developing interactions with other R&I initiatives and key stakeholders. "PARC is fully committed and constructed in such a way as to promote transparent dialogue, collaboration and capacity building, which is essential for the identification of needs, opportunities for harmonisation actions and development and use of tools that respond to these needs" explains Sanders. It is important to promote a transparent dialogue between scientific and regulatory bodies" stresses the expert.

Additionally, solid links will be created at the European, national and regional scale among the entities relevant for risk assessment. These will be supported by the network of National Hubs actively managed by the National Hub Contact Points.

PARC will provide chemical exposure risk assessors and managers with new data, innovative methods and tools. It will strengthen the networks of actors specialised in the various scientific fields contributing to risk assessment. It will contribute to the development of the scientific skills needed to address current and future challenges in chemical safety.

The first step will be to review the current state of the art in chemical monitoring in order to set up new schemes or broaden the scope of substances monitored in existing schemes, and to innovate with regard to the analytical methods used.

Learn more about PARC here. For further questions you can contact parc@anses.fr.



science and policy for a healthy future

Day 1, 27 April

Registration 30 min
8h30

Welcome 5 min
9h00 | Moderation: Katrin Prüfig

Opening 25 min
9h05 | Marike Kolossa-Gehring
German Environment Agency (UBA), Coordinator of HBM4EU

The HBM4EU Link to Policy 15 min
9h30 | Thomas Jakl
Deputy Director General, Chemicals Policy, Austrian Environment Ministry, HBM4EU Governing Board Chair

Q&A 10 min
9h45

HBM4EU – the DG RTD perspective 15 min
9h55 | Irene Norstedt
Director, DG Research and Innovation, European Commission

HBM4EU – the DG ENV perspective 15 min
10h10 | Cristina de Avila
Head of Sustainable Chemicals Unit, DG Environment, European Commission

Q&A 5 min
10h25

HBM4EU results exhibition 10 min
10h30 | Roser Gasol
European Environment Agency (EEA)

Coffee break and opening of the exhibition 40 min
10h40

Impact of HBM4EU from national perspectives

Lessons learnt from HBM4EU in Belgium 10 min
11h20 | Zuhal Demir
Flemish Minister for Justice and Enforcement, Environment and Spatial Development, Energy and Tourism

Lessons learnt from HBM4EU in Israel 10 min
11h30 | Zohar Barnett Itzhaki
Ministry of Health, Israel

Q&A 5 min
11h40

Lessons learnt from HBM4EU in Spain 10 min
11h45 | Pilar Aparico Azcárraga
General Director of Public Health, Ministry of Health, Spain

National Hubs – integral to the success and sustainability of HBM in Europe 10 min
11h55 | Ovnair Sepai
National Hub Coordinator, UK Health Security Agency

Q&A 5 min
12h05

Interactive session "Participating countries" 5 min
12h10 | Moderation

Lunch Break 60 min
12h15

New exposure data and risk assessment I

Interactive session "Exposure data and risk assessment" 10 min
13h15 | Moderation

Exposure of European citizens to HBM4EU priority chemicals 15 min
13h25 | Eva Govarts
Flemish Institute for Technological Research (VITO), Belgium

PFAS data from Europe – results and policy implications 10 min
13h40 | Maria Uhl
Environment Agency Austria

Q&A 10 min
13h50

Bisphenol data from Europe – results and policy implications 10 min
14h00 | Robert Barouki, Elena Tarroja
National Institute of Health and Medical Research (INSERM), France

Flame Retardants from Europe – results and policy implications 10 min
14h10 | Lisa Melymuk
Masaryk University (MU), Czech Republic

Q&A 5 min
14h20

Lead data from Europe - results and policy implications 10 min
14h25 | Tamas Szigeti
National Public Health Center (NPHC), Hungary

Arsenic data from Europe – results and policy implications 10 min
14h35 | Wojciech Wasowicz,
Nofer Institute of Occupational Medicine (NIOM), Poland

Q&A 5 min
14h45

Interactive session "Exposure data and risk assessment" 10 min
14h50 | Moderation

14h55 | Peter Korytar
DG Environment, European Commission

Coffee Break 30 min
15h00

The impact of HBM4EU beyond the EU – international perspectives

HBM as a bridge between environmental health studies and policy building 10 min
15h30 | Shoji Nakayama
Deputy Director, Japan Environment and Children Study

International Human Biomonitoring (i-HBM): HBM4EU's Leadership Role - How Health Canada National Biomonitoring Program Benefited from the HBM4EU Initiative 10 min
15h40 | Annie St. Amand
Section Head, National Biomonitoring, Health Canada

A Look at Chemical Exposures in the USA: The Human Biomonitoring Program within the National Health and Nutrition Examination Survey (NHANES) 10 min
15h50 | Antonia Calafat
US Centers for Disease Control and Prevention (CDC)

Q&A 10 min
16h00

HBM4EU's contribution to achieving a toxic-free environment in Europe 15 min
16h10 | Dirk Messner
President of the German Environment Agency (UBA)

Q&A 5 min
16h25

Harmonisation

Harmonising efforts to support policy making 10 min
16h30 | Liese Gilles
Flemish Institute for Technological Research (VITO), Belgium

The sustainable network of laboratories – the basis of an HBM system in Europe 10 min
16h40 | Marta Esteban López
Institute of Health Carlos III (ISCIII), Spain

Q&A 5 min
16h50

Sound methods for sound science to support policy 10 min
16h55 | Holger Koch
Institute for Prevention and Occupational Medicine (IPA), Germany

HBM platform conclusions: achievements and sustainability 5 min
17h05 | Argelia Castaño
Institute of Health Carlos III (ISCIII), Spain

Q&A 10 min
17h10

Closing day 1 5 min
17h20 | Moderation

End of day 1
17h25

Day 2, 28 April

Welcome and interactive session "Future paths for the continuation of HBM in Europe" 15 min

9h05 | Moderation & Jana Klánová
Masaryk University (MU), Czech Republic

9h10 | Argelia Castaño
Institute of Health Carlos III (ISCIII), Spain

9h15 | Q&A and results of interactive sessions

Chemical Risk Assessment – Translation to Policy I

Exposure assessment of pesticide mixtures: can we identify hotspots? 10 min

9h20 | Mirjam Luijten
National Institute for Public Health and the Environment (RIVM), Netherlands

Seeking emerging substances: hope or hype? 10 min

09h30 | Jean-Philippe Antignac
French National Institute for Agriculture, Food, and Environment (INRAE)

Q&A 5 min

09h40

Health effects of mixtures 10 min

09h45 | Andreas Kortenkamp
Brunel University London (URBUN), UK

Mixture exposure assessment; can we move to risk assessment? 10 min

09h55 | Erik Lebret
National Institute for Public Health and the Environment (RIVM), Netherlands

Comments on the strategy for mixtures 10 min

10h05 | Fleur van Broekhuizen
European Chemicals Agency (ECHA)

Q&A 10 min

10h15

New exposure data and risk assessment II

Acrylamide data from Europe - results and policy implications 10 min

10h25 | Federica Laguzzi
Karolinska Institute (KI), Sweden

Mycotoxin data from Europe - results and policy implications 10 min

10h35 | Paula Alvito, Maria Silva
National Institute of Health Doutor Ricardo Jorge (INSA), Portugal

Q&A 5 min

10h45

UV filter data from Europe - results and policy implications 10 min

10h50 | Tamar Berman
Ministry of Health, Israel

Q&A 5 min

11h00

Coffee Break 35 min

11h05

Chemical Risk Assessment – Translation to Policy II

The use of HBM data for policies, measures or further research 20 min

11h40 | Greet Schoeters
Flemish Institute for Technological Research (VITO), Belgium

Use for citizens and stakeholders 15 min

12h00 | Joana Lobo Vicente
European Environment Agency (EEA)

Q&A and interactive session "Targeted communication of results" 10 min

12h15 | Moderation

New exposure data and risk assessment III

Mother's exposure to mercury 10 min

12h25 | Andromachi Katsonouri
Ministry of Health, Cyprus

Q&A 5 min

12h35

Policy implications from the occupational studies 10 min

12h40 | Tiina Santonen
Finnish Institute of Occupational Health (FIOH)

Biomarkers of effect: implementation in occupational studies as a proof of concept 10 min

12h50 | Marieta Fernandez
University of Granada (UGR), Spain

Q&A 5 min

13h00

Comment by OSHA 5 min

13h05 | Elke Schneider
European Agency for Safety and Health at Work (EU-OSHA)

Lunch Break 60 min

13h10

Discussion on exposure data: modelling vs. measuring 10 min

14h10 | Denis Sarigiannis
Aristotle University of Thessaloniki (AU), Greece

14h15 | Holger Koch
Institute for Prevention and Occupational Medicine (IPA), Germany

Q&A 5 min

14h20

Novel Methods – Ways forward to link HBM and Health

From chemical exposure to health outcomes (AOPs) 10 min

14h25 | Ludek Blaha
Masaryk University (MU), Czech Republic

The benefits of combining HBM and health data – results from HBM4EU 10 min

14h35 | Hanna Tolonen
Finnish Institute for Health and Welfare (THL)

Q&A 5 min

14h45

From exposure to health 10 min

14h50 | Robert Barouki
National Institute of Health and Medical Research (INSERM), France

Q&A 5 min

15h00

The added value of human biomonitoring for chemicals policy making 15 min

15h05 | Hans Bruyninckx
Executive Director of the European Environment Agency (EEA)

Q&A 5 min

15h20

Coffee Break 35 min

15h25

The use of HBM4EU results from different perspectives for the support of chemical policy and the protection of human health

45 min

16h00| Ofelia Bercaru
Director, Prioritisation and Integration, European Chemicals Agency (ECHA)

16h05| Georges Kass
Lead Expert, European Food Safety Authority (EFSA)

16h10| Sylvie Lemoine
Executive Director Product Stewardship, European Chemical Industry Council (CEFIC)

16h15| Jutta Paulus
Member of the European Parliament

16h20| Frida Hök
Senior Policy Advisor, ChemSec

16h25| Discussion

Last but not least 15 min

16h45 | Marike Kolossa-Gehring
German Environment Agency (UBA), Coordinator of HBM4EU

Greet Schoeters
Flemish Institute forTechnological Research (VITO), Belgium

End of conference

17h00

Marike Kolossa-Gehring
German Environment Agency (UBA),Coordinator of HBM4EU

Thomas Jakl
Deputy Director General, Chemicals Policy, Austrian Environment Ministry, HBM4EU Governing Board Chair

Irene Norstedt
Director, DG Research and Innovation, European Commission

Cristina De Avila
Head of Sustainable Chemicals Unit, DG Environment, European Commission

Roser Gasol
European Environment Agency (EEA)

Zuhal Demir
Flemish Minister for Justice and Enforcement, Environment and Spatial Development, Energy and Tourism

Zohar Barnett Itzhaki
Ministry of Health, Israel

Pilar Aparico Azcárrag
General Director of Public Health, Spain

Ovnair Sepai
National Hub Coordinator, Principal Toxicologist at UK Health Security Agency

Eva Govarts
Flemish Institute for Technological Research (VITO), Belgium

Maria Ulh
Environment Agency Austria

Robert Barouk
National Institute of Health and Medical Research (INSERM), France

Elena Tarroja
National Institute of Health and Medical Research (INSERM), France

Lisa Melymu
Masaryk University (MU), Czech Republic

Tamás Szigeti
National Public Health Center (NPHC), Hungary

Wojciech Wasowicz Nofer
Institute of Occupational Medicine (NIOM), Poland

Shoji Nakayama
Deputy Director, Japan Environment and Children Study

Annie St. Amand
Section Head, National Biomonitoring, Health Canada

Antonia Calafat
US Centers for Disease Control and Prevention (CDC)

Dirk Messner
President of the German Environment Agency (UBA)

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Carlos III Health Institute (ISCIII), Spain

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Andromachi Katsonouri
Head, Human Biomonitoring and Control of Industrial Products Laboratory, Cyprus

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We are HBM4EU

HBM4EU

aims to advance human biomonitoring in Europe by providing evidence of the exposure of EU citizens to chemicals and their effects on human health in order to support policy making.

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science and policy
for a healthy future