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What is 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.
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.

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

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.

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

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.

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

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

— 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 as phthalates and bisphenol s, and potential health impacts, support regulatory action to make products safer. Health-based human biomonitoring guidance values and 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 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 DNIC6, a non-phthalate plasticizer. These indicators can be used to assess the effectiveness of chemical-specific regulatory measures and to identify the need for additional action to protect citizens.

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 DNIC6, a non-phthalate plasticizer. These indicators can be used to assess the effectiveness of chemical-specific regulatory measures and to identify the need for additional action to protect citizens.

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.

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. 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” approach is in fact the first step towards a mechanism-inspired assessment of chemicals and towards an improved rational assessment of mixtures.
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 non-reversible breathing difficulties. COPD is usually caused by a long-term exposure inhaled irritants such as tobacco smoke, which damage lungs and airways.

**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 in vitro studies.

**Brain development**
Thyroid hormone is important for brain development especially during the fetal and postnatal period. Thyroid hormone deficiency may cause retardation, 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 hyperthyroidism 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 170,000 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 acrylamides 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.
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.

Asthma with specific sensitization

Exposure to PAHs and pesticides can increase asthma symptoms.

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.

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.

Obesity

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

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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 GerES studies (Germany), C-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.

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 meaning 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.

“Samples were collected between 2014-2021 to reflect recent exposure levels”, she adds. “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 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 open-access 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 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 harmonised 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 laboratories in Europe.

"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 open-access 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".

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.
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.
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<th>Flame retardants</th>
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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.

“We have defined a strategy, published in the International Journal of Hygiene and Environmental Health, consisted of three main 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 polycrylamides 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, reproductive system, 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 types of cancer 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, who works at the Karolinska Institutet. 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. 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.
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 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 focused on whole weight 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 (HMA) Granada cohort, a team of Spanish and Danish scientists reported that higher urinary concentration of TCPy, 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 hormones concentration in pregnancy can affect fetal 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 symptom improved 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 neurotoxins 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 for use 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 (IARC). 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 its renewal 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 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 increased the human exposure to mixtures of four pyrethroids using physiological-based toxicokinetic (PBTK) modelling in a study from the French INNS 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 fertilizers 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

- Food
- Breast milk
- Contaminated drinking water
- Prenatal ingestion
- Occupational exposure (processing, mixing and applying pesticides in the field)
- Contaminated air and dust
- Residual air concentrations at home
- Occupational exposure (in contact with pesticides directly to the skin)
- Contaminated surfaces (residual use of biocides)
- Handling pets (after treatment with pesticides)
- Medical product to combat head lice and scabies
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—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, vitamins 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 Estevez, 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. Birgirur Halldorsson 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 Halldorsson. 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".
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. "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."

**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
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)

<table>
<thead>
<tr>
<th>Cadmium:</th>
<th>Adults 21-30 years: 0.3 µg/g creatinine</th>
<th>Adults 31-40 years: 0.5 µg/g creatinine</th>
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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-dependent 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 Jozef 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 epigenetics. Furthermore, 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 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 consumption data available from contaminated soil through diet. Therefore, we exploited European databases to obtain cadmium concentrations in soil, percentages of agricultural areas 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 cadmains than non-smokers”.

Main achievements

- 5 peer reviewed papers published, 2 in preparation
- Age-dependent 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

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.
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.

Curren

“...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 96 pesticide-related markers (parent compounds and metabolites), of which 41 were the parent pesticides in the sample. 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.

Humans are continuously exposed to a multitude 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.

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.

### Chemical pollutants in the home

1. **PFAS chemicals in waterproof clothing**
2. **Siloxanes, parabens, and many others in shampoo, shaving foam, deodorants**
3. **Oxybenzone UV filter in sunscreens**
4. **Phthalates, flame retardants and bisphenols in children’s toys**
5. **Flame retardants in virtually all electronics**
6. **Phthalates and other substances in fragrances found in air fresheners, cleaning products, cosmetics, soaps**
7. **Pharmaceuticals and other contaminants in drinking water**
8. **Tattoo inks can contain a mixture of harmful chemicals**
9. **Flame retardants in furniture and mattresses**
10. **Unknown and unwanted chemicals in recycled products**
11. **Bisphenols in till receipts**
12. **Phthalates and many other plastics additives in food packaging**
13. **PFAS in microwave popcorn bags, bakery bags and compostable food packaging**
14. **PFAs in microwave popcorn bags, bakery bags and compostable food packaging**
15. **PFAs in microwave popcorn bags, bakery bags and compostable food packaging**
16. **PFAs in microwave popcorn bags, bakery bags and compostable food packaging**
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
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-methyleneedianiline (MDA), which 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 a carcinogen. 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 to support 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 diisocyanates market volume: hexamethylene diisocyanate (HDI), toluene diisocyanate (TDI), and 4,4′-methylene diphenyl 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 diisocyanate levels in urine: in the case of TDI, urinary toluene diamine (TDA); and in the case of MDI, urinary toluene diamine (MDA) and 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 exposure 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 (OEL) 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 surface treatments 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 (CVI) 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 showed elevated levels, these seem to be lower than the levels seen in workers performing chrome plating,” explains Dr Beatrice Blocca, 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 control”, 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.

“The 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 chromatography 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)
• 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 DNBC 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, foodstuffs or other materials and thus are ubiquitous in the environment. They can enter 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, DBP, DNP and DnBP 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 adverse health effects. 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 adverse health effects. Phthalates investigated

**Phthalates investigated**

<table>
<thead>
<tr>
<th>BBzP</th>
<th>Butylinyl phthalate</th>
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<td>CAS-No.: 84-69-5</td>
</tr>
</tbody>
</table>

Note: Full names and CAS-No. are given below this article. All substances investigated are listed at the end of this article.
HBM4EU’s priority substances - Phthalates

HBM4EU aligned studies revealed geographical differences. Samples from the most exposed country had at 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 (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 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 DINP 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, DEHP and DPHP and DINCH.
• First European HBM indicators for phthalates and DINCH have been derived.
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.

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.

Scientists have observed that these substances” stated Barouki. “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 substitutes”. 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 substitutes to toxic chemicals.

**Exposure and health impacts of bisphenols call for additional regulatory action**

HBM4EU exclusively aims to support European regulatory processes on chemicals. By providing data on current exposure and on the actual impacts of regulatory
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.

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To date, many alternatives to the regulated PFASs are used worldwide, although key data gaps remain on the potential human health effects.
Over the time we have seen a decreasing trend for PFDA 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 PFOA by 20 and 21%, 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 IBM 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 PFAS 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.
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 Arito, Investigator from the Food and Nutrition Department at the National Institute of Health Doctor 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 unregulated 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"
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, seafood, foods, particularly meat, dairy and processed meats, car seats, building insulation, paper and cardboards, electronics, plastics, toys, and a wide range of other synthetic products. 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; Pravaneh Hajeed, 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.

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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-methyl)phosphate - TCP, 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, TCP 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.
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, phytosanitory products, environmental persistent organic pollutants such as flame retardants (FRs), other non persistent contaminants such as phalates 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 analysis 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 LABERICA 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 methodological harmonization. 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.

**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 ECHIMEU 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.

**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** 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.

**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
- 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

**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** 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 phthalates, bisphenols, phthalates, DINCH and organosilicon substances.

1 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 of 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-1 – 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; 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 and BP-1,” explains Dr Tamir 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 Germany. “These new data, which will be published in June 2022 on the HBM4EU website, provide exposure data on a range of benzophenones. BP-3 was found to be the most frequently occurring benzophenone,” notes Berman.

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.

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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 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. 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). These 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 (GenES 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 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 decades. However, data from other European countries are still missing. We don’t know the pattern of geographical distribution of exposure to aprotic 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 "individually and combined NMP and NEP exposures 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-ethylpyrrolidin-2-one (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 products being 1 mg/L 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.

"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 these 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

Household products (aprotic solvents-containing household cleaning products)
Personal care products
Oriental exposure:
• Rubber and plastics
• Pharmaceuticals and chemicals
• Polishes and waxes
• Inks and toners
• Textiles
• Fragrances and air fresheners
• Cleaning products
• Occupational exposure (factories, car services, cleaning services, labs)
• Ph-regulators
• Neutralisation agents
• Flocculants
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

Harmonisation 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, guidelines and methods to harmonise HBM across the EU, also implementing a full quality assurance (QA)/quality control (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, how to recruit to participants, requesting their consent for use of their personal data and describing the sampling process and follow up have been designed to help. Questionnaires for survey participants for each HBM4EU 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) 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 PBTK 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 development methodology 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 DiMeP, 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 support adverse outcome pathways development and fostering communication between AOP developers and users.

Biomarkers of effect

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 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 neurodevelopmental 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 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 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.

Scientific achievement
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 and 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.

A paper publication underway from the NHs

Strongly welcomed initiative has positioned HBM on the political agenda.

Awareness raising among citizens

Partners benefits as NHs

Fostered national collaboration

NH meetings were very useful to learn from each other

Collaboration between scientists and policy makers

Comprehensive discussion and evaluation of HBM results at national level

Connections and collaborations

Policy Leads Ministries

Researchers

HBM4EU Country Partners

Wider Stakeholders

NHPC

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 different HBM4EU National Hubs.

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 ESPR.

Robert Barouki & Elena Tarroja

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 list 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 Siri 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 Bernan

SLOVENIA:
The 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 Jozef 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).

Slovenian National Hub is represented by key authorities which are users of HBM-data on a policy level: the Slovenian National Food Administration, National Institute of Public Health, the Chemicals Office of the Republic of Slovenia (CORS), Clinical Occupational Medicine Institute, National Biology Institute and Jozef Stefan Institute. There is constant communication and cooperation between ministries via intersectoral conferences and round table discussions on environmental health and chemicals.

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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, Israel, 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. “They want to know where they live, where they work, where they are exposed to chemicals and what is their actual body burden.”

The focus group highlighted citizens’ desire for information and transparency of the measures taken to protect them. “There is a need for citizens to develop a sense of empowerment and to be heard in the management of chemical exposure levels. This would help them make informed decisions about their health and the environment.”

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.

The results of the focus groups were linked to 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.

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 flavours, 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.”

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 exposures 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.

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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 groups’ 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 ran 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 pollutants, 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 respondents 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 has also 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 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.
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.

Biophenols, 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 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 peoples’ lives?

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 reassessment 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 (CSS) 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 HBMs, 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 of the LABERCA research Unit (Nantes, France), and member of expert working groups for the French Food Safety Agency (ANSES). His area of research requires harmonized and standardized advanced expert bioinformatics applications, 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.

What is new? There is so much work that still needs to be done. For instance, CECiScreen database could be combined with the MS reference library and 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.

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What are chemicals of emerging concern (CECs)?

Chemicals of Emerging Concern (CECs) include a very wide group of chemical compounds 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. The “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 has been identified, or old contaminants with new information arising regarding their risks.

What are the differences between the two approaches? “Suspects” are known compounds of 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 exposure 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 ist 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 technical protocols to better compare data and results from different laboratories, and 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.

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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

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 channeling 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 socioeconomic 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.

The European Environment Agency’s Scientific Committee on 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 national level, to make a whole far 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.

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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.

### Training Programme Overview

- **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

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### Training School Attendance

<table>
<thead>
<tr>
<th>Date</th>
<th>Number of Participants</th>
<th>Number of Nationalities Represented</th>
<th>Total Number of Person-Trainings</th>
<th>Total Number of Person-Days of Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Training School</td>
<td>79</td>
<td>32</td>
<td>177</td>
<td>211</td>
</tr>
<tr>
<td>2nd Training School</td>
<td>37</td>
<td>14</td>
<td>185</td>
<td>280</td>
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<tr>
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<td>339</td>
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<tr>
<td>4th Training School</td>
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<tr>
<td>5th Virtual Training</td>
<td>95</td>
<td>21</td>
<td>280</td>
<td>751</td>
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<tr>
<td>TOTAL</td>
<td>516</td>
<td>135</td>
<td>1027</td>
<td>1027</td>
</tr>
</tbody>
</table>

*Based on signed list of attendance*
Measuring impact

- +90 oral and poster presentations
- +100 HBM4EU events
- 37 policy briefs
- +5000 substance videos
- +18 factsheets and infographics
- 18 Science Digest
- 12 HBM4EU newsletter
- 8 research briefs
- 18 animated videos
- 17 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 undergo 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.

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Learn more about PARC here. For further questions you can contact parc@anses.fr.
Day 1, 27 April

Registration 30 min
8h30

Welcome 5 min
9h00 | Moderation: Katrin Prüfig

Opening 25 min
9h15 | 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

Q&A 5 min
10h25

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

Coffee break opening of the exhibition 40 min
10h40

National Hubs – integral to the success and sustainability of HBM in Europe 10 min
11h05 | Ovamir Sepal
National Hub Coordinator, UK Health Security Agency

Q&A 5 min
12h00

Interactive session “Participating countries” 10 min
12h10 | Moderation

Lunch Break 60 min
12h15

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

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

Q&A 5 min
14h05

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

Interactive session “Exposure data and risk assessment” 10 min
14h50 | Peter Korytar
DG Environment, European Commission

Coffee Break 30 min
15h00

National Hubs – integral to the success and sustainability of HBM in Europe 10 min
11h05 | Ovamir Sepal
National Hub Coordinator, UK Health Security Agency

Q&A 5 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 Molyneux
Masaryk University (MÚ), Czech Republic

Q&A 5 min
14h20

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

Lead data from Europe – results and policy implications 10 min
14h05 | Tamas Szigeti
National Public Health Center (NPCH), Hungary

Q&A 5 min
14h05

National Hubs – integral to the success and sustainability of HBM in Europe 10 min
11h05 | Ovamir Sepal
National Hub Coordinator, UK Health Security Agency

Q&A 5 min
12h00

Interactive session “Participating countries” 10 min
12h10 | Moderation

Lunch Break 60 min
12h15

Lessons learnt from HBM4EU in Belgium 10 min
11h20 | Zuhel Demir
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 Lopez
Institute of Health Carlos III (ISCC), Spain

Q&A 5 min
16h45

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 Lopez
Institute of Health Carlos III (ISCC), Spain

Q&A 5 min
16h45

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 (ISCC), Spain

Q&A 5 min
17h10

Closing day 1 5 min
17h20 | Moderation

End of day 1 5 min
17h25

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
15h55 | Antonia Calafat
US Centers for Disease Control and Prevention (CDC)

Q&A 5 min
16h00

The impact of HBM4EU beyond the EU – international perspectives 5 min
16h10 | Dirk Messner
President of the German Environment Agency (UBA)

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

Q&A 5 min
16h25

The impact of HBM4EU beyond the EU – international perspectives 5 min
16h10 | Dirk Messner
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15h30 | Shoji Nakayama
Deputy Director, Japan Environment and Children Study

Q&A 5 min
16h25
Day 2, 28 April

Welcome and interactive session “Future paths for the continuation of HBM in Europe”

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?

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

Seeking emerging substances: hope or hype?

9h30 | Jean-Philippe Antignac
French National Institute for Agriculture, Food, and Environmen

Q&A

9h40

Health effects of mixtures

9h45 | Andreas Kortenkamp
Brunel University London (URBUN), UK

Mixture exposure assessment; can we move to risk assessment?

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

Q&A

10h05

Comments on the strategy for mixtures

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

Q&A

10h15

Coffee Break

11h05

Chemical Risk Assessment – Translation to Policy II

Mycotoxin data from Europe – results and policy implications

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

Q&A

10h45

UV filter data from Europe – results and policy implications

10h50 | Tamar Berman
Ministry of Health, Israel

Q&A

11h00

Coffee Break

11h05

New exposure data and risk assessment I

Acrylamide data from Europe – results and policy implications

10h25 | Federica Laguzzi
Masaryk University (MU), Czech Republic

Q&A

10h35

Use for citizens and stakeholders

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

Q&A and interactive session “Targeted communication of results”

12h15 | Moderation

New exposure data and risk assessment II

Comment by OSHA

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

Lunch Break

13h10

Discussion on exposure data: modelling vs. measuring

14h10 | Denis Sangianni
Anstitute of Occupational Medicine (AUI), Greece

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

Q&A

14h20

Novel Methods – Ways forward to link HBM and Health

From chemical exposure to health outcomes (AOPs)

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

Q&A

15h00

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

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

Q&A

14h45

From exposure to health

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

Q&A

14h55

End of conference

17h00
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.