



science and policy  
for a healthy future

# HBM4EU NEWSLETTER

Delivering chemical safety for European citizens

Newsletter n°5 - October 2019  
HORIZON2020 Programme  
Contract No. 733032 HBM4EU

Europe stands at a crossroads. Will we continue along the same path of production and consumption, or will we shift to clean, circular and sustainable patterns? The new political ambition at the highest level in the European Union is to take the latter path and deliver a pollution-free environment for European citizens.

HBM4EU is producing robust evidence of how our bodies are polluted by chemicals and how this affects citizens' health across Europe. This scientific evidence provides the basis for determined efforts to eliminate that pollution. We are using cutting-edge science to support European efforts to deliver chemical safety.

**“For the health of our citizens, our children and grandchildren, Europe needs to move towards a zero-pollution ambition. I will put forward a cross-cutting strategy to protect citizens' health from environmental degradation and pollution, addressing air and water quality, hazardous chemicals, industrial emissions, pesticides and endocrine disruptors.”**

Ursula von der Leyen, A Union that strives for more - My agenda for Europe

## In this issue:

- Delivering chemical safety for European citizens
- Successful governance through partnership
- Responding to citizens' concerns
- Understanding stakeholder needs
- HBM4EU National Hubs: a network of excellence
- From science to policy
- Firm foundations: building the European Human Biomonitoring Platform
- Understanding the health impacts of chemical exposure
- Looking forward to a sustainable future initiative

<https://www.hbm4eu.eu/>



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.



Umwelt  
Bundesamt

Dr Marike Kolossa Gehring  
Project Coordinator

# SUCCESSFUL GOVERNANCE

through partnership

HBM4EU is first and foremost a partnership.

Under HBM4EU, we have built links between scientists, risk assessors and risk manager. Our partners are reaching across national borders to foster collaboration across countries.

The initiative includes over 115 partners clustered under a network of [National Hubs in 28 countries](#). Our geographical scope covers 24 Member States of the European Union (EU), as well as Iceland, Norway, Israel and Switzerland. Looking forward, we anticipate that Estonia and North Macedonia will soon be joining our partnership.

The European Environment Agency is also an active partner in the project.

## HBM4EU partner countries



■ EU Member States ■ Associated States ■ Partly Associated States

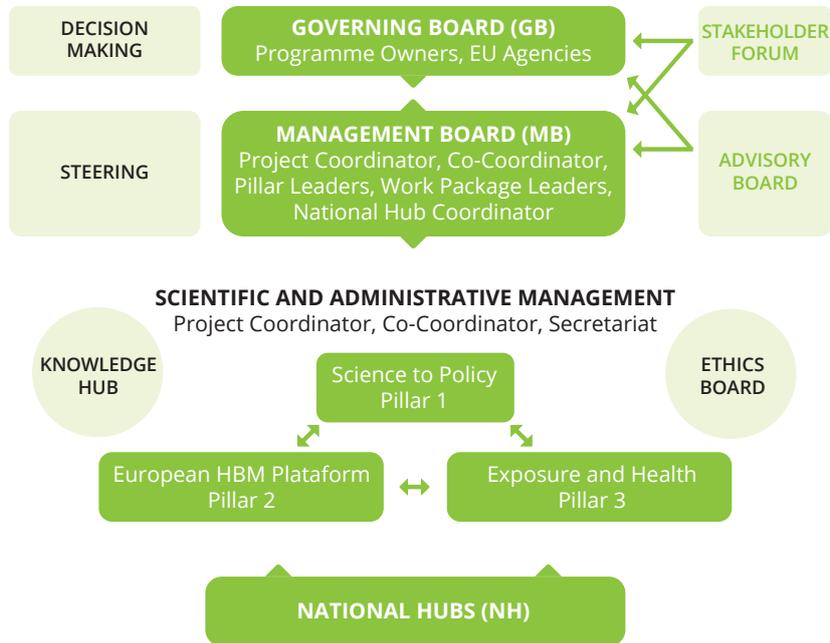
“We are building and developing a European network of scientists, regulators and policy makers to promote science and policy for a healthy future in Europe by use of human biomonitoring and research on the impact of chemicals on human health”.

Governing a project of this scale and diversity is both exciting and challenging. To meet this challenge, our project coordinator, the German Environment Agency, established governance structures, now in their third year of effective operation.

As the highest decision-making body, the HBM4EU [Governing Board](#) provides high-level steering and guarantees the political engagement of our partner countries. The membership of the European Environment Agency, the European Chemicals Agency and the European Food Safety Authority cements the link to the European level.

The German Environment Agency, has successfully built procedures for decision-making by the HBM4EU [Management Board](#), on administrative and financial aspects, as well as on our scientific direction. Project oversight is supported by our Co-coordinator, VITO.

Our [Advisory Board](#) includes international human biomonitoring experts with the knowledge and experience to provide a valuable outside perspective on our work.



© Sofie Nørager

Tuomo Karjalainen - Senior Expert for Environment and Health, Sofie Nørager - Scientific Officer and Laia Quiros Pesudo - Scientific Officer

HBM4EU is co-funded under the European Union's Horizon 2020 research and innovation fund. We are working in close collaboration with the European Commission's Directorate General for research and innovation, co-creating excellent science in support of European chemicals policies.

"We are delighted to see how a co-funded EU project structures stakeholders at national and EU level. HBM4EU's ground breaking work is laying the foundations for a sustainable European human biomonitoring platform to protect citizens."

DG Research and Innovation, Environment and Health Team



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

# RESPONDING TO CITIZENS' CONCERNS

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. Citizens also vote, and can choose to back parties that promise greater protection of health and the environment.

Citizens have an interest in understanding their own chemical body burdens. They therefore have a personal interest in the scientific results produced under HBM4EU and may be affected by any policy measures based on these results. Indeed, HBM4EU results are co-produced with citizens who participate in sampling exercises and agree to the use of their data in research.

To better understand public concern regarding chemicals, HBM4EU runs online questionnaires and focus groups with members of the public. Thus far, we have talked to people in Austria, Portugal, Ireland and the UK, with more planned. The results of outreach activities to date are documented in a report on [HBM4EU outreach to European citizens](#).

**HORIZON2020 Programme**  
Contract No. 733032 HBM4EU

### BISPHENOLS: WHAT YOU NEED TO KNOW

**WHAT ARE BISPHENOLS?**  
Bisphenols are a group of man-made chemicals that are used in the manufacturing of polycarbonate plastics and epoxy resins. The most widely used chemical in the group, produced in high volumes, is bisphenol A, also known as BPA.

The use of other bisphenols, such as bisphenol S (BPS) and bisphenol F (BPF) is limited in comparison, although volumes are increasing as these chemicals are being used as replacements for BPA in some products, following restrictions on the use of BPA.

**POLYCARBONATE PLASTICS MAY CARRY ONE OF THE FOLLOWING PICTOGRAPHS:**

PC POLYCARBONATE  
CRN1

**How are bisphenols used?**  
BPA is used as a building block in the production of polycarbonate plastics. The resulting plastic is clear and tough and is used in the manufacture of a wide range of consumer goods including sports equipment, CDs, DVDs, impact-resistant safety equipment and automobile parts. BPA-based plastic is also used in food containers, such as reusable beverage bottles and reusable plastic tableware.

Another primary use of BPA is to produce epoxy resins. These resins are used to line food and beverage cans to avoid corrosion of the metal and to avoid migration of certain metals into the contents. They are also used to line water pipes and in the manufacture of thermal papers used for shop sales receipts, ATM receipts, public transport tickets, parking tickets and airline boarding passes. Finally, BPA is used in dental sealants.

In terms of other bisphenols, both BPS and BPF are also used in the manufacture of plastics. In particular, BPS is increasingly used in the production of thermal papers. This is driven by an upcoming ban on the use of BPA in thermal papers in the European Union due to enter into force in January 2020.

**How can bisphenols enter your body?**  
Most human exposure to BPA is through the consumption of food and beverages that have been in contact with epoxy resin linings or polycarbonate plastic containers. Food or drinks may contain very low levels of BPA that have migrated from containers and linings. Small children have an increased risk of becoming exposed to BPA due to their higher food consumption compared to their size.

People may also become exposed via the skin by handling thermal papers, such as till receipts. Limited exposure may also occur through breathing in contaminated air and dust. Once BPA enters the human body, it is rapidly broken down into metabolites and passes out of the body in urine.

**UNDERSTANDING CHEMICAL RISK**  
The risk of harm from any chemical results from the hazard associated with the chemical, combined with exposure to the chemical.

Hazard refers to the properties of the chemical that make it toxic, meaning it can cause harm to human health.

Exposure describes the amount of a chemical that an individual comes into contact with, as well as the frequency of exposure.

The term threshold is used to indicate the concentration, or level, of a chemical at which people according to current knowledge can be exposed without suffering negative health effects. Exposure up to this level is considered safe. Some chemicals can cause health effects at any concentration and are considered as having no threshold. For such chemicals, no level of exposure is safe.

**How might bisphenols affect health?**  
BPA is classified in the European Union (EU) as a substance that has toxic effects on the ability to reproduce, meaning that it may damage fertility or the unborn child. It is also classified as an endocrine disruptor, meaning that it can interfere with the functioning of the hormonal system. Identification of these hazards led the EU to take measures to reduce exposure to BPA.

Evidence from scientific studies suggest that exposure to BPA could be linked to obesity and diabetes, and may cause adverse effects to the immune system. Despite the wealth of studies, questions remain regarding the health impacts of BPA and the exposure levels and durations at which these impacts occur.

BPS is suspected to have many of the same adverse health effects as BPA, and is currently under evaluation by the European Chemicals Agency.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

For more information please contact: [HBM4EU@uba.de](mailto:HBM4EU@uba.de)

To channel our messages to citizens, we use [videos](#) and [factsheets](#), and have presented our results in informal public settings, such as the “Pint of Science” talk given in an English Pub.





science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

# UNDERSTANDING STAKEHOLDER NEEDS

Engagement with stakeholders is crucial to the success and sustainability of the HBM4EU project.

In order to deliver science for policy-making, we are talking to risk assessors and risk managers to understand their need.

Policy makers have been systematically involved in project inception and implementation, through an ongoing dialogue with the EU Policy Board. A broad range of services of the European Union is represented on this board.



We also talk to non-governmental stakeholders, through our [Stakeholder Forum](#) and at workshops and events. Dr Maria Uhl at the Austrian Environment Agency is the HBM4EU contact point for stakeholders, facilitating a dialogue with stakeholders to ensure we listen to actors with diverse perspectives. Their input helps us to:

- Understand societal needs;
- Set research priorities that respond to those needs;
- Keep our activities are legitimate and credible;
- Ensure our procedures are transparent and accountable;
- Deliver result that generate benefits for society.

## Members of the HBM4EU Stakeholder Forum

Industry	Workers	Consumer	Health	Environment
Downstream Users of Chemicals Coordination Group	European Trade Union Confederation	European Consumer Organisation	Health and Environment Alliance	Chem Trust
Eurometaux			European Federation of Allergy and Airways Diseases Patients' Associations	European Environmental Bureau
Small and Medium Enterprises United				Women Engage for a Common Future
European Chemical Industry Council				
Plastics Europe				PAN Europe

Stakeholders also act as multipliers in the dissemination of HBM4EU results. Recognising this, we have written articles for external newsletters and introduced our project in webinars organised by stakeholders. Our partners are open to further engagement with stakeholders.

Please contact [stake-hbm4eu@umweltbundesamt.at](mailto:stake-hbm4eu@umweltbundesamt.at) with your enquiries or proposals for collaboration.

**umweltbundesamt**<sup>U</sup>  
ENVIRONMENT AGENCY AUSTRIA



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

# HBM4EU NATIONAL HUBS:

a network of excellence



[National Hubs](#) have been established in each country to coordinate activities, so creating a robust HBM Platform at pan-European level. Throughout this newsletter, we feature stories of successful efforts to strengthen governance and implementation human biomonitoring at national level from across our network.

Our network of National Hubs is coordinated by Dr Ovnair Sepai of Public Health England.



Public Health  
England

## News from our National Hubs - Consulting stakeholders in Israel

The Israeli National Hub organized their first stakeholder consultation in February 2019, where the National Hub Contact Point presented the HBM4EU project and discussed the policy relevance of HBM results in Israel. Participants came from a range of government institutions, including the Ministries of Health, Environmental Protection, and Agriculture, as well as from academic institutions, non-governmental organizations, an industry organization and a pesticide manufacturer.

The Israel Ministry of Health, together with the Environment and Health Fund, is advancing Israel's human biomonitoring programme. The Hub presented new results from Israel's human biomonitoring programme, showing urinary concentrations of organophosphate pesticides in children, and participants learnt about the Ministry's plan to measure organophosphate and pyrethroid pesticides in children's urine in future HBM cycles. The stakeholder consultation is the start of a fruitful process of stakeholder engagement in human biomonitoring in Israel.

[Berman, T., Amitai, Y., Almog, S., & Richter, E. D. \(2012\). Human biomonitoring in Israel: Past, present, future. International journal of hygiene and environmental health, 215\(2\), 138-141.](#)



Dr Tamar Berman



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

## Training

The HBM4EU training school provides a space for exchanges of best practice and capacity building and fosters a harmonised approach to human biomonitoring in Europe. The HBM4EU Training School activities kicked-off in 2018, with two training events made available to HBM4EU partners. The 3rd Training School took place in June 2019, back to back with the "15th Summer school on toxic compounds in the environment" at the RECETOX Institute of the Masaryk University in Brno, Czechia. The training school was well attended and exceeded the planned capacity by 26 %. It included 64 participants from 12 EU member states, and from India, Israel, Turkey and Ukraine.

The 3rd training school covered topics such as toxicology, adverse outcome pathways (AOPs), training on modelling, laboratory skills, risk assessment, risk communication and participatory processes. There was also a dedicated session for networking with an active contribution (oral/posters) from the participants.

The training schools provide for professional exchange and personal interaction, foster a sense of community and build a common understanding of our joint endeavours under HBM4EU.



© Paul Scheepers

We look forward to welcoming HBM4EU partners at our 2020 training events.

For up-to-date information, please consult the [Training webpage](#).

### News from our National Hubs - Innovation through collaboration in France

The French National Hub includes representatives of the ministries of health, environment, research and education and scientists, as well as stakeholders and meets four times per year to coordinate activities. As an example, discussions in the Hub about analytical methods led to a proposal for the development of a toolbox for collecting innovative methods on the chemical exposome. The ambition is to implement the proposal in collaboration with several institutes in the near future.

Looking forward, Santé Publique France is charged with preparing proposals for the next French human biomonitoring study. It will be inspired by the achievements of HBM4EU, in particular by implementing research activities in parallel to the assessment of internal exposure.



Prof Robert Barouki



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.



**vito**

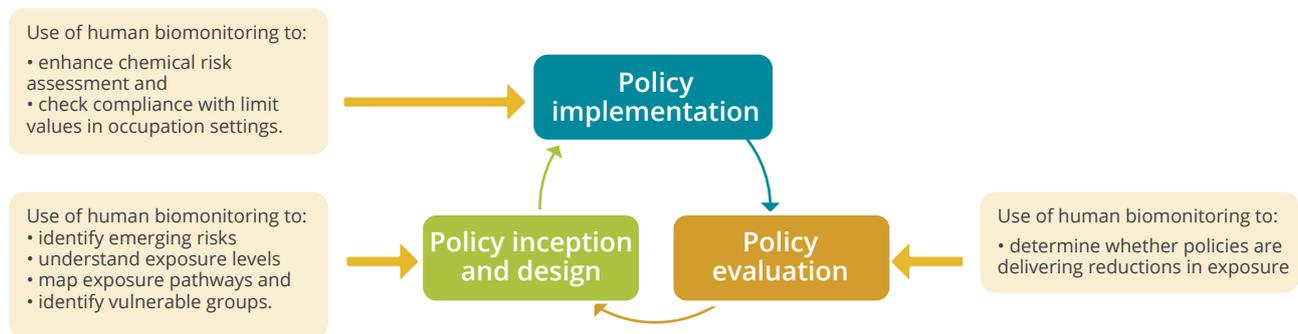
**Prof Greet Schoeters**  
Co-coordinator of HBM4EU  
and leader of pillar 1 on  
science to policy

"We are building a common understanding with risk assessors and risk managers of the value of human biomonitoring data in supporting chemical safety in Europe."

# FROM SCIENCE TO POLICY

HBM4EU is bridging science and policy, exploring current questions to deliver answers that help policy makers protect human health.

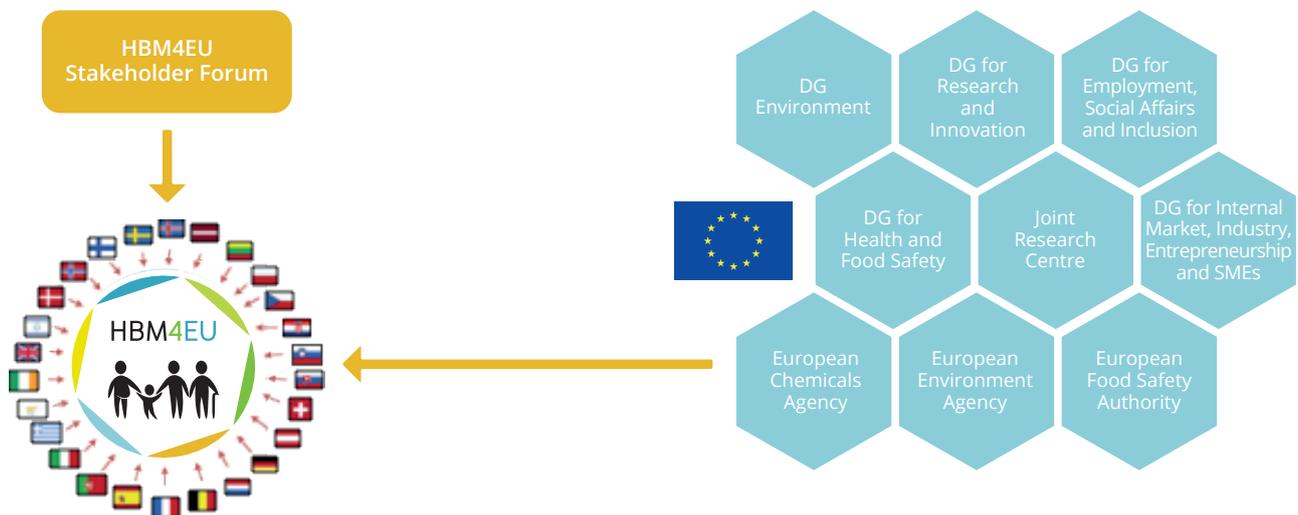
Our evidence will support policy makers at different stages of the policy cycle, including inception and design, implementation and evaluation.



## HBM4EU Priority Substance Groups

Selecting [substances to be the subject of research activities under HBM4EU](#) was a key step. To secure the legitimacy, credibility and societal relevance of our work, HBM4EU partners consulted policy makers, scientists and stakeholders when developing and implementing the [strategy](#)

[for the prioritisation of substances](#) for monitoring and research activities. The process for the prioritisation of chemicals has been fully documented on the [HBM4EU website](#), making the process accountable and transparent to external interested parties.





We have run two rounds of prioritisation, with the resulting two lists of HBM4EU priority substances shown below. Scoping documents are

available for each substance group, with further information on hazards, exposure and legislative status, as well as relevant HBM4EU activities.

1st list of HBM4EU priority substances				
<a href="#">Anilines</a>	<a href="#">Bisphenols</a>	<a href="#">Cadmium</a>	<a href="#">Chromium VI</a>	<a href="#">Flame retardants</a>
<a href="#">Polycyclic aromatic hydrocarbons</a>	<a href="#">Per-and poly fluorinated compounds</a>	<a href="#">Phthalates</a>	<a href="#">Emerging substances</a>	<a href="#">Mixtures</a>
2nd list of HBM4EU priority substances				
<a href="#">Acrylamide</a>	<a href="#">Aprotic solvents</a>	<a href="#">Arsenic</a>	<a href="#">Benzophenones</a>	<a href="#">Diisocyanates</a>
<a href="#">Lead</a>	<a href="#">Mercury</a>	<a href="#">Mycotoxins</a>	<a href="#">Pesticides</a>	

The list of HBM4EU priority substances that are the subject of research under HBM4EU includes a number of chemicals that are either recognised or suspected to show endocrine disrupting properties, including bisphenols, phthalates, per-and poly fluorinated compounds, and several flame retardants.

In parallel to the prioritisation process, we have also established a [Rapid Response Mechanism](#).

This mechanism allows policy makers to channel emerging needs for information to the HBM4EU partners. We are currently working on a request from the Directorate General for Health and Food safety for information on human exposure to copper.

**Dr Catherine Ganzleben  
and Dr Joana Lobo Vicente**  
European Environment Agency



## Translating results into policy

For HBM4EU results to be used by policy makers, they must:

- answer specific policy-relevant questions;
- clearly communicate science; and
- be delivered at the right moment.

To meet these criteria, HBM4EU partners are actively identifying openings in regulatory processes on chemicals where we might feed in evidence, in collaboration with the EU Policy Board.

<b>What?</b>	What new evidence is needed to support ongoing or future regulatory activities to assess or manage the risks of HBM4EU priority substances?
<b>When?</b>	What is the timing of the regulatory processes that demand this new evidence? What is the timeframe under which evidence is required?
<b>For who?</b>	Which actors in the regulatory process need the new evidence? At what technical level should we communicate results?
<b>How?</b>	How can HBM4EU produce that evidence? What research activities are needed?



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

It is crucial to the robust application of science in policy-making that the results of human biomonitoring activities are interpreted with a clear understanding of how aspects of study design, such as sample size, analytical methods and statistical tools, influence results.

HBM4EU is developing a [process for the joint interpretation of HBM results](#) between regulators, scientists and stakeholders, to foster consensus around results and their translation into targeted policy measures. HBM4EU partners have already engaged in dialogue with decision makers and stakeholders on how to interpret human biomonitoring results for use in policy-making, with a focus on phthalates and bisphenols. Going forward, HBM4EU scientists stand ready to work in partnership with risk assessors and risk managers to ensure a robust and reliable interpretation and application of HBM4EU results.

We are also developing tools to decision-makers to guide the interpretation of HBM results. Human biomonitoring guidance values have

been consolidated by experts for DEHP for the general population and for workers, and for Hexamoll® DINCH® for the general population. More guidance values are in the pipeline.

HBM4EU has produced a report on [current practice with the use of human biomonitoring in chemical risk assessment](#). The report identifies HBM as a tool to survey the real-life body burden of humans resulting from 'total' exposure to chemicals via different routes, which may be controlled under distinct legislative frameworks. The report presents examples of the advanced use of HBM and provides recommendations for the better inclusion of HBM in human risk assessment and health impact assessment.

Achieving impact with our messaging requires clear communication. We are working on ways to visualise evidence on human exposure to chemicals. This involves exploring options for an indicator on chemical exposure in the European population.

Prof Greet Schoeters



## Peer-reviewed articles:

Buekers, J., David, M., Koppen, G., Bessems, J., Scheringer, M., Lebret, E., ... & Trier, X. (2018). [Development of Policy Relevant Human Biomonitoring Indicators for Chemical Exposure in the European Population](#). International journal of environmental research and public health, 15(10), 2085.

Ganzleben, C., Antignac, J. P., Barouki, R., Castaño, A., Fiddicke, U., Klánová, J., ... & Sepai, O. (2017). [Human biomonitoring as a tool to support chemicals regulation in the European Union](#). International journal of hygiene and environmental health, 220(2 Pt A), 94.

## News from our National Hubs - Solid foundations in Slovenia

The first national human biomonitoring programme ran from 2007 to 2014 in Slovenia and made significant progress. The National Hub was established, including health and environment institutes, the Environmental Agency and the Agency for Research and Administration for Food Safety. This structure has carried forward to support HBM4EU.

Before kicking off the second national human biomonitoring programme, running from 2018-2022, Slovenia collated data under a national human biomonitoring database. Metadata were also included in IPCHEM.

Efforts are now underway to conduct human biomonitoring surveys at national level, from study design, through to recruitment and sampling, while conforming to all ethical requirements.



Dr Lijana Kononenko



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.



**Prof Argelia Castaño**  
Leader of Pillar 2 on the European HBM Platform

“We are building a European platform for human biomonitoring, with harmonizing tools and laboratory networks to provide comparable information on the levels and determinants of chemical exposure in citizens.”

# FIRM FOUNDATIONS:

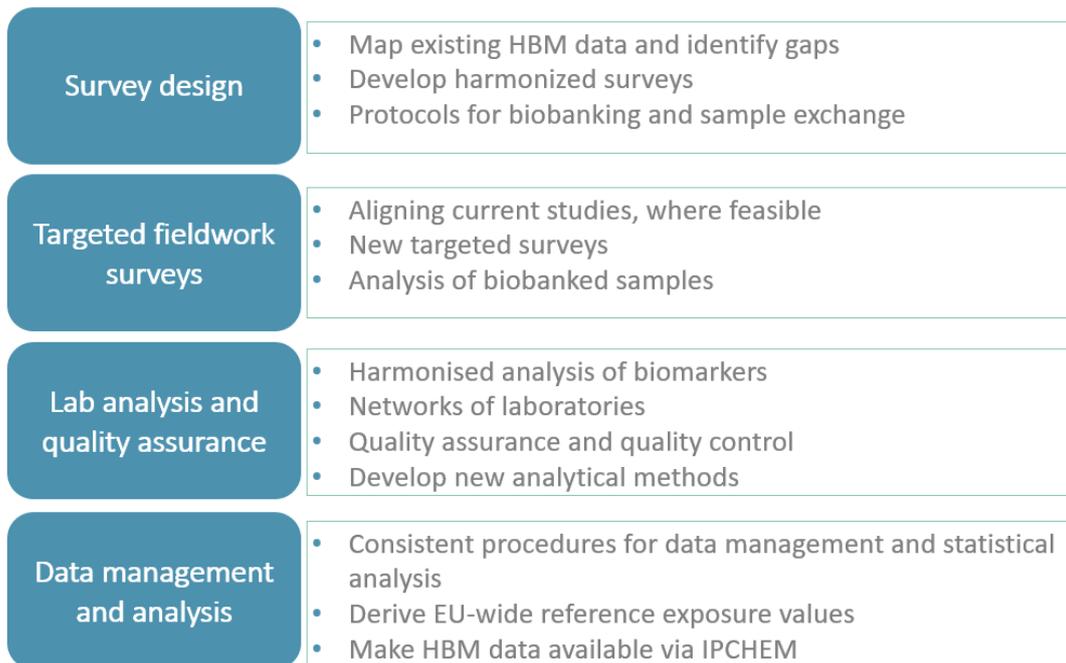
building the European Human Biomonitoring Platform

A major hurdle to the reliable assessment and management of chemical risks is the lack of harmonised information at European level concerning the exposure of citizens to chemicals.

HBM4EU is coordinating scientific excellence and building capacities to creating a robust Human Biomonitoring Platform at pan-European level.

This platform will deliver comparable, European data on human exposure to chemicals and mixtures of chemicals to policy makers, as a robust basis for policy making to improve chemical safety.

Producing coherent European datasets requires harmonised approaches to study design, implementation and sample analysis, as well as consistent approaches to data management and analysis.



## News from our National Hubs - Building institutions for human biomonitoring in Spain

In Spain, a chapter on human biomonitoring has been included in the draft of the National Plan on Health and Environment, cementing the establishment of the National human biomonitoring Hub. In follow up, the Spanish National Hub has received the go-ahead to establish a Human Biomonitoring Expert Committee and a National Human Biomonitoring Laboratory Network.



Dr Susana Pedraza Díaz



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

## Common protocols for survey design and fieldwork

We have developed guidelines (Deliverables 7.3 and 7.6) on how to run human biomonitoring studies for the general population and for workers, ensuring high-quality harmonised approaches across our network. This includes Standard Operating Procedures (SOPs) for recruiting participants, undertaking fieldwork, taking samples from participants and exchanging samples for analysis. We have also developed recommendations for handling bio-banked human samples, to ensure sample quality and stability.

Clear communication materials explain our study objectives to participants; requesting their consent for use of their personal data and describing the sampling process and follow up. Our materials target the different age groups we are working with,

including children, teenagers and adults, and are available in multiple languages (Deliverable 7.7).

We have also developed questionnaires for survey participants for each HBM4EU substance group, exploring the different dimensions of lifestyle and behaviour that may influence chemical exposure. These questionnaires are available on our website for use by other researchers worldwide.

With the aim of mapping human biomonitoring activities across our partner countries, we have collected information on past, ongoing and planned studies, and are capturing this information in a user-friendly online tool.

**Ulrike Fiddicke**



### Peer-reviewed articles:

"Towards Harmonized Biobanking for Biomonitoring – A Comparison of Human Biomonitoring-related and Clinical Biorepositories" (submitted for publication in 'Biopreservation and Biobanking')

### News from our National Hubs - Presenting science to policymakers in Austria

Austria's human biomonitoring platform includes experts from both science and policy and is an official advisory body of the Federal Ministry of Sustainability and Tourism, advising on the interface between the environment and human health.

In 2019, a report will be presented to Austria's National Council introducing human biomonitoring, the Austrian platform and HBM4EU, as well as relevant studies in Austria. Looking forward, a progress report will be delivered to the National Council every two years.

Under HBM4EU, the Austrian Environment Agency is the Chemical Substance Group Leader for per- and poly-fluorinated substances (PFAS), with the Austrian National Hub actively contributing to research on exposure to and the health effects of PFAS. For example, a mother-child study, the NEWDA-cohort of the Medical University of Vienna, is currently investigating birth outcomes related to PFAS levels in healthy mother-child-pairs, as well as for low-birth-weight for gestational age neonates. The study is measuring total organic fluorine, in order to screen for unknown or not yet detectable PFAS compounds. In addition, in vitro toxicity testing with placental cells is exploring mechanistic action.

The 2018 conference "[Human biomonitoring in Europe – science and policy for healthy citizens](#)" took place in Vienna, organised by the Austrian Presidency and the European Commission. Participants agreed on the benefits of human biomonitoring for policy making, reviewed the first results of HBM4EU and helped shape the future of human biomonitoring in Europe. Directly before the conference, the 2018 HBM4EU meeting week, as well as a workshop on PFAS, were also successfully hosted in Vienna.

**umwelt**bundesamt<sup>U</sup>  
ENVIRONMENT AGENCY AUSTRIA

Dr Maria Uhl



## Targeted fieldwork surveys and alignment at EU level

Align and Deliver – this is one of HBM4EU's unique selling points.

A unique selling point is a factor that differentiates a product from its competitors. Why would our stakeholders, the European Commission, European agencies and national policy makers, feel that we have been successful? HBM4EU's unique selling point, or at least one of them, is the delivery of a European HBM Platform which in the future continues to be the major European instrument to collect data on the internal chemical exposure of citizens across Europe.

The challenge was to collect biological samples, plus associated information through questionnaires, and assess exposure and effect biomarkers to ultimately produce comparable data on citizen exposure across Europe.

Europe needs a framework through which to generate this scientific evidence to support policy. Aligning studies across Europe sounds like an easy task, but to bring together disparate studies for a common purpose is a great achievement. The strategy proposed was to build on current experience and projects - not to start from scratch. This was more challenging than we could have imagined.

The number of countries that have population representative studies was limited to those in red in the figure below, thus the ambition to produce European representative exposure data could not be achieved. The compromise was to look for studies that would allow us to assess differences across European regions. To this end, Europe was divided into North (with approx. 21% of the population), South (28% of the population), East (11% of the population) and West (41% of the population).

### Sampling framework for the aligned studies

27 European countries- 497 Million inhabitants

North - 21%      West - 41%      South – 28%      East-11%

10-11 sampling units / age group, 300 participants per sampling unit



	~2950 Children 6-11 y			
Phthalates / DINCH Flame retardants	NO	<b>FR</b>	IT	HU
	DK	<b>DE</b>	SL	SK
		NL	EL	PL
	~2900 Teenagers 12-18 y			
Phthalates / DINCH PFASs	NO	<b>FR</b>	<b>ES</b>	CZ
	<b>SE</b>	<b>DE</b>	SL	PL
		BE	EL	SK
	~3165 Adults 19--39 y			
Bisphenols Cadmium PAHs	DK	<b>FR</b>	<b>PT</b>	CZ
	FI	CH	HR	PL
	<b>IS</b>	<b>DE</b> LU		



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

Project leads in each country had to obtain ethical approval and informed consent over 2018 and 2019. Three age groups were defined to capture the most sensitive population for each of the exposures to be assessed. The age groups are:

- children age 6 to 11;
- adolescents age 12 to 19; and
- adults age 19 to 39.

The figure shows how the studies from across 21 countries are being aligned to collect samples from relevant age groups for human biomonitoring of the first list of HBM4EU Priority Substances. Chemicals from the second priority list will also be included. By the end of 2019, the aim is to have

collected all the samples from across 21 countries. This will represent a huge achievement.

A network has been created which will allow future studies to be carried out and deliver comparable data. This is a success story that will have a sequel, the next success story will show how HBM4EU has gathered data from occupational studies - HBM4EU strikes again!

Dr Ovnair Sepia



L. Gilles and  
Prof Greet Schoeters



### News from our National Hubs - Effective networking in Portugal

The Portuguese National Hub has been active in reaching out to scientific networks at the national level. The 1st Workshop on Human Biomonitoring in Portugal, held in May 2018, saw the participation of more than 80 representatives from science, policy, industry and other stakeholders. In May 2019, a focus group was held with citizens in Portugal to discuss public concerns around chemical safety. Looking forward, a 2nd Workshop on Human Biomonitoring in Portugal is planned for October 25th, 2019.



© FCT

**FCT**

Fundação para a Ciência e a Tecnologia Dr Rita Cavaleiro



science and policy  
for a healthy future

## Laboratory analysis and quality assurance

As a result of close collaboration among experts across Europe, a network of human biomonitoring laboratories based on robust quality assessment and control criteria has been established to support future activities in Europe.

In July 2019, we published the first list of laboratories qualified ([Deliverable 9.6](#)) to undertake the harmonised chemical analysis of our first list of HBM4EU priority substances in human samples. This represents the result of an extensive process to ensure the quality and comparability of our analytical results, delivered through the combined efforts of HBM4EU partners across Europe.

The work started with a review of the biomarkers, matrices and analytical methods for the different groups of substances, to identify the optimal methods in each case. Based on this, we then selected parameters for inclusion in the Interlaboratory Comparison Investigations (ICI) and External Quality Assurance Scheme (EQUAS), including as many biomarkers as possible to foster innovation.

At the same time, our Quality Assurance Unit prepared standard operating procedures ([SOPs](#)) and defined the quality assessment and quality control (QA/QC) programme. We also worked with the National Hubs to identify the candidate laboratories that would participate in the programme.



© ISCIII



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

The first ICI kicked-off in February 2018, involving candidate laboratories from 24 countries and covering more than 70 biomarkers in four biological matrices. The evaluation of laboratory performance is specific to each parameter or biomarker. Laboratories qualify after successfully completing two rounds of ICI/EQUAS. Led by [IPASUM](#) and [ISCIII](#), seven laboratories prepared and tested control materials and managed the ICI/EQUAS for specific substances.

We have since run two more rounds, including one ICI and one EQUAS, in which expert laboratories from across the world participated as reference laboratories. A fourth round is now planned to continue building excellent capacities for human biomonitoring across Europe. As the results of these additional rounds become available, the list of qualified laboratories on the HBM4EU website will be updated to reflect the outcome.

In delivering this work our team overcame many challenges, such as the low availability of laboratories to support the ICI/EQUAS, the high number of biomarkers to tackle, and not least the balance to be struck between pursuing cutting-edge science and building capacity across our network of laboratories.

Based on this solid foundation, the analytical phase can now kick-off. We are proud to have reached this important milestone in our project and are now ready to generate the first new human biomonitoring data under HBM4EU!

**Dr Marta Esteban López,  
Dr Susana Pedraza Díaz and  
Prof Argelia Castaño**





science and policy  
for a healthy future

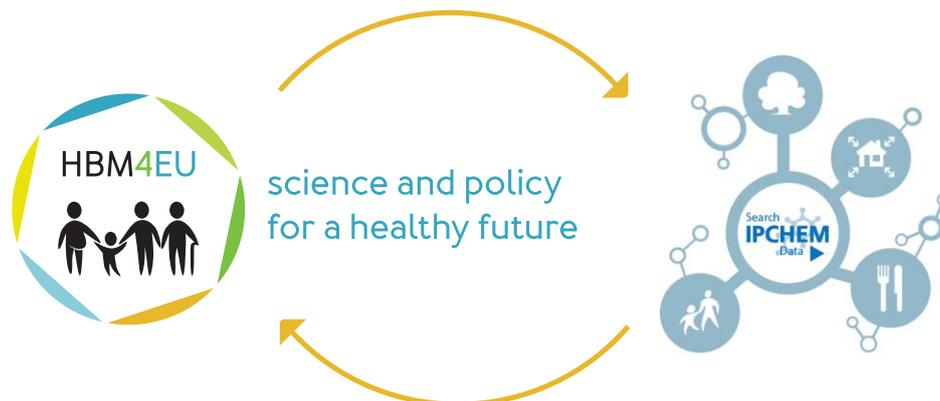


The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

## Data management and analysis

HBM4EU is operating on the FAIR principle – whereby human biomonitoring data from European citizens are Findable, Accessible, Interoperable, and Re-usable. All new human

biomonitoring data generated under the project will be available to policy makers, with metadata accessible via the [Information Platform for Chemical Monitoring \(IPCHEM\)](#).



Our [data management plan](#) describes the data management life cycle for all datasets collected, processed and generated under the project, while our [data policy](#) describes the data management procedures we follow. Collecting and using human biomonitoring data is sensitive and we work hard to ensure compliance with the EU General Data Protection Regulation.

To ensure a harmonised approach to data analysis, HBM4EU has developed a [statistical analysis plan](#), including statistical plans for the evaluation of time trends, geographic comparisons, evaluation of exposure determinants, a strategy for the calculation of EU reference values, and a plan for conducting uncertainty analysis.

Thus far, 37 harmonised human biomonitoring datasets on seven HBM4EU Priority Substances are currently available to partners for analysis. These data have been provided through lead scientists of national and regional studies. They will be reused for data analysis at the European level yielding a broader picture of human chemical exposure in Europe.

Existing data used under HBM4EU are being made available via IPCHEM to the extent possible, while respecting all ethics and legal restrictions that apply. To date, the metadata from 94 studies across Europe can be accessed via IPCHEM.

**Eva Govarts, Dr. S. Remy and Prof Greet Schoeters**





science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.



Institut  
thématiques **Inserm**  
Institut national  
de la santé et de la recherche médicale

**Professor Robert Barouki**  
Leader of Pillar 3 on exposure and health

"We are using state of the art methodologies to identify exposures pathways and health outcomes of chemical substances, including emerging chemicals."

# UNDERSTANDING THE HEALTH

## impacts of chemical exposure

In response to policy demand, we are generating the evidence for a causal link between chemicals and health impacts. We are combining health information with human biomonitoring data to understand exposure-response relationships.

Taking into account socio-economic status, lifestyle, diet and environmental conditions, we are assessing the health impacts of chemical exposures across age groups and genders.

Using modelling tools, we relate internal exposure to environmental sources and identify external exposure pathways.

We are addressing pressing questions in chemical risk assessment, producing evidence on human exposure to chemical mixtures and using cutting-edge technologies to search for emerging substances in human matrices that may serve as early warnings of future concern.

### News from our National Hubs - Towards a sustainable human biomonitoring programme in the UK

In the UK, HBM4EU has catalysed the establishment of a steering group at the policy level, focused on human biomonitoring for the UK (HBM4UK). The group includes relevant government departments and agencies, namely the Department for Environment, Food and Rural Affairs, the Department of Health and Social Care, the Health and Safety Executive, the Environmental Agency, the Foods Standard Agency and Public Health England. The UK National Hub meets every quarter and includes representatives from the steering group, as well as the Institute of Occupational Medicine, UK Research & Innovation, Brunel University and the Health and Safety Laboratory. The UK National Hub presented HBM4EU to the [UK Chemical Stakeholder Forum](#), a group with membership from industry, environmental, animal protection and consumer organisations, trade unions and the scientific community. The forum discussed the strategy for the prioritisation of chemicals and the HBM4EU work programme, with members being asked to contribute their knowledge and, if possible, data.

With an eye to sustainability post-HBM4EU, the steering group will encourage the Department of Health and Social Care to continue human biomonitoring activities in the UK. The need for a national HBM programme is flagged in two prominent documents.

The [Chief Medical Officer's 2017 review](#) recommends that "Public Health England explore the creation of an English health bio-monitoring data set, which includes human exposure to pollutant and health outcomes, and report publicly on their findings."

The [2019 report for the Parliament's Environmental Audit Committee](#) stated "We need to better understand which chemicals we are exposed to in greatest measure and what the risk from that exposure is. To do this, a long-term, UK wide, human and wildlife biomonitoring programme should be established".

The first hurdles have been overcome, with high-level recognition of the need for a national HBM programme. The second hurdle will be higher, but the appetite has now been whetted so watch this space!



Public Health  
England

Dr Ovnair Sepia, Dorothy Ubong and Dr Lorraine Stewart



## Exploiting synergies: linking human biomonitoring to health studies and registers

[HBM4EU has reviewed the opportunities and obstacles to combining human biomonitoring and health studies.](#) Many countries have a health examination survey (HES) and/or disease specific health studies at national or regional level. In some cases, a human biomonitoring module is already included, while in others it could be added.

HESs typically collect blood samples (plasma) and in many cases, spot urine, and usually part of the samples is stored for future use. In 50% of the reported studies, ethical approval covers chemical analysis of the collected samples. However, a limiting factor is that for the majority of the studies, it is unclear whether the data, such as the results of chemical analysis, could be made available for broader use.

In terms of registers, health-related administrative registers include information on births and deaths, malformations, hospitalizations, medical prescriptions and disease specific registers, such as cancer registry. Most HBM4EU partner countries have health registers that cover some of these elements. Just over half use a unique personal identifier (PIC), which could be used to link register data on individual level to health examination surveys or human biomonitoring studies. In some countries, the opportunities to link records across registers and to surveys are limited by national legislation.

A single chemical substance may have several known health effects. At the same time, one health outcome may be influenced by exposure to a number of different chemicals. Chemical exposure along a lifetime and the resulting health effects therefore play out across a complex matrix.

Information about health outcomes can be gathered in several ways, including:

- self-reporting through questionnaires and interviews;
- objective health measurements in the context of a health survey; and
- the use of medical records to obtain reliable information.

The validity and comparability of information from different data sources often varies, for example due to awareness in self-reporting.

Health measurements tend to be rather sensitive to variations in measurement procedures, and different measurement devices can produce significantly different results. Implementing standardized operating procedures (SOPs) for health measurements can increase data comparability and quality. The [European Health Examination Survey Manual](#) includes SOPs for a range of measurements in adults and corresponding SOPs for children have been prepared under HBM4EU.

### Dr Hanna Tolonen

 Finnish institute for health and welfare

## Peer-reviewed articles:

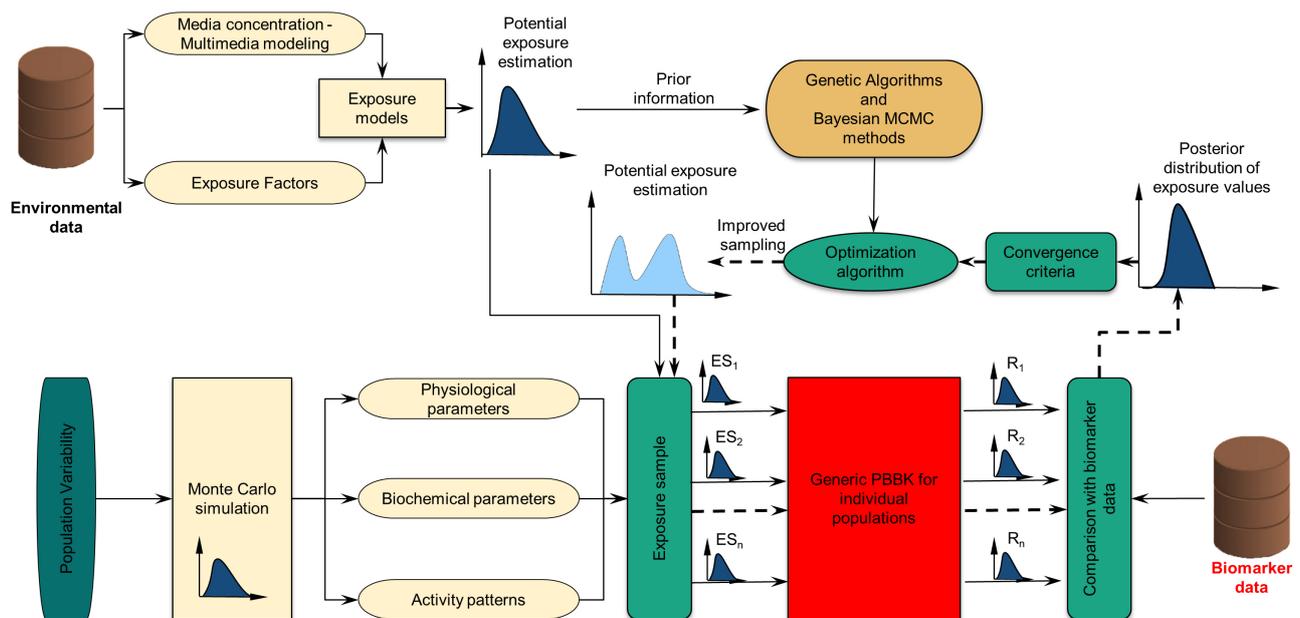
Louro, H., Heinälä, M., Bessems, J., Buekers, J., Vermeire, T., Woutersen, M., ... & Alvito, P. (2019). [Human biomonitoring in health risk assessment in Europe: Current practices and recommendations for the future.](#) International journal of hygiene and environmental health.

## Using human biomonitoring to understand exposure

### Modelling exposure levels in Europe for 1st list HBM4EU priority substances via exposure reconstruction based on human biomonitoring data

We have adapted the integrated exposure modelling platform, INTEGRA, to meet the needs of HBM4EU. Using validated models, we reconstructed external exposure levels and derived exposure estimates over the life-course for the general population across the EU for as many substances in the 1st list of HBM4EU priority sub-

stances as possible. The exposure reconstruction algorithm is based on the Markov chain Monte Carlo (MCMC) and Differential Evolution Markov Chain techniques (DEMC). The process starts from ancillary exposure-related data that are fed into the exposure model taking into account multiple exposure routes. The results are evaluated against the biomonitoring data distributions, aiming at the reduction of uncertainty in back-calculating doses, by minimizing the error between the predicted and the actual biomonitored data. The methodological framework for exposure reconstruction starting from HBM data is graphically illustrated below:



Occupational exposure was also considered for those compounds for which human biomonitoring data for workers were available.

Exposure reconstruction has been carried out based on HBM data for the following compounds:

- Bisphenol A (BPA)
- Phthalates - DEHP, DiNP, BBzP, DnBP, DINCH
- Poliyaromatic hydrocarbons (PAH): Pyrene, Benzo(a) pyrene
- Cadmium
- O-toluidine
- Flame retardant TCEP (tris(2-carboxyethyl)phosphine)
- Per- and Poly-fluoroalkyl substances (PFOS, PFAS)

Our results show that for the majority of the compounds examined, estimated daily intake levels are below the existing regulatory thresholds. However, a direct assessment of human biomonitoring concentrations is only possible, if Human Biomonitoring Guidance Values (HBMGV) exist. As mentioned earlier in this newsletter, establishing such values is a task under HBM4EU.

For BPA, the mean daily intake is estimated to be almost two orders of magnitude below the respective threshold proposed by the European Food Safety Authority (EFSA). For phthalates, daily



intake estimates are usually one or two orders of magnitude below the respective Tolerable Daily Intake (TDI). Firmer conclusions will be drawn when the human biomonitoring data to be collected under the aligned studies with detailed descriptive statistical metrics become available.

Regarding PAHs, estimated intake levels of pyrene result in a cancer risk significantly lower than  $10^{-6}$  (an increased lifetime risk of 1 in 1,000,000 for developing cancer). However, the lack of data for a benzo[a]pyrene specific biomarker posed a problem when estimating intake levels of the compound driving PAHs mixture carcinogenicity.

For cadmium, we estimated a daily intake of almost 0.2  $\mu\text{g}/\text{kg}$  of body weight per day (kg bw/d), indicating that the highly exposed individuals might be close to the tolerable weekly intake of 2.5  $\mu\text{g}/\text{kg}$  bw/d set by EFSA.

For o-toluidine, the mean daily intake of 1  $\mu\text{g}/\text{kgbw}/\text{d}$  results in a cancer risk that is in the range of  $10^{-4}$  (an increased lifetime risk of 1 in 10,000 for developing cancer), which is considerable. This risk is twice as high for smokers and increases by a couple of orders of magnitude for workers in specific chemical industries. It would be interesting to estimate the intake levels based on representative human biomonitoring data for the EU.

Regarding TCEP, a typical emerging flame retardant, the mean daily intake is estimated to be below 0.1  $\mu\text{g}/\text{kg}$  bw/d, far below the calculated 'provisional' TDI of 13  $\mu\text{g}/\text{kgbw}/\text{d}$ . However, since the available data were very limited, these exposure levels are rather indicative than representative for Europe. Finally, regarding the estimated intakes of PFAS, intake levels of perfluorooctanesulfonic acid (PFOS) are very close to the TDI of 0.15  $\mu\text{g}/\text{kg}$  bw/d proposed by EFSA's Panel on Contaminants in the Food Chain (CONTAM), while intakes for PFOA are estimated to be one order of magnitude below the respective TDI of 1.5  $\mu\text{g}/\text{kg}$  bw/d.

## Using integrated exposure models to identify the multiple pathways and routes of exposure for 1st list HBM4EU priority substances - differentiated by age in Europe

The capacity to identify the main pathways and routes of exposure for chemicals is a *sine qua non* for effective risk management when estimated exposure levels generate concern. For this reason, we undertook a thorough analysis of plausible routes and pathways of exposure for the 1st list HBM4EU priority substances, taking into account differences in exposure modifiers, such as age, across Europe. The results outlined below are expected to support cost-effective risk management in the EU.

BPA is a compound that has been extensively studied, as a result of scientific and regulatory interest. For BPA, the major source of exposure for the general population is dietary intake of canned food and beverages from plastic bottles, while for specific occupational groups such as cashiers, dermal exposure from thermal receipts might account for 20-30% of overall intake.

For phthalates like DEHP, rich datasets are available for environmental media and food residues. Less data is available for phthalates of a lower molecular weight. Phthalates exposure is associated to various pathways and routes, which are influenced by the uses and physicochemical properties of the specific substance. As a result, the contribution of different exposure pathways, such as the ingestion of dust, inhalation and consumer exposure, can differ significantly, both for different phthalates and across demographic groups for the same substance. However, oral exposure is the dominant exposure pathway for phthalates, including diet, dust ingestion and object-to-mouth behaviour amongst children.

For PAHs, while much discussion focuses on ambient air sources, the major exposure pathway is diet, in particular the consumption of smoked food. In addition, smoking and second-hand



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

smoke are significant sources, with smoking a more important pathway than diet for smokers.

For cadmium, diet and drinking water are the major sources, followed by smoking. Other pathways of exposure like ambient air particles or settled dust constitute minor sources.

Exposure to flame retardants is related to diet in adults, with ingestion of settled dust potentially representing a significant pathway for neonates and infants. While consumer products could also be an important source of exposure, this is an area where further experimental work is needed to derive realistic exposure factors and loading mechanisms.

Exposure to PFAS is also dominated by diet and drinking water. However, due to their slow elimination from the human body, toxicokinetic considerations are important to estimate the actual body burden and the resulting health risk.

Finally, there is still a lack of data on general population exposure to anilines. Nonetheless, current exposure models can be used to describe occupational exposure to anilines, dominated by inhalation.

**Prof Denis Sarigiannis and  
Dr Spyros Karakitsios**



ARISTOTLE  
UNIVERSITY OF  
THESSALONIKI

## Peer-reviewed articles:

Sarigiannis, D.A., Karakitsios, S., Dominguez-Romero, E., Papadaki, K., Brochot, C., Kumar, V., Schumacher, M., Sy, M., Mielke, H., Greiner, M., Mengelers, M., Scheringer, M. [Physiology-based toxicokinetic modeling in the frame of the European Human Biomonitoring Initiative](#). Environmental Research (2019), 172, 216-230, Academic Press.

## News from our National Hubs - An Action Plan on Environment and Health for Slovakia

In the Slovak Republic, there is currently no human biomonitoring programme in place at national level. However, experience from other countries demonstrate that without a robust evidence-base, the creation, implementation and enforcement of environmental health policies is challenging, if not impossible.

An Action Plan for the Environment and Health of the Inhabitants of the Slovak Republic was adopted by the Slovak government in January 2019. The Action Plan implements the conclusions of the 6th Ministerial Conference on Environment and Health, held in Ostrava in June 2017. It was developed through intersectoral cooperation, involving the Ministries of Environment, Agriculture and Rural Development, the Economy, Transport and Construction and the Ministry of Education, Science, Research and Sport.

The Action Plan tackles environmental determinants of health, including air pollution, water pollution, drinking water supply, dangerous chemical substances, noise, contaminated sites, climate change and the residential environment. For the first time in the Slovak Republic, the Action Plan sets the long-time aim of introducing a national programme of human biomonitoring in the Slovak Republic.

Support activities include:

- Establishing an intersectoral working group on human biomonitoring;
- Mapping existing technical infrastructure and resource capacities for human biomonitoring;
- Assessing the HBM4EU Priority Substances in relation to national priorities;
- Raising the awareness of both experts and the public concerning the benefits of human biomonitoring; and
- Developing a proposal for a Slovak human biomonitoring platform.



Dr Michal Jajcaj and Dr Milada Estokova



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

## Establishing relationships between chemical exposure and health

For a decade, toxicity testing has been shifting away from animal studies to rely on alternative tests such as in vitro assays in cells. In this context, predictions of the impact of a chemical on population health must be derived from its effects at the molecular or cellular level to inform risk assessment. This requires comprehensive knowledge of the mechanisms by which a chemical exerts toxicity. Adverse Outcome Pathways (AOPs) provide a framework to describe the mechanisms leading from the effect at the molecular level, through to the final adverse outcome on health at the level of the organism.

Within HBM4EU we integrate information under AOPs for HBM4EU priority substances. We focus on substances for which available toxicity data is very limited, such as emerging chemicals used to replace chemicals restricted on the basis of known hazards.

As an example, HBM4EU identified two AOPs by which Tetrabromobisphenol A, a flame retardant used to substitute previously banned substances, may lead to a decrease in hearing or in cognitive performances through its effects on thyroid hormones. For other novel flame retardants, we for the first time identified causal mechanisms by which they could decrease fertility in males by affecting steroid hormone production in testicular cells.

HBM4EU scientists have also established links between bisphenol-S and obesity. Bisphenol-S is used as a substitute for the known endocrine disruptor, bisphenol-A (BPA). The advanced text mining AOP-helpFinder tool led to the identification of a network of potential targets of bisphenol-S, so called nuclear receptors that disrupt several lipid metabolism pathways beyond obesity development.

Prof Jana Klánová and  
Prof Luděk Bláha

MASARYKOVA  
UNIVERZITA

Prof Robert Barouki and  
Dr Karine Audouze

Instituts  
thématiques  **Inserm**  
Institut national  
de la santé et de la recherche médicale

### Peer-reviewed articles:

Carvaillo, J. C., Barouki, R., Coumoul, X., & Audouze, K. (2019). [Linking Bisphenol S to Adverse Outcome Pathways Using a Combined Text Mining and Systems Biology Approach](#). *Environmental Health Perspectives*, 127(4), 047005.

Bajard, L., Melymuk, L., & Blaha, L. (2019). [Prioritization of hazards of novel flame retardants using the mechanistic toxicology information from ToxCast and Adverse Outcome Pathways](#). *Environmental Sciences Europe*, 31(1), 14.

Forthcoming: Marylène Rugar, Xavier Coumoul, Jean-Charles Carvaillo, Robert Barouki, Karine Audouze (2019) Deciphering adverse outcome pathway network linked to Bisphenol F using text mining and systems toxicology approaches. *Toxicological Sciences*.

## Using effect biomarkers to unpack causality

One of the objectives of HBM4EU is to generate scientific evidence on the causal relationships between exposure to prioritized chemical stressors and adverse health effects. To this end, biomarkers of exposure are complemented with biomarkers of effect, which are measurable molecular, cellular, biochemical, physiologic, behavioural, structural or other alterations in an organism

occurring along the temporal and mechanistic pathways connecting exposure to chemicals and an established or possible impact on health.

HBM4EU has produced an inventory of both traditional and novel effect biomarkers for the 1st list of HBM4EU priority substances, based on each chemical family, health outcomes of highest concern and susceptible windows of development for childhood, adolescence or adulthood. This inventory is based on comprehensive litera-



science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

ture searches. A similar effort is ongoing for the 2nd set of prioritized substances.

Additionally, we have developed a strategy to select the best effect biomarkers to be used in observational studies to link chemical compounds to the most concerning adverse health effects, connecting the fields of epidemiology and toxicology. As a proof of concept, we have published work on effect biomarkers and AOP information for phthalates and reproductive health (Baken et al, 2019). Ongoing work following the same approach will help to develop an integrative framework to approach the field of effect biomarkers in a more systematic and comprehensive way.

What is the practical application of this corpus of knowledge? Human biomonitoring studies inside HBM4EU are being aligned to produce comparable chemical exposure data, together with effect biomarkers data, for Europe. We have identified relevant effect biomarkers and addressed the technical challenges to enable their use in the aligned studies, and in ongoing European prospective birth cohorts. Moreover, for novel effect biomarkers we fine-tuned the methodologies and quality controls needed to guarantee the quality of the data generated.



**Prof Mariana F. Fernández**

## Peer-reviewed articles:

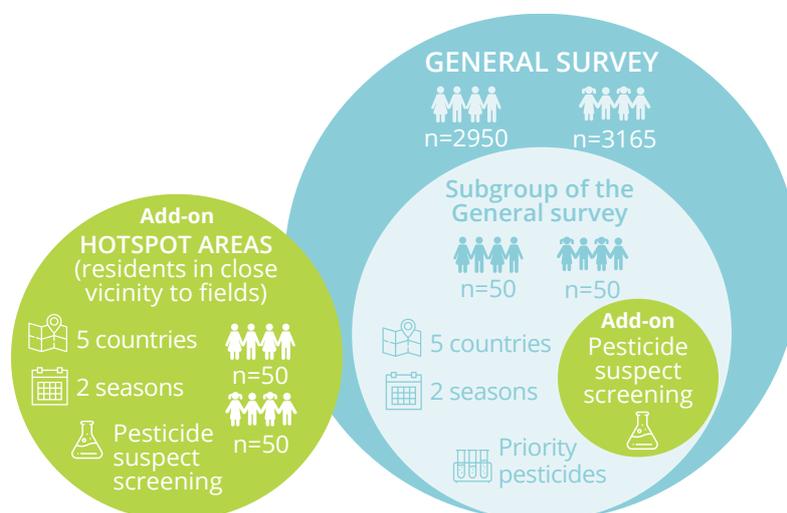
Baken, K. A., Lambrechts, N., Remy, S., Mustieles, V., Rodríguez-Carrillo, A., Neophytou, C. M., ... & Schoeters, G. (2019). [A strategy to validate a selection of human effect biomarkers using adverse outcome pathways: Proof of concept for phthalates and reproductive effects](#). *Environmental Research*, 175, 235-256.

## Tackling chemical mixtures

A key question in chemicals policy today is how to conduct robust risk assessments of chemical mixtures.

HBM4EU is running a survey of human exposure to mixtures of pesticides in across six of our par-

tner countries. This survey, entitled 'SPECIMEn', has a so-called 'hotspot' design and builds on an established sampling framework. Sample collection started in the autumn of 2019, with first results expected in the second semester of 2020.





science and policy  
for a healthy future



The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733032.

In parallel, we are developing a set of case studies, to explore how human biomonitoring data can be used to identify the health effects of exposure to chemical mixtures. In terms of analyzing existing datasets, we are running the first application of statistical scripts to a human biomonitoring dataset on mixtures produced under the [Flemish Environment and Health Survey](#), to identify patterns and correlate exposure across mixtures of chemicals.

HBM4EU partners have teamed up with four other EU funded research projects to tackle knowledge gaps on exposure to and effects of chemical mixtures; EDC-MixRisk, EuroMix, EU-ToxRisk and

SOLUTIONS. The joint position paper "[Preventing risks for people and environment from hazardous chemical mixtures](#)" was co-signed by 127 scientists and sent to the Director Generals of DG Environment, DG Research and Innovation and DG Health and Food Safety. The paper calls for the stepwise translation of the latest science into the development of new approaches, methodologies and tools. It proposes 12 key actions and recommendations to improve risk assessment of chemical mixtures.



National Institute for Public Health  
and the Environment  
Ministry of Health, Welfare and Sport

Dr Mirjam Luijten and  
Prof Erik Lebret

## Peer-reviewed articles:

Bopp, S. K., Barouki, R., Brack, W., Dalla Costa, S., Dorne, J. L. C., Drakvik, P. E., Kolossa-Gehring, M. (2018). [Current EU research activities on combined exposure to multiple chemicals](#). *Environment International*, 120, 544-562.

## Identifying emerging chemicals

People today are exposed on a daily basis 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. Conventional targeted quantitative analytical methods are only available to support risk assessments for a limited number of these chemicals.

The need for a wider exposure characterization is noteworthy, particularly concerning the detection of chemicals of emerging concern, for which knowledge is limited.

This open and integrative view of the chemical space contaminating the environment-food-human continuum is supported by advanced chemical profiling instrumentation that enables the holistic characterization of biological samples. Large-scale suspect and non-targeted screening approaches based on current and future generations of instrumentation dedicated to chemical

profiling (high resolution mass spectrometry) today open the door to the simultaneous detection of a number of chemical descriptors never achieved before. Among which we find markers of human chemical exposure of interest for exposure assessment, biomonitoring and environmental health studies. 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 is developing and applying such new suspect and non-targeted screening approaches, establishing a European network of cutting-edge analytical laboratories, and promoting the necessary methodological harmonization.



## Suspect screening of human urine and serum samples reveals the first markers of exposure

As a first proof of concept, laboratories in four countries (France, Germany, Belgium and Austria) undertook suspect screening of blood and urine human samples originated from different cohorts, including general and occupationally exposed populations. Each laboratory applied its own analytical workflow to capitalize on existing analytical capabilities and maximize their complementarities. The reasoning behind it is to look for the presence of a predefined (extended) list of suspect markers for which we have already inventoried the expected detected signal characteristics within a dedicated annotation MS reference library.

First results confirmed the relevance of the approach by allowing the simultaneous detection of dozens of markers of exposure from various substance groups (such as pesticides, plasticizers and PFAS) based on the current capabilities of our databases. Several of these chemicals were detected 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. These first results open the way to further studies on chemicals of emerging concern, to confirm these new approaches as powerful tools for testing research hypotheses and supporting the prioritisation of substances for risk assessment and risk management.

Next steps will focus on improving and harmonizing the underlying analytical protocols and databases. Importantly, the suspect screening approach will be applied to a pesticide focused proof-of-concept study on mixtures of pesticides, foreseen for 2020. Using semi-quantitative determination for detection frequencies and variability data, we will monitor several thousand pesticide-related markers in 2,000 human urine samples from five countries, through a harmonized methodology implemented in laboratories in France, the Netherlands, Germany, the Czech Republic and Spain.

## First application of non-targeted screening of halogenated markers of exposure leading to newly identified emerging chemicals of concern

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 a priori information. One of strategies to address this challenge is a chemistry-based approach, aiming to detect the particular chemical signatures of compounds. This is the case for halogenated substances, as the presence of halogen atoms lead to distinctive signals (isotopic patterns) detectable with high resolution mass spectrometry (HRMS) coupled to liquid (LC) or gas chromatography (GC).

As a first proof of concept, a workflow for the open detection of halogenated markers of human internal exposure was elaborated. A first step was to develop user-friendly software to handle the huge and complex data sets generated by LC-HRMS, based on advanced bio-inspired computing algorithms capable of spotting the signals associated with the typical characteristics of halogens (isotope pattern and mass defect). The resulting Haloseeker software, was released as an open access resource available on request ([contact.haloseeker@oniris-nantes.fr](mailto:contact.haloseeker@oniris-nantes.fr)) and described in Léon et al. 2019.

A second step was to develop the sample preparation strategies to isolate, in a non-selective way, potential markers of exposure of interest from various human matrices. To maximize the chances of detection, this work focused on biological compartments favorable to the bioaccumulation of halogenated and POPs (e.g. adipose tissue, breast milk, or meconium). These protocols were applied to a first set of human samples originated from various sources. Using this workflow, we



were able to identify 4-hydroxy-chlorothalonil in several breast milk samples.

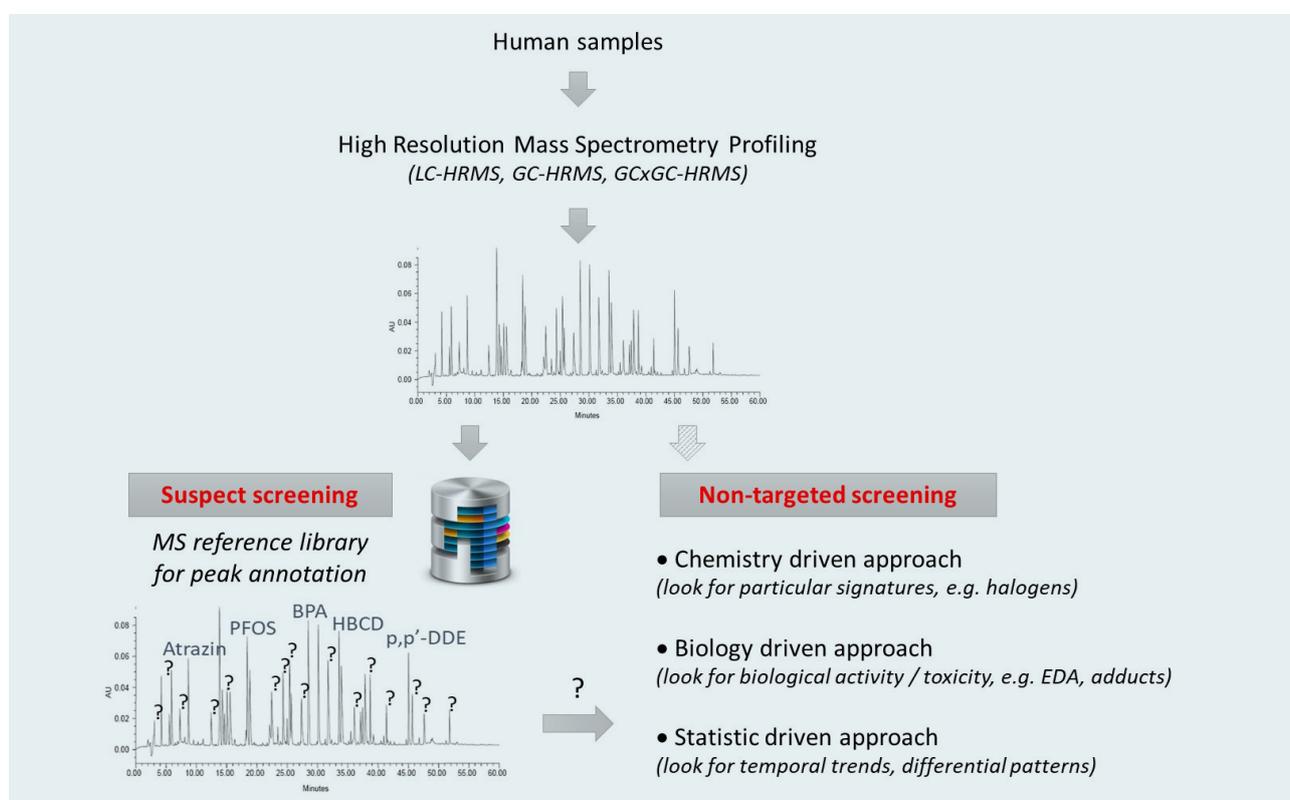
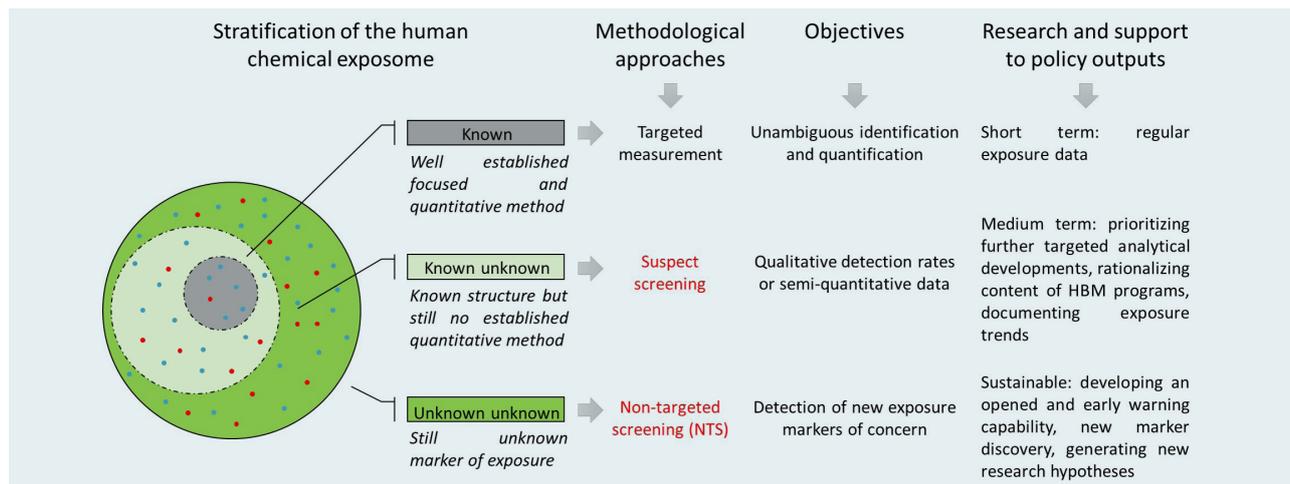
(GC-HRMS), and to apply it to a wider range of real samples to identifying more relevant markers.

Next steps for 2020/2021 will be to expand our work to include the complementary profiling technology



Dr Jean-Philippe Antignac and  
Dr. Laurent Debrauwer

## New approaches to profiling chemicals in humans



## Peer-reviewed articles:

Léon A, Cariou R, Hutinet S, Hurel J, Guitton Y, Tixier C, Munsch C, Antignac J-P, Dervilly-Pinel G, Le Bizec B. [HaloSeeker 1.0, a user-friendly software to highlight halogenated chemicals in non-targeted high resolution mass spectrometry dataset.](#) Analytical Chemistry 2019,91:3500–3507.



science and policy  
for a healthy future

# LOOKING FORWARD

to a sustainable future initiative

Chemicals are high on the political agenda. Citizens care about chemical impacts on their health and the health of their children. At a high-level conference on future chemicals policy held June 2019, consensus coalesced around the need for an ambitious chemicals policy for 2030.

The [EU Council](#) has highlighted the value of human biomonitoring for understanding human exposure to chemicals and called for a sustainably funded structure for applied research to provide the scientific basis for chemicals risk assessment and management.

HBM4EU has built a network of excellent in human biomonitoring across Europe, fostering good practice and promoting harmonised approaches to producing coherent European datasets. The partners in this network are ready to build on these firm foundations and contribute to the development of a future partnership on chemical risk assessment, to serve the chemical policies of the future.

## Project contact & coordination

HBM4EU is coordinated by the German Environment Agency, Section II 1.2 Toxicology, Health Related Environmental Monitoring. Email: [HBM4EU@uba.de](mailto:HBM4EU@uba.de)

VITO is the co-coordinator of HBM4EU.  
Email: [HBM4EU@vito.be](mailto:HBM4EU@vito.be)

The Austrian Environment Agency is responsible for maintaining the dialogue with stakeholders under HBM4EU.  
Email: [stake-hbm4eu@umweltbundesamt.at](mailto:stake-hbm4eu@umweltbundesamt.at)

Visit us at [www.hbm4eu.eu](http://www.hbm4eu.eu). Follow HBM4EU on [Facebook](#), [Twitter](#) @HBM4EU and [Instagram](#).

The European Environment Agency is managing the Knowledge Hub. For questions regarding this publication and for media enquiries please contact the European Environment Agency at [HBM4EU@eea.europa.eu](mailto:HBM4EU@eea.europa.eu).

Editor: HBM4EU EEA Team

Cover photo: © HBM4EU

Layout: HBM4EU/Formato Verde

